# Discovery Origins of All Approved Drugs

## Supplementary Data 1

**for**

**Biological Sciences and Physics Unified: Internal Evolution and Urging the Second Scientific Revolution**

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See the main article for detailed method.

I highly prioritized the accounts from the original reporting papers (denoted as *From the discovery paper:*) or other accounts from the discoverer(s) themselves.

I tried to quote with the highest fidelity, exactly transferring any style or even incorrect spellings; except most in-between-commas details and most in-text citations (I have kept a few in case they would be informative).

Titles of the drugs are hyperlinked to their webpages on National Center for Advancing Translational Sciences (NCATS)(*1*) or drugbank(*2*). All these links have been archived, majorly between 16th and 18th of June 2021, and are accessible via the Wayback Machine (web.archive.org); the archived URLs are also available at doi.org/10.5281/zenodo.5732942.

ALCOHOL

652

Historically used

MORPHINE

1827

Historically used

NITROUS OXIDE

1844

"Nitrous oxide ($N_2O$) was discovered by Joseph Priestley in 1772, about 1 year after he had described oxygen as a chemical compound. The newly identified substance was called by him 'dephlogistated air'. In 1798, Thomas Beddoes founded the Pneumatic Medical Institution in Bristol in order to study the use of gases in medicine and to treat patients with these new substances. A year later, Humphry Davy came to the Institution and experimented with $N_2O$ inhalation, conducting many of his experiments on himself. On one occasion he inhaled the gas when suffering from the discomfort of an erupting wisdom tooth and noted that a definite relief from pain was effected by this inhalation. In a publication titled 'Researches, Chemical and Philosophical, Chiefly Concerning Nitrous Oxide' he mentioned the possibility of using this agent as a remedy for operative pain: 'As nitrous oxide in its extensive operation appears capable of destroying physical pain, it may probably be used with advantage during surgical operations in which no great effusion of blood take place'. Nevertheless, his idea did not take root in spite of the fact that his book was well received and widely read, no-one was there to accept the idea of painless surgery. Thus mankind was to suffer for another 40 years.

In America and, to a lesser extent, in England, students very soon made use of the drug in their frolics or it was inhaled for public entertainment. During a popular lecture on laughing gas given by Gardner Quincy Colton, an itinerant lecturer in chemistry, a drugstore clerk inhaled the gas in 1844. While under the influence of the gas, he became rather rowdy, ran into a bench and lacerated his leg without feeling pain. The dental surgeon Horace Wells who was one of the audience observed that this happening appeared to cause no pain to the man. This train of events caused him to ponder the possibility of using the gas for the painless extraction of teeth. The following day, Colton himself successfully administered the anaesthetic to Wells to extract one of his teeth and Wells announced vigorously as he returned to consciousness: 'A new era in tooth pulling. It did not hurt me as much as the prick of pain. It is the greatest discovery ever made'(*3*)."

SALICYLIC ACID

1860

"Willow bark has been used as a traditional medicine for more than 3500 years. […]

Evidence for this early use of willow as an analgesic and antipyretic first surfaced in 1862. Edwin Smith, an American trader living in Cairo purchased a pair of ancient documents, the provenance of which was unknown. These scrolls dated back to around 1500 BC and are amongst the most important historical documents in medicine. One of these is now known as the Edwin Smith Surgical Papyrus and details 48 surgical cases and their management. The other is now known as the Ebers Papyrus. This was an Egyptian record of around 160 herbal and vegetable remedies. One of these remedies is the first written record of the use of tjeret or salix (now known as willow) for treatment of non-specific pains. This herbal knowledge was passed on as empires rose and fell. The use of willow bark for pain relief continued through ancient Greece, where it was recommended by Hippocrates to relieve the pain of childbirth, through to Roman times, when its

use was recorded by Pliny the Elder. […]

The active ingredient in willow bark was not discovered until 1828 when Johann Buchner first refined willow bark into yellow crystals and named it Salicin (after Salix, the genus of the willow tree). In 1829, the process was further refined by Pierre-Joseph Leroux in France and taken a step further in 1838 when Raffaele Piria produced a stronger compound from the crystals isolated from willow bark, which he named salicylic acid. […]

In 1876, the first clinical trial of salicin was published by Thomas Maclagan a Scottish physician at the Dundee Royal Infirmary. He investigated the effects of salicylate in relieving the symptoms of rheumatic fever. His first step was to take salicin himself: 'I determined to give salicin; but before doing so, took myself first five, then ten, then thirty grains without experiencing the least inconvenience or discomfort'. He proceeded to treat eight patients with rheumatic fever with 12 grains of salicin every 3 h, demonstrating its antipyretic and anti-inflammatory effects(*4*)."

## COCAINE

1860

"The first description of the use of cocaine by humans can be found in the memoirs of the Florentine traveller Amerigo Vespucci. For the next 300 years mostly the advantages of cocaine use, also as a medication, were emphasized. In 1860 Albert Niemann isolated an active ingredient of coca leaves, which he named cocaine. After his death, his work was carried on by his disciple Wilhelm Lossen, who finally, in 1865, determined its proper chemical formula. Although the first observations concerning the effect of cocaine on mucous membranes were made by Niemann and Lossen, the first experimental studies involving the application of cocaine to animals were performed by the Peruvian surgeon Moréno y Maïz. In 1880 Basil von Anrep(*5*)"

## OXYGEN

1868

## BETAINE

1880

"Betaine is used as a dietary supplement and has a beneficial effect on the human health. In the USA, FDA approved a betaine-containing drug Cystadane for the treatment of homocystinuria(*1*)."

## APOMORPHINE

1880

"Awareness of the effects of apomorphine on the brain probably extends back to ancient civilisations. The bulbs and roots of the water lily species (*Nymphaea caerulea*, the blue lotus and *Nymphaea ampla*, which has a white flower) are now known to contain a wide range of aporphines including apomorphine. Ethno-botanical scholars have suggested that the *Nymphaea* species were employed for their narcotic, aphrodisiac and hallucinogenic properties in magical-religious rites by the Maya civilisation of Central America (2000 BC–250 AD). Their ritual use has also been depicted within Ancient Egyptian tomb frescoes and in early papyrus scrolls. […]

Apomorphine was first synthesised by Arppe in 1845, from morphine and sulphuric acid, and later by Matthiesen and Wright who introduced the synthesis of apomorphine from morphine and hydrochloric acid. Not long after its discovery, the drug was investigated by veterinary scientists and recommended as a treatment for stereotypies in farmyard animals.

For the first comprehensive pharmacological study of the effects of apomorphine, we turn to Erich Harnack. […]

In 1874, at the age of 22 years and when working in Dorpat, Erich Harnack published a 50-page account 'Ueber die Wirkungen des Apomorphins am Saugerthier und am

Frosch' (The effects of apomorphine in mammals and frogs) in the 'Archiv für experimentelle Pathologie und Pharmakologie', the journal that was founded in 1873, and is now known as Naunyn-Schmiedeberg's Archives of Pharmacology. By then his colleague Vincent Siebert, also at the University of Dorpat (Tartu), had already studied the emetic effects of apomorphine and established that its associated circulatory changes were restricted to certain species, including humans, dogs and cats but not frogs or rabbits; but in his dissertation of 1871, Siebert who had been supervised by Oswald Schmiedeberg, concluded that knowledge of the possible effects of apomorphine on the central nervous system 'remained shrouded in darkness'.

In his introduction, Harnack emphasised that while drugs may have obvious effects such as emesis, there may be other less evident but important actions equally worthy of attention, and it was this tenet that became his main experimental strategy in relation to apomorphine. In addition to a detailed review of the literature, Harnack went on to describe his own extensive animal experiments. These included studies on the effects of apomorphine at different dosages on dogs, cats, rabbits and frogs(*6*)."

BISMUTH CATION

1882

"The first documented medical use of bismuth was in 1733, when its use in salves was described. While some internal use of bismuth may have occurred in Europe before the late 1700s, in 1799 the editors of a prestigious English medical journal described bismuth as a potent remedy for the relief of spasmodic pain of the stomach and bowels. Shortly thereafter, bismuth salts were reported by Chambers in the United Kingdom and Kussmaul in Germany to be an effective treatment for dyspepsia(*7*)."

METHENAMINE

1884

"Following its discovery in 1859 by Aleksandr Butlerov, first medical usage of methenamine was reported in 1894, which demonstrated its prominent efficacy as a urinary antiseptic, including sterilization of urine in patients with typhoid fever. Thereafter, clinical studies were conducted in cholecystitis, appendicitis, encephalitis, and meningitis(*8*)."

BENZOCAINE

1885

"Schon 1888 hatte sich R. mit der Herstellung einer fiebersenkenden Substanz befaßt, um die damals verwendeten, toxisch nicht unbedenklichen Mittel Phenacetin und Acetanilid zu ersetzen. Der von ihm dargestellte p-Aminobenzoesäureethylester zeigte zwar keine fiebersenkende, wohl aber eine lokalanästhetische Wirkung. R. überließ die neue Substanz der Firma Hoechst, wo sie unter der Bezeichnung 'Anaesthesin' geführt(*9*)"

Translation from Google Translate:

"As early as 1888, R. had dealt with the production of an antipyretic substance in order to replace the toxic substances phenacetin and acetanilide used at the time. The p-aminobenzoic acid ethyl ester presented by him did not show any antipyretic effect, but it did have a local anesthetic effect. R. left the new substance to the Hoechst company, where it was marketed under the name 'Anesthesin'(*9*)"

NITROGEN

1899

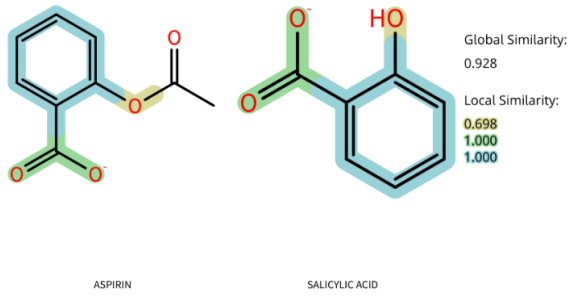
ASPIRIN

1899

Analogue of salicylic acid

"As physicians became increasingly aware of the benefits of salicylate medicines and improved the effectiveness of dosing, the use of these drugs accelerated through the middle of

the nineteenth century until salicylics became a standard component of every physician's medicine bag. Even so, salicylic acid produced highly unpleasant side effects, particularly gastric irritation, tinnitus, and nausea. If Duisberg could find a way to reduce the side effects of salicylic acid while retaining its anti-inflammatory properties, then Bayer would have a chance to improve the drug—and make a fortune. All it needed, Duisberg hoped, was the right chemical tweak […]




In the mid-1890s, Eichengrün, the head chemist, became interested in acetyl groups, small molecules with two carbon atoms that could be attached to many plant compounds, including the salicylics. In August of 1897, Eichengrün instructed Felix Hoffman, a junior chemist in his department, to add acetyl groups to two prominent plant-derived drugs, morphine and salicylic acid. Hoffman added an acetyl group to morphine (derived from poppy flowers) and created a new synthetic compound called diacetylmorphine. He also added an acetyl group to salicylic acid (derived from meadowsweet) and created a new synthetic compound called acetylsalicylic acid.

These two new drug candidates, diacetylmorphine and acetylsalicylic acid, were sent to Dreser (the head pharmacologist) for evaluation on animals and humans. Both synthetic compounds passed Dreser's initial animal trials. But Dreser feared that he did not have a large enough budget to pursue a complete evaluation for both compounds. He believed that, given his limited resources, he could pick only one drug to develop. But which one? […]

Dreser was more concerned about spending resources on acetylsalicylic acid because of salicylic acid's reputation for weakening the heart, which he feared would remain a side effect in the tweaked version. He judged that the morphine tweak was the more promising candidate and redirected all of his efforts into the development of diacetylmorphine, which Dreser renamed 'Heroin.'

Eichengrün (Bayer's head chemist) arrived at the opposite judgment. He felt that if there were only resources to pursue a single compound they should keep fishing with acetylsalicylic acid, since there would be almost unlimited applications for an effective remedy that reduced fever and relieved pain? He did not have any hard evidence showing that the salicylic acid tweak would not produce side effects, however. In order to demonstrate that acetylsalicylic acid was safe and effective, he needed data from human trials—and Dreser was blocking any further clinical trials on the drug. Eichengrün knew he could appeal to their shared boss, Duisberg, but Eichengrün also knew that Duisberg held Dreser in high esteem. Not only that, in the team-focused culture of German business, it would have been highly unlikely that Duisberg would override the judgment of a man he had just put in charge of Bayer's biological research. Even today, German drug companies abhor loose cannons and lone wolves. Eichengrün felt the pressure to toe the company line, but since he was convinced that the commercial potential of acetylsalicylic acid was simply too great to ignore he did something that daring drug hunters have always done—he went behind management's back.

Eichengrün approached a friend and colleague named Felix Goldmann, Bayer's representative in Berlin, and quietly arranged for low-profile human trials of acetylsalicylic acid in Germany's capital. This was truly the

very dawn of human drug trials, so modern ethical concepts like informed consent had not yet been conceived, let alone implemented. Berlin doctors (and dentists) simply took the unidentified compound that Goldmann handed them and fed it to their patients. One dentist tested Eichengrün's compound on a patient with a toothache and reported that a few minutes later, 'He jumped up saying the toothache was completely gone.' Since fast-acting anti-inflammatory drugs did not exist in any form, both Eichengrün and the dentist regarded the patient's speedy relief as near-miraculous. Further tests of acetylsalicylic acid on other patients were also highly encouraging: subjects reported relief from pain, fever, and inflammation, and—crucially—they did not report gastrointestinal distress or other notable side effects(*10*)."

SCOPOLAMINE

1899

Historically used(*11*)

EPINEPHRINE ASCORBATE

1901

"In 1859, English physician Henry Salter reported that 'asthma is immediately cured in situations of either sudden alarm or violent fleeting excitements'. Examining that statement might lead you to believe that this could be the first description of the therapeutic effects of circulating endogenous epinephrine and its ability to activate adrenergic receptors. […]

In 1894, at the University College of London, George Oliver, an English physician, and Edward Schafer, an English physiologist, visualised the potent effect of adrenal medulla extract on the heart rate and blood pressure of animals using handmade laboratory apparatus constructed from steel hooks, fine cotton threads, pulleys, and a few writing pens. Their conclusion captured the attention of the scientific community: the extract of adrenal glands (also known as suprarenal glands), which sit just above the kidneys, increases heart rate and blood pressure by stimulating arteriole contraction.

Oliver and Schafer's next move was to challenge the adrenal extract with whatever they could find—including heat, acid, and peptic digestion—to determine the physical and biochemical properties of this substance. Their work provided the perfect base for John Jacob Abel, an American biochemist and pharmacologist at Johns Hopkins University in Baltimore. Abel's research culminated in the purification of the extract's active ingredient, epinephrine, in 1899. Somewhat frustratingly for Abel, the purity of his isolated epinephrine was challenged by Otto von Furth, an Austrian physician, physiologist and biochemist, and by Jokichi Takamine, a Japanese biochemist. Takamine, driven by the widely recognised 'marvellous therapeutic value of the suprarenal extract', successfully isolated the 'pure, stable, crystalline form' of epinephrine, which he named adrenalin. […]

Crude epinephrine extract was initially tested on patients with asthma and hayfever in around 1900 by Solomon Solis-Cohen, a professor of clinical medicine in Philadelphia. Solis-Cohen reported that oral doses of desiccated adrenal glands relieved symptoms, and described the mechanism as 'vasomotor ataxia of the relaxing variety'(*12*)."

From the discovery paper of Oliver and Schäfer cited in the previous quotation:

"Pellacani, both alone and in conjunction with Foà, appears to have been the first to investigate the effect of injecting extract of suprarenal capsule into animals. These observers used for the most part filtered aqueous extract of fresh suprarenal of the dog and calf, administering it subcutaneously. The following are some of the results which they obtained:-In a dog weighing 2,700 grammes having injected nearly the whole of an extract of neutral reaction made from two

suprarenals of the calf, they observed on the same day no effect; temperature, respiration and the heart's action remaining normal: on the following morning, however, they found the animal dead. In a guinea-pig weighing 770 grammes they injected five grammes of an aqueous extract; this amount containing the active principles extracted by water from about one-quarter of a gland of the calf. They note that twelve hours after injection the animal refused food, and that the temperature was lowered by one degree. One hour later the animal was found dead. Similar results were obtained in rabbits. They further injected into rabbits extracts from the liver of the calf and from the kidney of the calf, the injection being made into the jugular vein. In these cases also they found that death was produced. They seem to infer that the effect is a general one, common to many gland extracts. In a further research an extract equivalent to one gramme of the capsules, neutralised by soda, was injected under the skin of a dog weighing five kilogrammes. The animal soon became agitated, and was attacked by vomiting; the respiration became irregular and was dyspnoeic. This was followed by somnolence and general prostration, the temperature remaining normal. This condition lasted six hours. The next morning the animal was found completely paralysed, sensibility was lost, the respirations were frequent and superficial. Death ensued nineteen hours after the injection and was produced apparently by suspension of respiration. In another dog, weighing nearly thirty kilogrammes, fifteen cubic centimetres of a strong watery extract made by digesting six capsules from the ox in 50 c.c. of water were injected into a vein. This produced dyspnoea, agitation, frequency of cardiac beats, and subsequently diminished frequency. The respirations became more superficial and the heart-beat diminished in force. There was an evacuation of the bowel. Four hours afterwards the temperature had gone up from 39°C. to 41.2; an hour later it was 400; four hours later 38°, accompanied by, great prostration. In another half-hour the animal died.

In the frog these observers found that injection of the extract into the dorsal lymph sac was followed in about fifteen minutes by slowness of movement, the reflexes however being persistent. After twenty minutes the animal bad ceased to move when placed on its back, and its sensibility and reflexes appeared diminished. Twenty-five minutes after the injection paralysis was general. […]

[O]ur own results agree with those of Tizzoni and of most recent observers which have served to confirm the conclusions of Brown-Séquard, viz. that extirpation of the suprarenal capsules is invariably followed sooner or later by death, and that the symptoms during life are those of extreme muscular prostration. […]

The suprarenals employed by us have been obtained mainly from the calf, but also from the sheep, the guinea-pig, the cat, the dog, and from man. The physiological effects which we have noticed have been identical in all, the only difference being in the case of diseased suprarenals in man (Addison's disease); in which case, if the disease be extensive, no effect whatever is obtained. […]

The animals which we have experimented upon have been chiefly dogs, but we have also made a certain number of experiments upon cats, rabbits, and guinea-pigs, and one upon a monkey. […]

III. THE PHYSIOLOGICAL EFFECTS OBSERVED.

(a) General effects.

(b) Effects on the arterial system.

(c) Effects of the extracts upon the isolated frog-ventricle.

(d) Effects on the mammalian heart.

(e) Effect on the Respiration.

(f) Effect on the Skeletal Muscles.

(g) Effect on Secretory Glands(*13*)."

POVIDONE-IODINE

1921

"Iodine was the other member of the halogen group to be used as an antibacterial agent. It is a solid, soluble in alcohol and aqueous potassium iodine solution. It was first suggested as a wound dressing by Davies (1839) and was evaluated by both Koch and Pasteur. Tincture of iodine, as the solution was called, was found in every medicine cabinet up to the 1950s at least. Hated by children and even adults for its stinging sensation when applied to open cuts, it is nevertheless an effective preparation and is still used in surgery as a skin antiseptic.

This type of iodine formulation, solutions in various solvents, was to be the only one until 1949 when Shelanski introduced solubilized iodine, the iodophors. He found that iodine could be solubilized in an aqueous solution of a non-ionic surface active compound. The product was non-stinging and less staining than true solutions(*14*)."

BENZYL ALCOHOL

1921

"One of the first described uses of benzyl alcohol was as a local anesthetic discovered accidentally by Macht in 1918. Upon tasting a sample of benzyl alcohol, he noticed his tongue becoming numb. He then went on to study its anesthetic properties(*15*)."

From the discoverer(s):

"The author found, while incidentally tasting a minute quantity of this substance, that his tongue was completely anesthetized by it. On tasting the drug a slight irritation was first experienced which irritation was followed by a sensation of numbness, coolness and hardness, very much like the sensation experienced after application of a cocain solution to the tongue. This striking observation was immediately followed up by the author(*16*)"

ARSENIC CATION (3+)

1921

IODINE

1921

BICARBONATE ION

1921

IRON

1921

RESORCINOL

1921

"Almost at the same time as his work on glycosides, Hlasiwetz began the investigation of resins. In the distillation products of guaiacum resin he detected guaiacol (*o*-methoxyphenol) and its homologue creosole (3,1,4-$CH_3OC_6H_3(CH_3)OH$). Guaiacol had been obtained in 1826 by the dry distillation of guaiacum by Unverdorben. With the help of Barth, his assistant, he studied a series of gums and resins by means of the following procedure: The crude substance was purified by treatment with alcohol or alkali to separate it from mechanical impurities. It was then melted with about three times its amount of potash until the usual strong. froth slackened; the mixture was acidified, filtered, and extracted with ether. The ethereal solution vas dried by evaporation and the various components separated by crystallization, etc. The resins explored were: guaiacum, gum benzoin, drachenblut, aloes, asafetida, gamboge, acaroid resin, sagepenum, opopanax, and galbanum. The various decomposition products obtained were acetic acid, benzoic acid, *p*-hydroxybenzoic acid, pyrotartaric acid (methyl succinic), protocatechuic acid, catechol, phloroglucinol, orcinol (5-methyl resorcinol), resorcinol, and homophthalic acid. They succeeded in isolating for the first time *p*-coumaric acid (*p*-hydroxy-cinnamic, *p*-

$HOC_6H_4CH=CHCOOH$) from aloes and ferulic acid (3,4,1-methoxy-hydroxy-cinnamic) from asafetida, both of which are intermediates, as the former may he broken down into acetic acid and *p*-hydroxybenzoic and the latter into acetic acid and protocatechuic acid.

Resorcinol (*m*-di-hydroxybenzene) obtained from galbanum was the subject of much research. It was recognized as an isomer of catechol (discovered in 1839 by Reinach) and hydroquinone (discovered 1844 by Wöhler) and a homologue of orcinol, and its use as a dye intermediate and in medicinals soon followed. It was later obtained by the dry distillation of umbelliferone (p-hydroxy-coumarin) which comes from the resins of a number of umbelliferae(*17*)."

## LITHIUM CATION

1921

"In 1841 Dr. *A. Lipowitz* reported that when the slightly soluble uric acid was boiled in water with crushed lepidolite (an ore of lithium), lithium urate was formed in solution. […]

Mr. *Alexander Ure*, a surgeon, became aware of Lipowitz's study and proposed that lithium salts might be used as solvents of uric acid where this accumulated in the human body; in 1843 *Ure* presented a paper before the Pharmaceutical Society in which he recorded the successful reduction of a urinary calculus (which contained uric acid) by immersion of the stone in lithium carbonate solution. He proposed that urinary calculi might be similarly dissolved in vivo by the direct introduction of lithium carbonate into the bladder […]

Sir *Alfred Baring Garrod* FRS, an eminent physician and contemporary of *Alexander Ure*, was much influenced by *Ure*'s writings, and in his treatise on gout, published in 1859, he made full use of *Ure*'s ideas. *Garrod* repeated *Ure* 's experiment, but used gouty phalanges instead of bladder stones; the gouty deposit disappeared from a bone suspended in lithium carbonate solution. Lithium salts, Garrod concluded, could be powerful adjuncts to other treatments in the alleviation of gout.

The story might have ended there, and lithium become just another in a long line of ineffective nostrums for gout, had it not been for *Garrod*'s decision to extend the concept of gout beyond the discomfort experienced at the joints. He noted that in association with the pain there were frequently other symptoms reported by the gouty patient, and sometimes such symptoms occurred even in the absence of pain.

This 'irregular' gout, as *Garrod* called it in the third edition (1876) of his book was, he believed, also caused by an excess of uric acid in the body and might, therefore, be treated by administering lithium salts which would convert the insoluble uric acid to the highly soluble lithium urate and allow it to be excreted.

The range of symptoms covered by his notion of 'irregular gout' were described by *Garrod* as manifestations of the 'uric acid diathesis', a concept which became firmly established in nineteenth century medical theory as a direct result of *Garrod*'s eloquent exposition. Under this general heading *Garrod* subsumed a wide variety of dis-orders, including mood disturbances (or 'gout retroceding to the head'); 'gouty mania' was a term which he also used. In advocating lithium treatment for such conditions, *Garrod* suggested that this might profitably be done on a long-term basis so as to give prophylactic control over the recurrence of mood disturbances and other symptoms of the uric acid diathesis. […]

The work of *Sir Alfred Garrod* became known to a Danish physician, *Carl Lange*. In 1886, *Lange* published a monograph in which he put forward the view that what he called periodic depressions occurred with very high frequency in general practice but were virtually unnoticed by the psychiatrists.

*Lange* wrongly believed this sediment to be uric acid and this led him to propose the use of lithium salts as a prophylactic treatment for the condition.

There can be no doubt that it is to *Carl Lange* that the credit must be given for presenting the first unequivocal account of lithium prophylaxis for a psychiatric condition.

*Lange's* ideas, though originally published in Danish (1886, 1895) and therefore inaccessible to the majority of European physicians, were subsequently translated into German (1896) and received wide currency as a result. *Haig* and *Lange* corresponded about their work and confirmed that their clinical observations on lithium prophylaxis were in broad agreement. (*18*)"

"The modern revival of lithium began in 1949 in the Bundoora Repatriation Hospital, a veterans' hospital in a suburb of Melbourne, Australia, when John Cade, aware of Garrod's success in using lithium a century previously in the treatment of gout, hypothesized that some condition involving uric acid might lie behind his manic patients' 'psychotic excitement'; Cade began treating 10 of them with lithium citrate and lithium carbonate. Some responded remarkably well, becoming essentially normal and capable of discharge after years of illness. […]

As Cade's son Jack, himself an intensive-care specialist in Melbourne, and Sydney psychiatry professor Gin Malhi noted in 2007: 'John Cade's discovery demonstrates the importance of clinical observation, the significance of reporting case findings, the value of being patient centered and the scientific benefit of an open and inquiring mind'(*19*)."

CARBONATE ION

1921

ALUMINUM CATION

1921

CALCIUM CATION

1921

BARIUM SULFATE

1921

KAOLIN

1921

"Kaolin is a hydrated aluminum silicate mineral. It occurs naturally as a clay that is prepared for pharmaceutical purposes by washing with water to remove sand and other impurities. Kaolin has traditionally been used internally to control diarrhea. Kaolin has also been used topically as an emollient and drying agent(*1*)."

FLUORIDE ION

1921

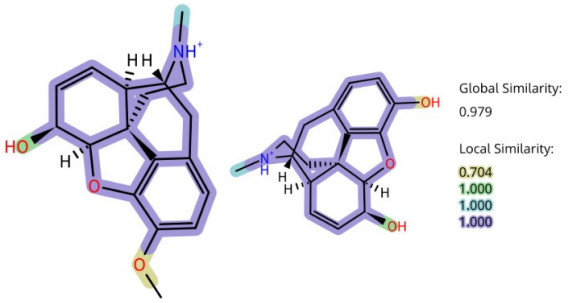
THEOPHYLLINE

1921

"The story begins with a report from the Pharmacological Laboratory at Johns Hopkins University which was published in December 1921. They became curious about the many drugs in the folklore of medicine advocated for 'the relief of bronchial spasm, or true asthma', and set about to study the relative anti-spasmodic action of a number of the popular remedies by means of strips of bronchial muscle obtained from pigs. Because strong coffee was among the favourites, these investigators took special interest in caffein or trimethyl xanthine. They found this compound to possess only weak relaxing effect on bronchial muscle. It occurred to them that other xanthine derivatives or purine compounds might be more potent, and it was found that dimethylxanthine (theophylline) was a much more effective bronchodilator than caffein. Furthermore, they showed xanthine and hypoxanthine to be even more potent, an observation worthy of further study. […]

Simultaneously, in March 1922 a paper by Samson Hirsch of Frankfurt, Germany was

published. He had been pursuing investigations of theophylline obviously unaware of Macht and Ting's activities. Hirsch was interested in the mode of action of purine derivatives which had been found useful as diuretics and in the treatment of dyspnoea in cardiac failure. He wondered if theophylline could be acting in part through an antispasmodic or dilating effect on bronchial smooth muscle. Using excised strips of bronchial muscle from the cow, he demonstrated the pronounced bronchodilator effect of theophylline in the laboratory. In addition, two asthmatic patients were treated with a theophylline preparation and the results were con-




sidered superior to those obtainable with other drugs in common use at the time(*20*)."

SODIUM CATION

1921

CODEINE

1921

Analogue of morphine(*21*)

COPPER

1921

AMMONIUM CATION

1921

CAMPHOR (SYNTHETIC)

1921

Historically used(*22*)

NITRITE ION

1921

FERROUS CATION

1921

MANGANESE CATION (2+)

1921

BENZOIC ACID

1921

"Benzoic acid was discovered in the 16th century. The dry distillation of gum benzoin was first described by Nostradamus (1556), and subsequently by Alexius Pedemontanus (1560) and Blaise de Vigenère (1596).

Justus von Liebig and Friedrich Wöhler determined the structure of benzoic acid in 1832. They also investigated how hippuric acid is related to benzoic acid.

In 1875 Salkowski discovered the antifungal abilities of benzoic acid, which were used for a long time in the preservation of benzoate containing fruits(*23*)."

From the 1875 discovery paper of Salkowski cited in the previous quotation:

"Gegenüber den Lobpreisungen, welche der Salicylsäure von allen Seiten zu Theil werden, gehört fast einiger Muth dazu, mit Beobachtungen hervorzutreten, welche die Werthschätzung der Salicylsänre bis zu einem gewissen Grade unberechtigt er scheinen lassen. Nichts desto weniger halte ich mich zur Mitheilung derselben verpflichtet und mache sie gerade an diesem Ort in der Absicht, sie den Praktikern möglichst zugänglich zu machen. Ich bin bei der Prüfung der Salicylsäure ganz vorurtheilsfrei zu Werke gegangen: ichhabe die Versuche zu nächst nur angestellt, um mir ein eigenes Urtheil zu bilden. Die Benzoësäure wurde nur als die nächstliegende Säure aus der Gruppe der aromatischen Substanzen zum Vergleich mi der Salicylsäure herangezogen. Bei Beginn der Versuche lag für mich keinerlei Veranlassung vor, an der

vorzüglichen Wirkung der Salicylsäure zu zweifeln– ich hatte also auch kei neswegs die Absicht, ein neues Antisepticum zu suchen oder der Salicylsäure Concurrenz zu machen; und wenn ich –wie sich weiterhin ergeben wird - doch in die Lage gekommen bin, die Benzoësäure als ein besseres Mittel zu finden und u empfehlen, so messe ich mir dabei keinerlei Verdienst bei – es wirken am Ende alle in die Reihe der sogenannten aromatischen Substanzen gehörenden Körper (die Sulfosäuren etc. ausgenommen), sofern sie nur die nöthigen physikalischen Eigen schaften besitzen, mehr oder weniger antiseptisch. Ich bemerke noch, dass sich die folgenden Angaben ausschliesslich auf faulige Zersetzung eiweissartiger Körper beziehen. Die Versuche sind höchst einfach in der Weise angestellt, dass gehacktes Fleisch mit Wasser resp. den betreffenden Lösungen — meistens 400 Cc. - übergossen und anfangs im Brütofen bei 25 bis 30 Gr. C., später bei gewöhnlicher Temperatur unter zeitweisem Ersatz des verdampfenden Wasser sich selbst überlassen wurde. […]

Geachtet wurde auf die trübe oder klare Beschaffenheit, Reaction, Fäulnissgeruch, Auftreten von Schimmel und Bacterien. […]

Die Benzoësäure besitzt weit stärkere antisep tische Eigenschaften wie die Salicylsäure. Wenn man frisches Fleisch, feingehackt oder in grösseren Stücken, in concentrirter wässeriger Benzoësäurelösung aufbewahrt, so tritt ein Fäulniss nach meinen Beobachtungen, die sich jetzt au über 3 Monate erstrecken, überhaupt nicht ein. Die Flüssigkeit bleibt vollkommen klar und bewahrt den Geruch nach Benzoësäure(*24*).”

Translation from Google Translate:

“In view of the praises which salicylic acid is given from all sides, it takes almost some courage to come forward with observations which make the esteem of salicylic acid appear to a certain extent unjustified. Nevertheless, I consider myself obliged to share them and make them precisely in this place with the intention of making them as accessible as possible to practitioners. In testing the salicylic acid I went to work quite free of prejudice: at first I only made the experiments in order to form my own judgment. Benzoic acid was only used as the closest acid from the group of aromatic substances for comparison with salicylic acid. At the beginning of the experiments there was no reason for me to doubt the excellent effect of salicylic acid - so I had no intention of looking for a new antiseptic or competing with salicylic acid; and if - as will be shown further on - I have been able to find benzoic acid as a better remedy and recommend it, I do not deserve any credit - in the end all of the so-called aromatic substances work bodies belonging to it (except for sulphonic acids, etc.), provided they only have the necessary physical properties, more or less antiseptic. I also note that the following information relates exclusively to putrid decomposition of proteinaceous bodies. The experiments are made very simply in such a way that minced meat with water resp. the solutions in question - mostly 400 cc. - poured over and initially in the incubator at 25 to 30 gr. C., was later left to itself at ordinary temperature with temporary replacement of the evaporating water. […]

Attention was paid to the cloudy or clear texture, reaction, putrefactive odor, occurrence of mold and bacteria. […]

Benzoic acid has much stronger antiseptic properties than salicylic acid. If fresh meat, finely chopped or in larger pieces, is kept in concentrated aqueous benzoic acid solution, putrefaction does not occur at all, according to my observations, which now extend over three months. The liquid remains perfectly clear and retains the benzoic acid smell(*24*).”

## CHOLECALCIFEROL

1921

One of the five forms of vitamin D(*1*)

SODIUM SULFATE ANHYDROUS

1921

ANHYDROUS CITRIC ACID

1921

Historically used via many common fruits

"Potassium citrate is indicated for the management of renal tubular acidosis with calcium stones, hypocitraturic calcium oxalate nephrolithiasis of any etiology, uric acid lithiasis with or without calcium stones(*1*)."

NITRIC OXIDE

1921

NITROGLYCERIN

1921

Analogue of isoamyl nitrite(*21*)

Discovery of isoamyl nitrite:

"The application of organic nitrates as antianginal agents has a long history, since they have been used for more then 100 years in the management of myocardial ischemia, without proper knowledge of their mechanism of action. It had been observed as early as the 19th century that people working with nitroglycerin in the production of explosives suffered from a syndrome consisting of severe headache and syncopal tendency but that, after a few days, these symptoms disappeared. These subjects were clearly developing tolerance to nitrate exposure(*25*)."

"Isoamyl nitrite was first synthesized in 1844 by Balard, who reported that its vapor had given him a severe headache. Further experiments revealed that the chemical produced throbbing of the carotid artery, flushing of the face, and an increase in heart rate. The first report on the clinical use of isoamyl nitrite in the treatment of angina pectoris was published by Brunton, who thought that its pain-relieving therapeutic effect was due to lowering of the blood pressure(*25*)."

The cited paper of Brunton was published in 1867(*25*).

SULFATE ION

1921

HYDROXOCOBALAMIN

1921

Vitamin $B_{12a}$

BACITRACIN

1921

"Bacitracin was discovered in 1945 from a leg injury of a seven-year-old American girl named Margaret Tracey. The collected debris from her wound grew isolates of several related cyclic polypeptides produced by a member of the Bacillus subtilis group. This discovery gave rise to the unique name, bacitracin.

The United States Food and Drug Administration (FDA) approved the use of bacitracin in 1948 for the short-term prevention and treatment of both acute and chronic localized skin infections(*26*)."

From the discovery paper:

"In the study of the bacterial flora of contaminated civilian mounds in the Presbyterian Hospital Unit, it was found that at times organisms appeared on the blood agar plates following direct plating of the injured tissue that were not recovered from broth cultures made at the same time from the same material. This occurred most frequently when the broth cultures contained a large number of aerobic Gram-positive sporulating rods.

Many of these strains had some degree of inhibiting action on subsequent plantings of the Gram-positive cocci which appeared with them on the direct plate. One strain isolated from tissue debrided from a compound fracture of the tibia was particularly active. We named this growth-antagonistic strain for the patient, 'Tracy I.' When cell-free filtrates of

broth cultures of this bacillus proved to possess strong antibiotic activity and to be nontoxic, further study seemed warranted. We have called this active principle 'Bacitracin.'(*27*)"

GLYCERIN

1921

"Glycerin is used in the pharmaceutical industry as a sweetener in syrups, lozenges, and as an excipient in eyewash solutions. As an individual prescription product, glycerin has uses as a hyperosmotic, osmotic diuretic, and ophthalmic agent. It may be used as an eye drop in the treatment of glaucoma to reduce intraocular pressure, as a solution or suppository for short-term treatment of constipation, to evacuate the bowel prior to a colonoscopy, and in some ocular surgeries. It may be given intravenously to reduce pressure inside the brain and used externally on the skin as a moisturizer(*1*)."

ANHYDROUS DEXTROSE

1921

D-isomer of glucose, human body's key source of energy

SULFUR

1921

CAFFEINE

1921

Historically used

COLCHICINE

1921

Historically used

"Colchicine is one of the oldest remedies still in use today. It is derived from the bulb-like corms of the *Colchicum autumnale* plant, also known as autumn crocus. Its history as an herbal remedy for joint pain goes back at least to the 1500 BCE Egyptian manuscript, the *Ebers Papyrus*(*28*)."

ICODEXTRIN

1921

"a colloid osmotic agent, derived from maltodextrin, used in form of an aqueous solution for peritoneal dialysis"

ATROPINE

1921

Historically used(*11*)

MAGNESIUM SILICATE

1921

UREA

1921

"Urea is an osmotic diuretic similar to mannitol but more irritant. Applied topically, urea promotes hydration of keratin and mild keratolysis in dry skin(*1*)."

MENTHOL

1921

Historically used(*29*)

QUININE

1921

"The discovery of quinine is considered the most serendipitous medical discovery of the 17th century and malaria treatment with quinine marked the first successful use of a chemical compound to treat an infectious disease. Quinine, as a component of the bark of the cinchona (quina-quina) tree, was used to treat malaria from as early as the 1600s, when it was referred to as the 'Jesuits' bark,' 'cardinal's bark,' or 'sacred bark.' These names stem from its use in 1630 by Jesuit missionaries in South America, though a legend suggests earlier use by the native population. According to this legend, an Indian with a high fever was lost in an Andean jungle. Thirsty, he drank from a pool of stagnant water and found that it tasted bitter. Realizing that the water had been contaminated by the surrounding quina-quina trees he thought he was

poisoned. Surprisingly, his fever soon abated, and he shared this accidental discovery with fellow villagers, who thereafter used extracts from the quina-quina bark to treat fever. The legend of quinine's discovery accepted in Europe differs though, and involves the Spanish Countess of Chinchon who, while in Peru, contracted a fever that was cured by the bark of a tree. Returning to Spain with the bark, she introduced quinine to Europe in 1638 and, in 1742, botanist Carl Linnaeus called the tree 'Cinchona' in her honour.

Before 1820, the bark of the cinchona tree was first dried, ground to a fine powder, and then mixed into a liquid (commonly wine) before being drunk. In 1820, quinine was extracted from the bark, isolated and named by Pierre Joseph Pelletier and Joseph Caventou. Purified quinine then replaced the bark as the standard treatment for malaria. Quinine and other cinchona alkaloids including quinidine, cinchonine and cinchonidine are all effective against malaria. The efficacies of these four alkaloids were evaluated in one of the earliest clinical trials, conducted from 1866 to 1868 in 3600 patients using prepared sulfates of the alkaloids. With the main outcome measure of 'cessation of febrile paroxysms', all four alkaloids were found to be comparable, with cure rates of >98%(*30*)."

QUINIDINE

1921

See the quinine entry.

METHYLENE BLUE

1921

"Methylene blue was the first synthetic drug used in medicine, having been used to treat malaria more than one century ago, and there has been renewed interest in using it against malaria in recent years. Methylene blue also was one of the first drugs used for the treatment of patients with psychosis at the end of the 19th century, and it was the lead drug in the serendipitous development of phenothiazine antipsychotic drugs in the mid-20$^{th}$ century. During the 1980s, methylene blue was studied in bipolar disorder. More recently, it has been investigated in dementia and related neurodegenerative disorders.

Prescription combination products containing methylene blue (e.g., Urelle®) are approved by the U.S. Food and Drug Administration (FDA) with an indication for the treatment of urinary tract irritation symptoms. Methylene blue (ProvayBlue®) is currently approved by the FDA as an orphan drug to treat acquired methemoglobinemia, but is also used off-label for the treatment of congenital methemoglobinemia. Other off-label uses of methylene blue include use as a clinical dye in therapeutic and diagnostic applications (e.g., parathyroid imaging, sentinel lymph node biopsy), and for treatment of hypotension (associated with shock or cardiac surgery), ifosfamide-induced encephalopathy, and cyanide poisoning. […]

Methylene blue was first synthesized as an aniline-based dye for cotton staining by the German chemist Heinreich Caro (1834-1911) in 1876, although its chemical structure would not be elucidated until 9 years later. Another German chemist, Heinrich August Bernthsen (1855-1931), first synthesized the drug thiodiphenylamine (phenothiazine) in 1883 while working on the development of dyes derived from aniline. Phenothiazine has a characteristic central tricyclic ring structure, and this drug represents the structural parent compound for many other drugs, including what would later become known as the phenothiazine group of antipsychotic drugs(*31*)."

LACTIC ACID, DL-

1921

"Sodium lactate is primarily indicated as a source of bicarbonate for prevention or control of mild to moderate metabolic acidosis in

patients with restricted oral intake whose oxidative processes are not seriously impaired. Sodium Lactate is most commonly associated with an E number of "E325" Sodium Lactate blends are commonly used in meat and poultry products to extend shelf life and increase food safety. They have a broad antimicrobial action and are effective at inhibiting most spoilage and pathogenic bacteria. In addition sodium lactate is used in cosmetics as a humectant, providing moisture(*1*)."

HYDROGEN PEROXIDE

1921

SODIUM GLYCEROPHOSPHATE

1921

Used to treat or prevent low phosphate levels(*2*)

PILOCARPINE

1921

"The introduction of jaborandi leaves to western medicine goes back to 1873, when Symphronio Coutinho went to Europe, taking with him samples of the leaves. The copious sweating and salivation brought about by the leaves attracted the attention of French physicians. Soon jaborandi leaves were being employed in the treatment of many diseases. In 1875, Hardy and Gerrard independently discovered the alkaloid pilocarpine.

Most therapeutic applications of jaborandi leaves and pilocarpine fell into disuse and were discontinued. What remained was the use of the latter in ophthalmology, where it had been introduced as a miotic by Weber in 1876. The mixture of pilocarpine and another natural product, physostigmine, remains to this day one of the mainstays in ophthalmology(*32*)."

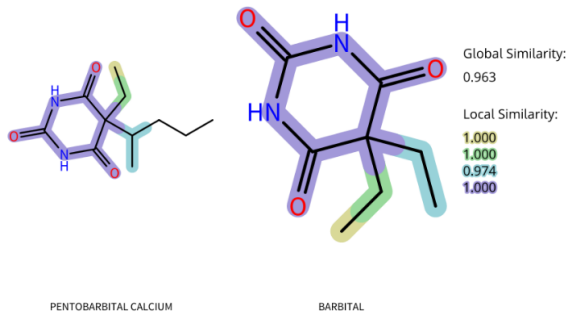
THIOSULFATE ION

1921

PENTOBARBITAL CALCIUM

1921

Analogue of barbital




"The first of the barbiturates to come onto the market was diethyl-barbituric acid, also known as barbital, malonal, or gardenal. Synthesized in 1881 by Conrad and Guthzeit, on treating the argentic salt of barbituric acid with ethyl iodide, it was introduced clinically as a hypnotic by the German companies E Merck (Darmstadt) and F Bayer and Co (Elberfeld) in 1904, thanks to the work of Josef Freiherr von Mering and Emil Fischer (Nobel Prize in Chemistry, 1902).

Von Mering, who taught pharmacology at the University of Halle, had observed that some of the synthetic compounds obtained towards the end of the 19th century and commercialized as hypnotics, such as sulphonal, contained in their molecular structure a carbon atom with two ethyl groups. Furthermore, knowing of von Baeyer's work with derivatives of urea, von Mering decided to study the hypnotic properties of diethyl-acetylurea, and found that it was even more potent than sulphonal. The next step was to analyze the properties of 5,5-diethyl-barbituric acid, for which he turned to Fischer, an old friend from his student days. At that time, Fischer, doyen of the German organic chemists, was Professor of Chemistry at the University of Berlin. Moreover, Fischer was well acquainted with the chemistry of malonylurea, as he had been von Baeyer's assistant in Munich for eight

years. Together with his nephew Alfred Dilthey, he tested the new, resynthesized product, demonstrating, in dogs, that its hypnotic power was far greater than that of von Mering's diethyl-acetylurea(*33*)."

Discovery of the anti-epileptic potential of barbiturates:

"It is to Hauptmann that the laurels must go for the introduction of this barbiturate as an anti-epileptic agent. It would be intriguing to know just exactly how this came about. In the clinic at the University of Freiberg where he worked, he dealt with institutionalized patients who were restless and excitable. Using Luminal rather than scopolamine, to treat them, he found not only was it successful but also controlled epileptic seizures. Although the observation was fortuitous he appreciated its significance. This serendipitous discovery—a combination of making a chance observation and realizing its importance has been a way in which many fields of medicine have advanced(*34*)."

CARBON DIOXIDE

1925

OXYTOCIN

1928

Also see the vasopressin entry in which the 1895 pioneering paper of Oliver and Schäfer has been quoted. They report there some effects of the pituitary gland extract(*35*).

"It was in 1895 that Oliver and Schäfer discovered the first biological effect of the pituitary gland. They found that the extracts of the pituitary when injected into mammals raised their blood pressure---the pressor effect. Howell showed a few years later that this activity resided in the posterior lobe. Since that time, other biological activities of posterior pituitary extracts were noted, particularly the uterine-contracting or oxytocic effect by Dale in 1906; the milk-ejecting effect by Ott and Scott in 1910; the blood-pressure-lowering effect in birds, the so-called avian depressor effect by Paton and Watson in 1912; and the inhibition of urine excretion in man, the antidiuretic effect by Von den Velden in 1913. It was indeed initially thought that oxytocin was devoid of pressor and antidiuretic activity. However, it was later found out that both the pressor and antidiuretic activity, were inherent properties of the oxytocin molecule.

In 1906, Sir Henry Dale found that extracts from the human posterior pituitary gland contracted the uterus of a pregnant cat. He coined the name oxytocin from the Greek words ωχνξ, τοχοχξ, meaning 'swift birth.' Sir Henry Dale also worked on histamine and acetylcholine among others and was jointly awarded the Nobel Prize in 1936 'for discoveries relating to chemical transmission of nerve impulses.' Forty seven years after Dale discovered it, oxytocin, a nine amino acid CNS neuropeptide, was the first ever polypeptide hormone to be sequenced and synthesized. It was done by Vincent du Vigneaud and for this achievement he was awarded the Nobel Prize in 1955(*36*)."

From the 1906 discovery paper of the uterine-contracting properties, cited in the previous quotation:

"The experiments here discussed are concerned only with such prompt effects of intravenous injection as can be observed directly, or with the aid of mechanical methods of recording, in the anaesthetised or pithed animal. No new observations have been made on the slowly developed effects of administration by the mouth or hypodermically to the intact animal, and these will be dealt with only incidentally. Most of the experiments were made on cats: a few also on rabbits, dogs, monkeys, ferrets, and fowls, the purpose for which each species was used being indicated in dealing with the results of particular experiments(*37*)."

Investigated parts(*37*):

1. THE CIRCULATORY SYSTEM.
   a. Primary or stimulant action.
   b. Secondary or paralytic stage.
2. THE SPLEEN.
3. THE MUSCULAR COATS OF TIHE INTESTINES.
   a. Stimulant stage.
   b. Paralytic stage.
4. THE INTESTINAL SPHINCTERS.
   a. The ileo-colic sphincter.
   b. The internal anal sphincter.
5. THE: STOMACH.
6. THE GALL-BLADDER.
7. THE URINARY BLADDER AND URETHRAL SPHINCTER.
8. THE PILO-MOTOR MUSCLES.
9. THE PLAIN MUSCLE OF THE EYE.
10. THE UTERUS.

"The reaction of this organ was examined in the cat, the rabbit, and the monkey. Contractions of the uterus and vagina were usually recorded together, since it was found that they contracted as one. In the cat records were made of the contractions of the non-pregnant uterus and of the uterus in the early stages of pregnancy […]

After the effect shown in Fig. 25, extract from 0.4 gram. dried ox-pituitary was given intravenously, producing the rise of blood-pressure and contraction of the uterus shown in the figure(*37*)."

11. RETRACTOR PENIS. (DOG.)
12. THE SUBMAXILLARY GLAND.

From the 1910 discovery paper of milk ejecting properties, cited in the first quotation of this entry:

"In the goat we have found in the early nursing period that infundibulin (the active principle of the posterior part of the hypophysis), when injected into the vein of the ear, rapidly and greatly increased the secretion of milk. The nipple had a cannula inserted into it, and a water aspirator produced the suction necessary to empty the udder. The milk before and after the injection was caught in a graduated flask and measured every five minutes. […]

The intra-venous injection of infundibulin starts the flow in about one minute from the beginning of the injection, and it reaches its height in four minutes, after which it rapidly falls to normal(*38*)."

## VASOPRESSIN

1928

"The neurohypophysial hormone arginine vasopressin (Avp) was originally detected by Oliver and Schäfer (1895) who demonstrated that extracts of the pituitary altered blood pressure. Subsequently, the antidiuretic properties of Avp were discovered. However, it was not until du Vigneaud and colleagues (1952) isolated the peptide that specific activities could be ascribed. Following this finding, the nine amino acid sequence and structures of Avp and the related hormone oxytocin were elucidated, followed shortly by their synthesis(*39*)."

From the 1895 discovery paper of Oliver and Schäfer cited in the previous quotation:

Also see the epinephrine entry where another pioneering article of these scientists which is mentioned herein is quoted:

"ACCOMPANYING our investigations into the physiological action of extracts of the suprarenal capsules published in preliminary form in the Proceedings of the Physiological Society, March, 1894, and in the Proceedings of the same Society, March, 1895, and which have just appeared at length in this Journal, we have pursued similar investigations into

the effects of certain other gland-extracts and especially extracts of pituitary body, of thyroid and of spleen. […]

The most striking immediate result of intravenous injection of extracts of any of the above organs is upon the blood-pressure. By pituitary extract this is markedly raised; by thyroid extract it is lowered; and by spleen extract it is at first lowered and then somewhat raised. Of the extracts of the three organs in question that of pituitary body is by far the most marked.

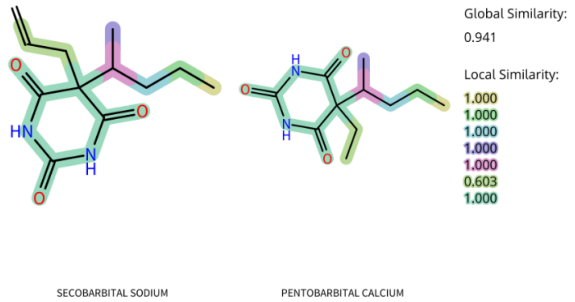
The action of water or glycerine extracts of thyroid (boiled) is the reverse of that of pituitary or suprarenal extracts. The effect upon blood-pressure is to produce a fall when injected into a vein, and it has been shown by one of us (Dr Oliver) that in man the inception of thyroid extract tends to produce enlargement of the calibre of the radial artery whereas inception of suprarenal tends to produce the opposite effect. […]

The action upon the circulatory system of the dog as shown by the tracings of blood-pressure indicate that the effect of thyroid extract is not only of a different character but also far less marked than that of pituitary and therefore of course very much less than that of suprarenal(*35*)."

## SECOBARBITAL SODIUM

1929

Analogue pentobarbital




## EPHEDRINE

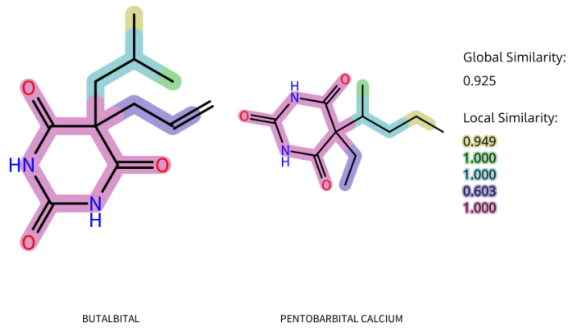
1929

Historically used(*40*)

## BUTALBITAL

1929

Analogue of pentobarbital




## DIBUCAINE

1930

Analogue of quinine

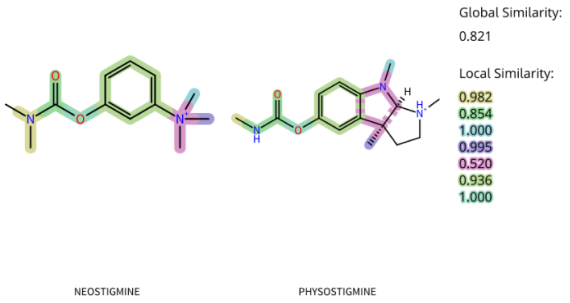
"Quinine and Urea as a local anesthetic was discovered by accident by Dr. Thibault of Arkansas. He had given a patient a hypodermic injection of Quinine and Urea for malaria and when it became necessary to repeat the injection it was noted that the site of the previous injection and a considerable area around it had become anesthetic. The doctor then experimented upon himself and ultimately used the newly discovered anesthetic in his surgical work with most excellent results(*41*)."

"During the early 1900's, hundreds of such chemicals were evaluated for their possible local anesthetic effects at the Swiss chemical company, Chemische Industrie Basel (Ciba). The utility of quinine in this regard was found to be limited by neurotoxicity and tissue necrosis. Experimenting with substitutions on the quinine nucleus, Ciba chemist Karl Meischer synthetized the clinically useful local anesthetic dibucaine in 1911(*42*)."

## NEOSTIGMINE

1931

Analogue of physostigmine




Discovery of physostigmine:

"In 1876 E. Harnack, working in O. Schmiedeberg's department at the University of Strassburg, showed that physostigmine potentiates the effect of electrical stimulation on mammalian striated muscle. Führer's work with leech muscle produced similar results […]

Physostigmine is extracted from the Calabar bean, indigenous to western Africa around the Gulf of Guinea. It is also called the 'ordeal bean,' because persons suspected of criminal actions or witchcraft who survived the ordeal of consuming the beans were judged innocent. The bean belongs to the genus *Physostigma*(*43*)."

"Gordon Alles thought he was testing a new asthma medicine. The Los Angeles chemist had tried without success to improve on ephedrine, the decongestant and bronchodilator that had in recent years become a blockbuster asthma, cold, and allergy treatment for drug maker Eli Lilly. Alles began to focus on a compound he called beta-phenyl-isopropylamine. He didn't know it at the time, but the drug had been first synthesized in 1887 by Romanian chemist Lazar Edeleanu. For over 40 years chemists had considered it pharmaceutically valueless, but Alles was about to prove them wrong, discovering what became the first psychoactive prescription drug—and igniting a decades-long controversy.

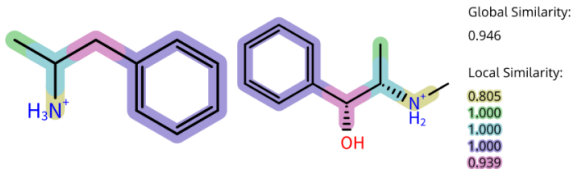
On June 3, 1929, a doctor injected 50 milligrams of amphetamine into Alles's body. In the early days of scientific drug discovery researchers routinely experimented on themselves. In addition to feeling they had a moral duty to future test subjects, they believed their training and familiarity with a compound made them the best observers of its effects. In this case Alles had tested his compound on guinea pigs, though he couldn't know exactly what to expect when he became his own guinea pig. He took what he estimated was a nonlethal dose—five times greater than later recommendations—and prepared himself. If amphetamine worked as he hoped, he'd have a lucrative, patent-protected drug that could go head-to-head with ephedrine.

Seven minutes later he sniffed: his nose was dry and clear. His blood pressure climbed dramatically. After 17 minutes he noted heart palpitations but also a 'feeling of well being.' He grew chatty and at a dinner party that night considered himself unusually witty. Some eight hours after taking the drug his blood pressure had nearly returned to normal. Still, he recorded, 'Rather sleepless night. Mind seemed to run from one subject to another'(*44*)."

## AMPHETAMINE

1931

Analogue of ephedrine




## PROGESTERONE

1934

From one of the discoverer(s):

The history of progesterone begins with a young Dutchman, REGNER DE GRAAF of Delft, who published in 1672 the first book-

length description of the female reproductive system, his *De mulierum organis generationi inservientibus*. […] [H]e was the first to publish a description of the corpus luteum, and the earliest illustration of that organ is seen in his plate of the cow's ovary (plate XIV). DE GRAAF recognized, moreover, that the presence of a corpus luteum is associated with that of a fetus in utero; that in species bearing more than one infant at a time there is a corresponding number of corpora lutea; and that the corpora lutea disappear after parturition. […]

In later years there were many other attempts to assign a function to this remarkable structure; the list of conjectures, plausible and implausible, runs to something like two dozen. In 1898, 226 years after DE GRAAF's book appeared, the French histologist LOUIS-AUGUSTE PRENANT at last gave us a valuable clue when he suggested that the corpus luteum is an organ of internal secretion. How bold a guess this was is apparent when we reflect that it was made at the very dawn of modern endocrinology, four years before BAYLISS and STARLING enunciated the concept of specific hormonal action at a distance, upon which our current thinking about internal secretions is based. As to the precise endocrine function of the corpus luteum, however, PRENANT did not hit upon the most profitable thought. His guess was that the function of the gland is to suppress ovulation during pregnancy. Because of the difficulty of testing it, PRENANT's hypothesis did not lead to productive experimentation.

It must have been about this same time that the great embryologist GUSTAV BORN, of Breslau, also reached the conclusion that the corpus luteum is an organ of internal secretion […] shortly before he died in 1900 he conceived the idea that the specific endocrine function of the corpus luteum is to protect the early embryo and facilitate its implantation in the uterus. Thus it was BORN who actually stimulated the experimentation of more than 50 years, which led to the discovery of progesterone. He was, however, overtaken by fatal illness before he could test his hypothesis. On his deathbed he bequeathed the duty and privilege of putting the idea to experimental test to one of his former students, the gynecologist LUDWIG FRAENKEL.

FRAENKEL's plan of attack was clever and effective. He knew from the embryological literature that rabbit embryos spend about seven days in the oviducts and uterus before they become implanted. The rabbit, moreover, is especially suited for his experiments because the doe ovulates only after coitus. He had only to mate females to a fertile buck and during the following week remove the corpora lutea by excision or cauterization. The result was that the pregnancy did not continue. Control operations in which he removed only one ovary, or cut into the ovaries without injuring the corpora lutea, did not prevent implantation, and pregnancy ensued. […]

About the same time two Frenchmen, the embryologist PAUL ANCEL and the histologist PAUL BOUIN, were investigating another aspect of corpus luteum physiology. They were the first to observe that during pregnancy the rabbit's endometrium undergoes a remarkable change characterized by proliferation and modification of the uterine glands, so that in cross-section the endometrium exhibits the beautiful lace-like pattern that we now recognize as the progestational state. Gynecologists quickly perceived that this pattern is similar to the premenstrual state of the human uterus, described only two years earlier by HITSCHMANN and ADLER. ANCEL and BOUIN correctly supposed that the histological alterations they had discovered are produced by endocrine activity of the corpus luteum. They proceeded to test this supposition by experiments in which female rabbits were mated to vasectomized males. Thus ovulation was not followed by pregnancy, and the only change in the animal's

physiology was the formation of corpora lutea. Their uteri developed typical progestational changes, for which, obviously, the corpora lutea were responsible.

These clear and well-controlled experiments, taken together with those of FRAENKEL, provided immediate clues for the identification and isolation of a corpus luteum hormone. FRAENKEL had shown that the fate of the embryo depends upon the integrity of the corpus luteum, while ANCEL and BOUIN had found that the functional state of the endocrine lining depends upon the same gland. […] By 1928, I felt I was at last equipped to conduct experiments that would tie together FRAENKEL's findings with those of ANCEL and BOUIN. In brief, I began much as FRAENKEL did, mating rabbits and removing their corpora lutea shortly thereafter. But instead of merely waiting to see if pregnancy ensued, I killed the does at the 5th or 6th day after mating. Recovering the embryos

for inspection, I found them degenerating. I also examined the endometrium as ANCEL and BOUIN had done. The outcome, duly checked by controls, was that the fate of the embryos depends upon the development of the progestational change, and this in tum depends upon the presence of the corpus luteum. Now that we understood these clear histological and embryological signs of corpus luteum function, the stage was set for an attempt to discover its chemical mechanism.

Without any idea of the chemical nature of the substance we were to look for, we reasoned that almost all physiologically active extractable materials are soluble in either water or alcohol. Therefore we divided the task; I extracted corpus luteum tissue with saline aqueous fluids, ALLEN with ethyl alcohol, subsequently distilling off the solvent and injecting the lipid residue. We tested our products on virgin rabbits to see whether they would cause progestational change of the endometrium. My rabbits showed no such result (those which survived the effects of my often toxic extracts); ALLEN's oily residues were immediately effective.

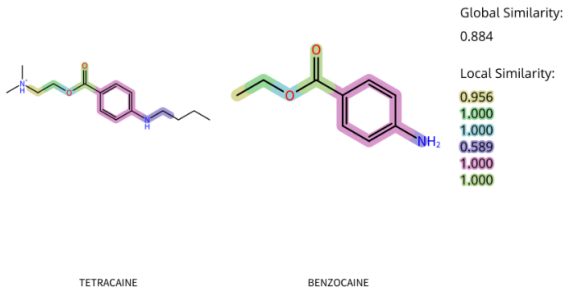
Within a year we secured crude preparations which induced full progestational changes and maintained pregnancy in castrated does.

Within the next two years ALLEN successively got rid of the irrelevant material in the extracts, began to get the hormone in crystalline form, and already suspected that it was a steroid. In 1931-1932 KARL SLOTTA, HANS RUSCHIG, and ERIC FELS of Breslau, and ALLEN also, obtained amost pure preparations(*45*)."

## TETRACAINE

1932

Analogue of benzocaine(*21*)




## SULFANILAMIDE

1936

In assessing different series of dyes for streptococcal infections in mice, Prontosil rubrum showed *in vivo* activity, while lacking *in vitro* effects(*46*).

"Domagk's essential basis for success in discovery of the sulphonamides can be traced back to his earlier work, in which he used animal experiments to assess the course of an infection, certainly necessary when investigating different processes in histological examinations. […]

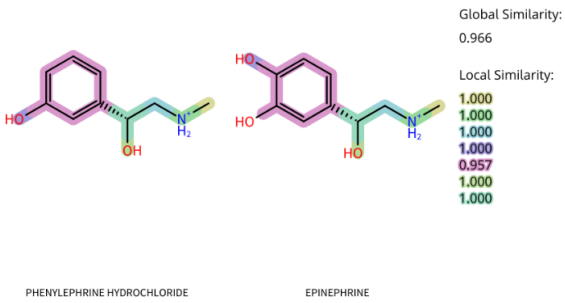
insights into the mechanisms of action of the sulphonamides caused a profound

disappointment. It became clear that the sulphonamide group introduced into an azo dye did not have the intended function of improving the activity as had been seen with textile dyes. Rather, linking it to an azo dye seemed to be superfluous, as the chemotherapeutic effect could be achieved by use of sulphanilamide alone. The working hypothesis which had been so successful in bringing about development of therapy for bacterial infections was now found to be false(*47*)."

PHENYLEPHRINE HYDROCHLORIDE

1934

Analogue of epinephrine




NIACIN

1937

Vitamin $B_3$

TESTOSTERONE

1937

"The importance of the gonads in the maintenance of homeostasis, however, has been recognized since antiquity: the Roman scholar Pliny the Elder addressed the beneficial effects of ingesting genital tissues from animals. […]

Observations of the effects of androgen ablation are an old story. In order to conserve grain for human consumption, Republican Rome passed the Laex Faunia (162 BC), which prohibited the fattening of hens, a favorite roman delicacy; the *Populus Romanus*, ingenuity circumvented the bureaucratic inconvenience by castrating roosters, thus making them more hen-like, less aggressive, and more tender and fatter. It took almost two millennia for John Hunter, the great Scottish advocate of observational medicine and scientific method, to report in 1771 that castrated roosters (capons) could recover some of their lost maleness after testicular implantation; there are no bibliographic references of his work in this area but only reports from attendees at his lectures. His reported observations took almost an additional 80 years (1849) to be confirmed by Adolph Berthold.

[…] The association of a decline in gonadal and sexual function has been widely acknowledged since the end of the 19th century. A great deal of interest developed after Dr. Charles E. Brown-Séquard made a presentation to the Societé de Biologie in June of 1889 on the self-administration of a *liquid testiculaire* prepared by him from animal gonads and his subsequent description, in the medical literature, on his observations about the improvement in his own physical strength, intellectual capacity, and sexual vigor following repeated treatments. It should be quoted here how cautiously Brown-Séquard concluded his article in *The Lancet*: 'My first communication to the Paris Biological Society was made with the wish that other medical men advanced in life would make on themselves experiments similar to mine as to ascertain . . . if the effects I have observed depended or not on any kind of autosuggestion.' One of his colleagues (a Dr. Variot) treated two additional men and described the positive results to Brown-Séquard, who included them in his publication […]

Animal models were employed to demonstrate the activity of autologous testicular transplants, eventually resulting in the isolation of androsterone and T. In 1927 in Chicago, Lamuel McGee and Fred C. Koch extracted, from 20 kg of bulls' testicles, 20 g of a substance that 'when injected into castrated animals would restore their maleness' but

this did not receive much attention from the scientific community. The credit goes to Ernst Laqueur and his team in Amsterdam who obtained larger amounts of the said substance by a process similar to Koch's(*48*)."

From the discovery paper of Brown-Séquard cited in the previous quotation:

"I put forward the idea that if it were possible without danger to inject semen into the blood of old men, we should probably obtain manifestations of increased activity as regards the mental and the various physical powers. Led by this view, I made various experiments on animals at Nahant, near Boston, in 1875. In some of those experiments, made on a dozen male dogs, I tried vainly, except in one case, to engraft certain parts or the whole body of young guinea-pigs. The success obtained in the exceptional case served to give me great hopes that by a less difficult process I should some day reach my aim. This I have now done. At the end of last year I made on two old male rabbits experiments which were repeated since on several others, with results leaving no doubt as regards both the innocuity of the process used and the good effects produced in all those animals. This having been ascertained, I resolved to make experiments on myself, which I thought would be far more decisive on man than on animals. The event has proved the correctness of that idea.

Leaving aside and for future researches the questions relating to the substance or substances which, being formed by the testicles, give power to the nervous centres and other parts, I have made use, in subcutaneous injections, of a liquid containing a small quantity of water mixed with the three following parts : first, blood of the testicular veins; secondly, semen ; and thirdly, juice extracted from a testicle, crushed immediately after it has been taken from a dog or a guinea-pig. Wishing in all the injections made on myself to obtain the maximum of effects, I have employed as little water as I could. […] I have hitherto made ten subcutaneous injections of such a liquid-two in my left arm, all the others in my lower limbs-from May 15th to June 4th last. […]

The day after the first subcutaneous injection, and still more after the two succeeding ones, a radical change took place in me, and I had ample reason to say and to write that I had regained at least all the strength I possessed a good many years ago. […]

My limbs, tested with a dynamometer, for a week before my trial and during the month following the first injection, showed a decided gain of strength. […]

I have measured comparatively, before and after the first injection, the jet of urine in similar circumstances-i.e., after a meal in which I had taken food and drink of the same kind in similar quantity. The average length of the jet during the ten days that preceded the first injection was inferior by at least one quarter of what it came to be during the twenty following days. It is therefore quite evident that the power of the spinal cord over the bladder was considerably increased.

[…] [A]fter the first days of my experiments I have had a greater improvement with regard to the expulsion of fecal matters than in any other function. […]

The last of these injections was made on June 4th, about five weeks and a half ago. I ceased making use of them for the purpose of ascertaining how long their good effects would last. For four weeks no marked change occurred, but gradually, although rapidly, from the 3rd of this month (July) I have witnessed almost a complete return of the state of weakness which existed before the first injection. This loss of strength is an excellent counterproof as regards the demonstration of the influence exerted on me by the subcutaneous injections of a spermatic fluid.

[…] Dr. Variot, a physician who believed that the subcutaneous injections of considerably

diluted spermatic fluid could do no harm, was made a trial of that method on three old men-one fifty-four, another fifty-six, and the third sixty-eight years old. On each of them the effects have been found to. be very nearly the same as those I have obtained on, myself. Dr. Variot made use of the testicles of rabbits and guinea-pigs(*49*)."

DEXTROAMPHETAMINE SULFATE

1937

Enantiopure amphetamine

PHENYTOIN

1938

Also refer to the pentobarbital entry to see how the anticonvulsant activity of barbiturates was discovered.

"In 1923, Dox and Thomas, two organic chemists working in the Parke, Davis laboratories, prepared different phenyl derivatives of barbituric acid. In particular, they attempted to synthesize 5,5-di-phenylbarbituric acid, one step beyond phenobarbital in the progression of increasing aromaticity, but had no success […]. However, they did manage to prepare several substituted diphenyl derivatives, namely 5,5-diphenoxybarbituric acid. These were tested in the Parke, Davis laboratories, but neither showed any hypnotic activity. […] 5,5-diphenylhadantoin was 'sitting on the shelf' in a Parke, Davis laboratory, just waiting to be discovered as an anticonvulsant drug a whole decade later! […]

**SCREENING TESTS IN ANIMALS**

The third line of research that contributed to the discovery of phenytoin included the development of test procedures in animals that could be used to predict the anticonvulsant effect of drugs in humans. […]

In brief, the equipment used by Putnam and Merritt consisted of a 45-V battery connected across the terminals of a potentiometer (50Ω). The current was interrupted 80 times per second with a motor-driven commutator. A millimeter (0-50 mA) was also provided to measure the amount of current passing through the brain. A cat was placed in a restraining box, and electrodes were placed in the mouth and on a shaven area of the skin between the ears. The current was turned on for 10 seconds. Each animal was found to have a characteristic convulsive threshold (6-15 mA of current), which did not vary more than 10% within a day. Once the convulsive threshold had been established, the drug under trial was administered and the electroshock procedure was repeated after several hours to allow time for absorption of the drug. The elevation in the threshold became a measure of anticonvulsant activity. […]

Since phenobarbital had far better anticonvulsant properties than Veronal, it was possible that a further increase in aromaticity might well produce a better drug for the treatment of seizures. Until that time, everyone had assumed that a good anticonvulsant drug had to be a good hypnotic; Putnam assumed otherwise, and therein lies his major contribution-the separation of anticonvulsant and hypnotic activity. When 5,5-diphenylhydantoin was tested in cats, a good anticonvulsant drug was discovered that had no significant hypnotic activity.

Presumably having the screening methodology at his disposal, Putnam contacted several drug companies to request compounds related in structure to phenobarbital, preferably those having more phenyl rings in the molecule. To quote Dr. Putnam:

'I combed the Eastman Chemical Company's catalogue, and other price lists, for suitable phenyl compounds that were not obviously poisonous. I also wrote to the major pharmaceutical firms, asking if they had available or could make suitable chemicals. The only one of them that showed any interest was Parke, Davis and Company. They wrote back to me that they had on hand samples of 19 different

compounds analogous to phenobarbital, and that I was welcome to them.'

The compounds, of course, were the ones prepared by Dox and included phenytoin, which had no hypnotic activity. Without the interest of the Parke, Davis chemists in structure/activity relationships and extensive animal testing for hypnotic activity, a whole decade earlier, it is doubtful that these compounds would have been available for screening as anticonvulsant agents. […]

In a letter dated November 30, 1936, Dr. Putnam wrote to Parke Davis as follows:

'We have at last succeeded in devising a thoroughly satisfactory preparation for testing anti-convulsants in which a cat can be given a convulsion at a surprisingly constant threshold by means of a well controlled electric current. A dose of phenobarbital too small to cause observable depression will double this threshold in cats. None of the drugs you sent me had a noticeable effect on the convulsive level short of the hypnotic dose except the diphenyl allantoin (sic) which appears to be effective in a smaller dose than luminal. Whether it has a higher therapeutic index remains to be seen, but the results at present are encouraging…(*50*)'"

From the discovery paper(*50*):

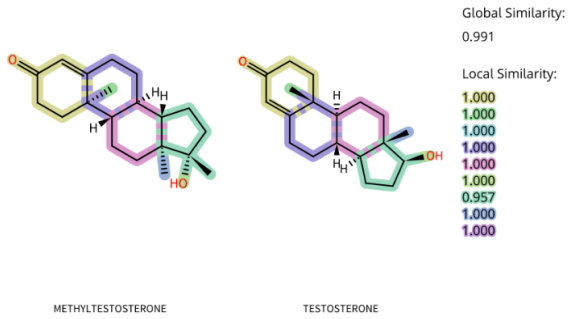
"The anticonvulsant effect of most of the common drugs has been studied by this apparatus, continuing the work of SpiegeLG Under the conditions of the experiment, it is easy to demonstrate that a dose of sodium bromide sufficient to prevent a cat from walking will raise the convulsive threshold only about 50 per cent., while a dose of phenobarbital producing similar symptoms may treble or quadruple it. Cats so protected may survive shocks of an intensity which proves fatal to untreated animals. Comparable doses of other familiar barbiturates have little anticonvulsant activity. This, and the fact that Harrison, Mason and Resnik have produced evidence that the conjugated phenols are responsible for the motor depression of uremia suggested a search among phenyl derivatives as well as among standard hypnotics.

Accordingly, a large number of the less toxic phenol compounds was studied. They included phenyl, cresyl and tolyl sulfonates, benzoates, ketones and esters of such radicals as carbamic, malic, barbituric acids and hydantoin. The compounds which appear to have the greatest anticonvulsant activity combined with the least relative hypnotic effect of those tested so far are diphenylhydantoin, acetophenone and benzophenone(*51*)."

## METHYLTESTOSTERONE

1938

Analogue of testosterone(*21*)




## GUANIDINE

1938

From the discovery paper:

"Frank, Nothmann and Guttman have reported that simple guanidine compounds greatly increase the sensitivity of striated muscles to the action of acetylcholine. Much work has been reported from this laboratory and others on the more general effect of guanidine compounds. Large doses (160-200 milligrams per kilo) of guanidine hydrochloride administered to animals produce intoxication. An early and prominent feature of the effect produced by these doses is the production of fibrillary tremors and tonic contractions of skeletal muscles. Other toxic manifestations include hypermotility of the

gastrointestinal tract, hypoglycemia and circulatory disturbances-changes which are compatible with increased parasympathetic activity. We have recently shown that this latter group of symptoms, but not those produced in muscles, can be largely prevented by atropine. In view of these findings it seemed possible that doses of guanidine far below the toxic level might improve the function of myasthenic muscles without the production of undesirable symptoms or that if such symptoms did develop they could be controlled by atropine without losing the effect of guanidine on muscles.

We have recently treated two cases of myasthenia gravis with guanidine hydrochloride. Both patients showed a marked temporary improvement in muscle strength as measured by ergographic studies(*52*).”

From the discovery paper of Frank, Nothmann and Guttman cited in the previous quotation:

“Der Nachweis der direkten Wirkung der Guanidine auf den Warm-blütermuskel.

Pekelharing hat bekanntlich nachzuweisen gesucht, daß das Kreatin Kennzeichen und Maß des Muskeltonus sei. Die Aufrechterhaltung einer einmal erreichten Verkürzung, die Rigidität und Starre (wie sie uns beim Säugetier insbesondere nach Enthirnung entgegentritt) sind nach seiner Ansicht Aktionsformen des Muskels, die mit einer Entbindung von Kreatin einhergehen, während die dutch diskontinuierliche Impulse unterhaltene tetanisehe Dauerkontraktion, selbst zum heftigsten Krampfe gesteigert, davon nichts erkennen läßt. Wie man auch zu dieser Lehre stehen mag, die gerade neuerdings manchen Widerspruch erfahren hat und sicherlich noch nicht genügend gefestigt ist, ihren heuristischen Wert wird man anerkennen müssen. Sie hat die Aufmerksamkeit von neuem auf die Guanidine gelenkt, nahe Verwandte des Kreatins, aber nicht harmlos wie diese, sondern stark wirksame körpereigene Pharmaca.

Pekelharing sieht im Kreatin lediglich das Produkt eines der tonischen Muskelaktion eigentümlichen Stoffwechselprozesses. Frank, Stern und Nothmann) haben die Vermutung ausgesprochen, daß das indifferente Kreatin der leicht nachweisbare Indicator der Entstehung physiologisch wirksamer Substanzen sei, welche vielleicht bereits vor dem tonischen Phänomen da sind und zu seinem Ursachenkomplex gehören, vielleieht aber auch erst während des tonischen Vorganges gebildet werden, dann abet diesen fördern und unterhalten.

Diese im Muskel entstehenden aktiven Körper könnten die Guanidine sein, insbesondere das Dimethylguanidin, welches sich vom Kreatin, der Methylguanidinessigsäure, nut durch das Fehlen einer CO2-Gruppe unterscheidet, und demnach aus diesem durch Decarboxylierung entstehen könnte, wie etwa die bekannten biogenen Amine Tyramin und Histamin aus der zugehörigen Aminosäure. Die Annahme, daß die Guanidine an der Entstehung tonischer Muskelaktion beteiligt seien, stützt sich zunächst auf eine allgemeine Erwägung: die Guanidine versetzen den Kaltblütermuskel in faszikuläre Zuckungen und vermögen beim Säuger hochgradige galvanisehe Übererregbarkeit zu erzeugen sowie die Curarelähmung aufzuheben). Substanzen, die eine oder mehrere dieser Eigenschaften besitzen (Physostigmin, Cholin, Nikotin), pflegen auch tonische Vorgänge (träge Zusammenziehungen, Rigidität, Starre) hervorzurufen. Ein in Guanidinlösung befindlicher Froschmuskel verrät denn auch, wie schon Fühner) bemerkt hat, Neigung zur Contractur, und die Guanidinkröte trägt nach Frank und Stern) ihren Rumpf auf langgestreckten Extremitäten steif wie auf Stelzen weiter.

Im folgenden suchen wir unsere Vermutung dadurch zu verifizieren, daß wir in Analogie

zu den in den früheren Mitteilungen dargestellten Nikotin-, Acetylcholin- und Kaliumexperimenten prüfen, ob wir mit Hilfe der Guanidine imstande sind, am motorisch entnervten Säuger-muskel tonische Kontraktionen hervorzurufen oder auf andere Weise erzeugte entscheidend zu beeinflussen.

Injiziert man einem Hunde mit durchschnittenem Hypoglossus zu einer Zeit, wo das Vulpian-Heidenhainsche Phänomen positiv ausfällt, Guanidin intraarteriell, eine Versuchsanordnung, die sich uns beim Acetylcholin besonders bewährt hat, so ist an der gelähmten Zungen- hälfte keine Veränderung zu beobachten. [...]

So ließ sich nachweisen, daß eine bestimmte Acetylcholindosis, die beim Kaninchen die Darmtätigkeit scheinbar noch ganz unbeeinflußt ließ, unter der Wirkung des Guanidins heftigste und unaufhörliche peristaltische Bewegungen hervorrief. Es konnte ferner gezeigt werden, daß Acetylcholin, welches beim normalen Tiere lediglich an der receptiven Substanz des Erfolgsorganes, also rein peripher angreift, beim Guanidintiere schwere klonischtonische Krämpfe auslösen kann(*53*)."

Translation from Google Translate:

"Evidence of the direct effect of guanidines on warm-blooded muscles.

As is well known, Pekelharing tried to prove that creatine was a characteristic and measure of muscle tone. The maintenance of a shortening once achieved, the rigidity and rigidity (as we encounter them in mammals especially after brain removal) are, in his view, forms of action of the muscle that go hand in hand with the delivery of creatine, while the continuous tetanic contraction maintained by discontinuous impulses is even the most violent Increased convulsions, showing nothing of it. Regardless of how one may feel about this doctrine, which has recently experienced many contradictions and is certainly not yet sufficiently consolidated, its heuristic value will have to be recognized. She has again drawn attention to the guanidines, close relatives of creatine, but not harmless like these, but highly effective endogenous pharmaceuticals.

Pekelharing sees creatine only as the product of a metabolic process peculiar to tonic muscle action. Frank, Stern and Nothmann) have expressed the assumption that the indifferent creatine is the easily detectable indicator of the development of physiologically active substances, which perhaps already existed before the tonic phenomenon and belong to its causal complex, but may also only be formed during the tonic process then encourage and entertain them.

These active bodies that develop in the muscle could be the guanidines, in particular dimethylguanidine, which differs from creatine, methylguanidine acetic acid, only in the lack of a CO2 group, and thus could arise from this through decarboxylation, such as the well-known biogenic amines tyramine and Histamine from the associated amino acid. The assumption that the guanidines are involved in the development of tonic muscle action is based initially on a general consideration: the guanidines cause the cold-blooded muscle to twitch in the fascicle and are able to produce high-grade galvanic hyperexcitability in mammals and to reverse curar paralysis). Substances that have one or more of these properties (physostigmine, choline, nicotine) also tend to cause tonic processes (sluggish contractions, rigidity, rigidity). A frog muscle in a guanidine solution reveals, as Führer already noted, a tendency to contracture, and according to Frank and Stern, the guanidine toad carries its trunk on elongated extremities, stiff as if on stilts.

In the following we try to verify our conjecture by examining, in analogy to the nicotine, acetylcholine and potassium experiments

presented in the earlier reports, whether we are able to induce or induce tonic contractions in the motor nervous mammalian muscles with the help of the guanidines other way generated to influence decisively. [...]

Thus it could be shown that a certain dose of acetylcholine, which in rabbits apparently left intestinal activity still completely unaffected, caused violent and incessant peristaltic movements under the action of guanidine. It could also be shown that acetylcholine, which in normal animals only attacks the receptive substance of the successor organ, i.e. purely peripherally, can trigger severe clonic-tonic convulsions in guanidine animals(*53*)."

## HEPARIN

1939

From one of the discoverers:

"This was a fortuitous decision. All I was trying to prove was that an ether-soluble, alcohol-insoluble extract of cephalin would accelerate coagulation of blood, and it did.

I became interested in the deterioration of cephalin (an unsaturated fatty acid), which I assumed became saturated on exposure to air (and ether-alcohol purification). It seemed sound to determine the iodine number of fresh cephalin in various stages of its decay down to no activity-about 3 months-by exposure to air. This Arbeit was completed and published the following year (1916-1917) at the University of Pennsylvania.

The various batches were tested down to the point of no thromboplastic activity, but two of those first prepared appeared not only to have lost their thromboplastic action, but actually to retard slightly the coagulation of the serum-plasma mixture. I had in mind, of course, no thought of an anticoagulant, but the experimental fact was before me; and I retested again and again until I was satisfied that an extract of liver (more than heart) possessed a strong anticoagulant action after its contained cephalin had lost its thromboplastic action.

At first I said nothing to Dr. Howell about this. It was not part of my planned problem […]

After more tests and the preparation of other batches of heparphosphatide, I went one morning to the door of Dr. Howell's office, and standing there, I said, "Dr. Howell, I have discovered antithrombin." He smiled and said, 'Antithrombin is a protein, and you are working with phosphatides. Are you sure that salt is not contaminating your substance?'

I told him I was not sure of that, but it was a powerful anticoagulant. He was most skeptical. So I had the Diener, John Schweinhant, bleed a cat. Into a small beaker full of its blood, I stirred all of a proven batch of heparphosphatides, and I placed this on Dr. How- ell's laboratory table and asked him to tell me when it clotted. It never did clot.

He still did not believe that I had discovered a natural anticoagulant, but it was at this point that he became associated in my research problem, namely the study of the effects of my anticoagulating substance (heparphosphatide), which gave greater yield and higher anticoagulating potential than cuorin in vivo in dogs. When I demonstrated new batches to him in vitro, and be became satisfied that it did actually inhibit the coagulation of the serum-plasma test mixture as well as whole blood in vitro, we planned the first in vivo experiment with a dog and administered the heparin intravenously(*54*)." Also see (*55*)

## ESTRADIOL

1940

Also see the progesterone entry.

"Soranus of Ephesus (AD 98–138), the most noted gynecologist at the time, contradicted Aristotle, in writing that both the male and female produce 'seeds' necessary for conception. Galen (AD 129–200) appeared to agree

with Soranus but not Aristotle. He observed female "testes" and concluded from these observations that the structures he saw corresponded to male testes and served the same purpose, namely production of semen. […]

He thought, based on appearance, that the ovaries and testes are similar and that damage to either results in infertility. He reasoned on this basis, as did Soranus and Galen, that the ovary must produce sperm. […]

In the 1880s, Robert Battey developed the ability to perform oophorectomy safely in women. This operation, called the Battey operation, became popular and was performed for multiple reasons, including dysmenorrhea and bleeding from myomata. After removal of the ovaries, patients developed hot flashes and vaginal atrophy, leading to the hypothesis that the ovary makes some type of substance that in its absence causes various symptoms.

In 1896, Emil Knauer from Vienna removed the ovaries from rabbits and observed uterine atrophy, which he could prevent by transplanting the ovary at a distant site, confirming the postulate of internal secretion by the ovaries. […]

In 1897, Hubert Fosbery successfully used ovarian extracts to treat a patient with severe hot flashes. […]

[I]n AD 1025, the Chinese prepared extracts of male and female urine, purportedly using powdered components to treat hypogonadism in men and dysmenorrhea in women, and other clinical disorders. […]

As the concepts regarding the function of the ovaries evolved, therapies were designed based on the current knowledge. In 1896, Sir George Beatson, a surgeon, described the first effective hormonal ablative therapy for treatment of breast cancer. He based his rationale on an experience 'moonlighting' on a farm where he was the physician for the owner. There he learned several facts about lactation and began to study this phenomenon. Based on his knowledge of histology, he appreciated similarities between the tissue appearance of lactational changes, characterized by increasing breast proliferation and the same phenomenon in histologic sections of breast cancer. Also, he knew that oophorectomy prolonged the time of lactation in cows, a practice common in Australia at that time. From these observations, he postulated a regulatory role of the ovary on benign and malignant breast and sought to apply this concept clinically. With seemingly great courage, he decided to remove the ovaries surgically in premenopausal women with breast cancer. Notably, he demonstrated both partial and complete, temporary remissions. This work initiated the field of surgical ablation of endocrine glands as treatment of hormone-dependent breast cancer(*56*)."

PHYTONADIONE

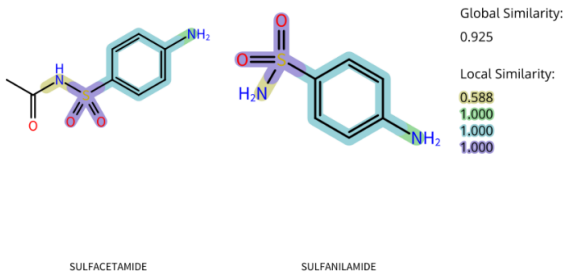
1940

Vitamin $K_1$

SULFACETAMIDE

1941

Analogue of sulfanilamide




ERGOCALCIFEROL

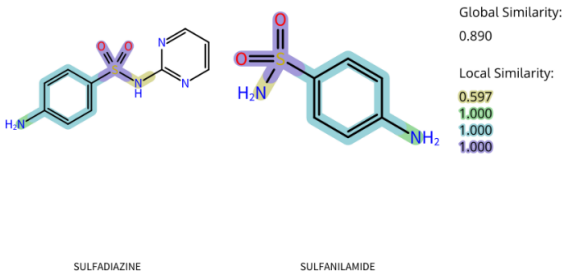
1941

Vitamin $D_2$

SULFADIAZINE

1941

Analogue of sulfanilamide




NAPHAZOLINE

1942

Although I could not find the following discovery papers, time of the discovery suggests that it was discovered probably based on therapeutic phenotypes in *ex vivo* or *in vivo* models.

A. M. Hild, Privine Ciba, a New Preparation for Reducing Congestion of the Nasal Mucosa, *Schweizerische medizinische Wochenschrift*, **71**, 557-561 (April 26 1941).

R. Meier, R. Müller: Pharmakologische Untersuchungen über eine neuartige Substanz mit anämisierender Wirkung auf den Schleimäuten, *Schweizerische medizinische Wochenschrift*, **71**, 554 (1941).

MEPERIDINE

1942

= Dolantin

Analogue of atropine

“Meperidine was first synthesized in 1939 as an anticholinergic agent, but it was soon discovered to have analgesic properties(*57*).”

From the discovery paper cited in the previous quotation:

“Mit der Erkenntnis der Struktur des Aropins als eines Tropasäureesters des basischen Alkohols Tropin setzten auch die Versuche zu einer Synthese ähnlich gebauter Verbindungen ein. Man verfolgte hier das gleiche Prinzip, das bereits beim Kokain zu so schönen Erfolgen geführt hatte, indem man sowohl den Säureanteil wie auch den basischen Alkohol des Atropins variierte. [...]

Es war nun interessant zu untersuchen, wie sich hier in der Atropinreihe eine Maßnahme auswirken würde, die bei den synthetischen Lokalanästheticis schon mit Erfolg ausgeführt worden war, nämlich die Verlegung der basischen Gruppe aus dem alkoholischen Anteil des Moleküls in den Säureanteii. Diese Frage wurde durch den Aufbau und die Untersuchung der Substanzen I und II entschieden; beide erwiesen sich als spasmolytisch wirksam.

Für die arzneiliche Verwendung kommt das Hydrochlorid in Betracht, das den Namen Dolantin erhalten hat. Dolantin ist ein farbloses Kristallpulver vom F.P. 187-188°, das in Wasser leicht löslich ist und neutral reagiert. Auf der Zunge verursacht es eine schwach bittere, nur kurz anhaltende Geschmacksempfindung.

Die pharmakologische Untersuchung ergab, daß dem Dolantin nicht nur die gleiche komplexe spasmolytische Wirkung zukommt wie den bisher bekannten Estern basischer Alkohole, sondern daß beim Dolantin außerdem eine in solchem Ausmaße bei synthetischen Verbindungen bisher nicht beobachtete analgetische Wirkung hinzutritt. Im folgenden seien nun mit der hier gebotenen Kürze die wichtigsten pharmakologischen Eigenschaften des Dolantins beschrieben.

I. *Spasmolytische Wirksamkeit*

a) *Vaguslähmende Wirkung*. Am isolierten Darm vermag Dolantin noch in einer Verdünnung von 1 : 5 Millionen die Azetylcholinkontraktur aufzuheben. Auch bei Versuchen an dem in situ belassenen Darm läßt sich dieser Antagonismus gegen pharmakologische Vagusreize nachweisen. Verhältnismäßig geringer ist die Wirkung des Dolantins auf die Speichelsekretion. Der durch die subkutane injektion von 10 mg Pilokarpin pro Kilogramm am urethanisierten Kaninchen ausgelöste profuse Speichelfluß wird durch 20 mg Dolantin pro Kilogramm subkutan zwar stark eingeschränkt, aber nicht

vollkommen aufgehoben, während Atropin bereits in einer Dosis von 0,1 mg pro Kilogramm subkutan unter den gleichen Bedingungen zu einem völligen Versiegen der Speichelsekretion führt.

Ebenso ist auch der Einfluß des Dolantins auf die Pupillenweite relativ geringfügig. Erst eine 1%ige Lösung führt bei Einträufelung in das Katzenauge zu einer geringfügigen Erweiterung der Pupille, während Atropin bereits in einer Verdünnung von 1 : 100000 stark wirksam ist.

Auch am Gesamtkreislauf ist die atropinartige Wirkung des Dolantins wenig ausgesprochen. Die blutdrucksenkende Wirkung des Azetylcholins läßt sich durch Dolantin erst bei sehr hoher Dosierung abschwächen; es ist hier etwa 10 000mal schwächer wirksam als Atropin. Ebenso wird durch relativ große Dosen von Dolantin die Pulsfrequenz nur wenig beeinflußt.

b) *Muskuläre Wirkung*. Zum Unterschied von Atropin besitzt das Dolantin auch eine ausgesprochen krampflösende Wirkung auf den durch Bariumchlorid erzeugten rein muskulären Spasmus. In dieser Hinsicht reicht es nahe an die typische Wirksamkeit des Papaverins heran.

Diese komplexe, sowohl neurotrope wie muskulotrope Wirkung des Dolantins kommt am augenfälligsten in seinem Antagonismus gegen Histamin zum Ausdruck. Am Histaminkrampf des isolierten Darmes ist Dolantin um ein Mehrfaches stärker wirksam als Atropin oder Papaverin.

Auch der Histaminkrampf der Bronchialmuskulatur wird durch Dolantin in spezifischer Weise gelöst. Am deutlichsten zeigen dies Versuche am Histaminasthma des Meerschweinchens. Nach der Methode von KALLOS und PAGEL kann man am Meerschweinchen durch Histamininhalation einen schwersten Asthmaanfall auslösen. Dieser läßt sich durch prophylaktische Injektion oder gleichzeitige Inhalation von Dolantin verhindern, während hier sowohl Atropin wie auch Papaverin wenig wirksam sind.

c) *Wirkung auf die Nierengefäße*. Durch Suprarenin und verwandte Verbindungen läßt sich an den Nierengefäßen eine weitgeher.de Drosselung der Durchblutung herbeiführen, die zu einer Verminderung der Diurese bis zur vollständigen Anurie führen kann. Dolantin hebt diese Sperre der Durchblutung auf und führt die Diurese zur Norm zurück.

II. *Analgetische Wirkung*

An weißen Mäusen führt die subkutane Injektion von 1/5 der tödlichen Dosis zu einer vollständigen Aufhebung der Schmerzempfindung. Diese zentrale Analgesie ist von keinerlei narkotischen Erscheinungen, sondern eher von einer leichten Erregungssteigerung begleitet. Als sichtbares Zeichen dieser zentralen Enthemmung zeigen die Tiere das für Morphin charakteristische Schwanzphänomen: Die Tiere tragen den Schwanz in eigentümlich starrer Haltung S-förmig über den Rücken gekrümmt.

Die zentrale Enthemmung gibt sich, wie beim Morphin, auch in dem Verhalten von Katzen nach subkutaner Injektion von Dolantin zu erkennen. Die Tiere halluzinieren und werden außerordentlich schreckhaft und bösartig.

Die morphinähnlichen Eigenschaften des Dolantins legten den Gedanken nahe, seine Wirkung gegenüber dem Hustenreflex zu untersuchen. Der experimentell an Katzen nach der Methode von ERNST erzeugte Hustenreflex läßt sich durch Dolantin etwa in der gleichen Dosierung wie durch Kodein unterdrücken(*58*)."

Translation from Google Translate:

"With the knowledge of the structure of aropine as a tropic acid ester of the basic alcohol tropine, attempts to synthesize similarly built

compounds began. The same principle was followed here that had already led to such beautiful successes with cocaine, by varying both the acid content and the basic alcohol of atropine. [...]

It was now interesting to investigate how a measure would affect the atropine series that had already been successfully carried out with synthetic local anesthetics, namely the transfer of the basic group from the alcoholic part of the molecule to the acid part. This question was decided by the structure and the investigation of substances I and II; both proved to be spasmolytic.

For medicinal use, the hydrochloride, which has received the name Dolantin, comes into consideration. Dolantin is a colorless crystal powder from F.P. 187-188°, which is easily soluble in water and reacts neutrally. On the tongue it causes a slightly bitter, short-lasting taste sensation.

The pharmacological investigation showed that Dolantin not only has the same complex spasmolytic effect as the previously known esters of basic alcohols, but that Dolantin also has an analgesic effect to such an extent not previously observed in synthetic compounds. In the following, the most important pharmacological properties of dolanthine are described with the brevity required.

I. *Spasmolytic Effectiveness*

a) *Vagus paralyzing effect*. In a dilution of 1: 5 million, Dolantin is still able to reverse the acetylcholine contracture in the isolated intestine. This antagonism to pharmacological vagus stimuli can also be demonstrated in experiments on the intestine left in situ. The effect of dolanthine on saliva secretion is relatively less. The profuse salivation triggered by the subcutaneous injection of 10 mg pilocarpine per kilogram in urethanized rabbits is severely restricted by 20 mg dolantine per kilogram subcutaneously, but not completely eliminated, while atropine at a dose of 0.1 mg per kilogram subcutaneously below the same conditions leads to a complete cessation of saliva secretion.

Likewise, the influence of Dolantin on the pupil size is also relatively minor. Only a 1% solution, when instilled in the cat's eye, leads to a slight dilatation of the pupil, while atropine is already highly effective at a dilution of 1: 100,000.

The atropine-like effect of Dolantin is also little pronounced in the overall circulation. The antihypertensive effect of acetylcholine can only be weakened by Dolantin at very high doses; it is about 10,000 times less effective here than atropine. Likewise, relatively large doses of Dolantin have little effect on the pulse rate.

b) *Muscular effect*. In contrast to atropine, dolantine also has a pronounced antispasmodic effect on the purely muscular spasm caused by barium chloride. In this respect it comes close to the typical effectiveness of papaverine.

This complex, neurotropic as well as musculotropic effect of dolanthine is most evident in its antagonism to histamine. Dolantin is several times more effective than atropine or papaverine on the histamine spasm of the isolated intestine.

The histamine spasm of the bronchial muscles is also resolved in a specific way by Dolantin. Experiments on histamine asthma in guinea pigs show this most clearly. According to the KALLOS and PAGEL method, histamine inhalation can induce a very severe asthma attack in guinea pigs. This can be prevented by prophylactic injection or simultaneous inhalation of Dolantine, while here both atropine and papaverine are not very effective.

c) *Effect on the renal vessels*. Suprarenine and related compounds can be used to reduce the blood flow to the kidney vessels, which can lead to a reduction in diuresis and even

complete anuria. Dolantin removes this blockage of blood flow and returns the diuresis to normal.

II. *Analgesic effect*

In white mice, the subcutaneous injection of 1/5 of the lethal dose leads to a complete abolition of the pain sensation. This central analgesia is not accompanied by any narcotic symptoms, but rather by a slight increase in excitation. As a visible sign of this central disinhibition, the animals show the tail phenomenon that is characteristic of morphine: The animals carry their tails in a peculiarly rigid posture, curved over their backs in an S-shape.

As with morphine, the central disinhibition can also be seen in the behavior of cats after subcutaneous injection of Dolantin. The animals hallucinate and become extremely jumpy and vicious.

Dolantin's morphine-like properties suggested investigating its effect on the cough reflex. The cough reflex produced experimentally in cats according to the ERNST method can be suppressed by Dolantin in about the same dosage as by codeine(*58*)."

## DEOXYCHOLIC ACID

1942

"Deoxycholic acid is a a bile acid which emulsifies and solubilizes dietary fats in the intestine, and when injected subcutaneously, it disrupts cell membranes in adipocytes and destroys fat cells in that tissue(*1*)."

## CHLOROQUINE SULFATE

1943

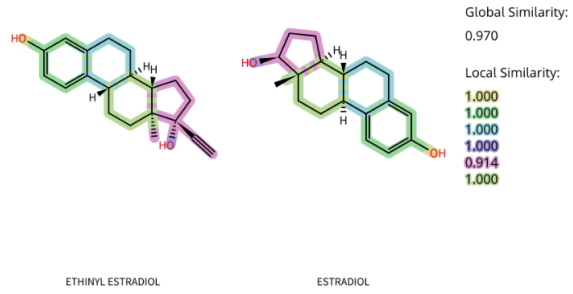
"The overall search for new antimalarial agents involved the screening of some 16,000 compounds, most of them for both suppressive and prophylactic activity against several avian malarias, plus a thorough study of the toxicology and pharmacology of many of the preparations in lower animals. Finally, the appraisal was undertaken of some 80 compounds against the malarias of man. […]

The most important of these new compounds was SN-7618 (SN = Survey Number) later known as chloroquine. The Germans had synthesized this compound before the war but, incredible as it may seem now, they discarded it(*59*)."

## ETHINYL ESTRADIOL

1943

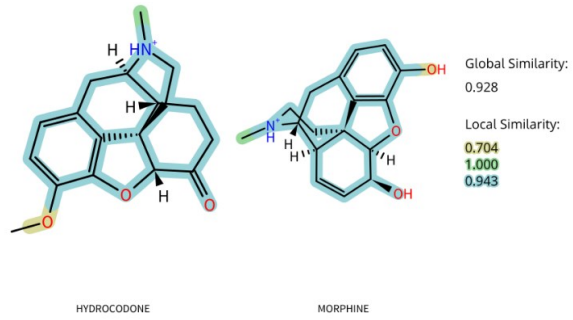
Analogue of estradiol(*21*)




## HYDROCODONE

1943

Analogue of morphine(*21*)




## PENICILLIN G

1943

"In August of 1928 bacteriologist Alexander Fleming, working in Sir Almroth Wright's Inoculation Department at St Mary's Hospital in London, discovered that a culture plate on which he was growing staphylococci colonies had accidentally become contaminated by a mold, which he mistakenly identified as

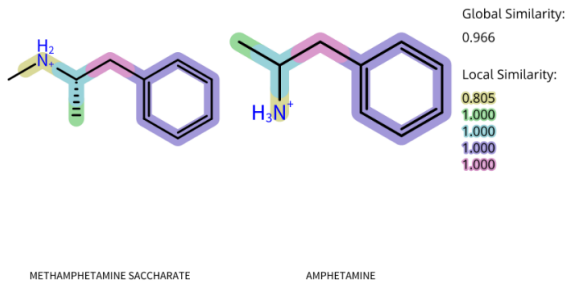
*Penicillium rubrum* (it was actually *Penicillium notatum*). But to Fleming's amazement, the staphylococci were unable to grow in the vicinity of the mold. This unusual activity led Fleming to investigate the mold more closely. He found that penicillin the name he applied to the filtrate of the mold broth would inhibit the growth in vitro of some Gram-positive bacteria, such as staphylococci, streptococci, pneumococci, and gonococci, in dilutions of up to 1 to 800; it had no effect on Gram-negative microorganisms. Furthermore, Fleming demonstrated that penicillin had little or no toxic effect in animals, and it displayed no toxic reactions when applied locally in man. However, he apparently did not foresee any chemotherapeutic possibilities for penicillin; Fleming believed that it was a member of the group of slow-acting antiseptics. Thus, while Fleming recognized the antibacterial properties of penicillin, he did not test his filtrate *in vivo* for antibacterial activity.

In 1938 the clinical, chemical, and industrial pieces of the penicillin puzzle finally began to fall into place, under the labor of Howard Florey, Ernst Chain, and others working at Oxford's Sir William Dunn School of Pathology. This group had been interested in antibacterial substances for some time, and part of their work involved the study of lysozyme, an antibacterial enzyme which Fleming had discovered in 1922. Their literature search on this enzyme led Florey and Chain to Fleming's 1929 paper on penicillin. So in 1938 the Oxford group, being interested in penicillin's ability to inhibit staphylococcal growth and its unusual chemical properties and instability, began to investigate this substance. By May, 1940, the Oxford workers had collected enough penicillin to test its therapeutic effects in animals. They infected two groups of animals with deadly hemolytic streptococci, and found that the group receiving penicillin survived at least three times as long as the untreated group(*60*)."

## METHAMPHETAMINE SACCHARATE

1943

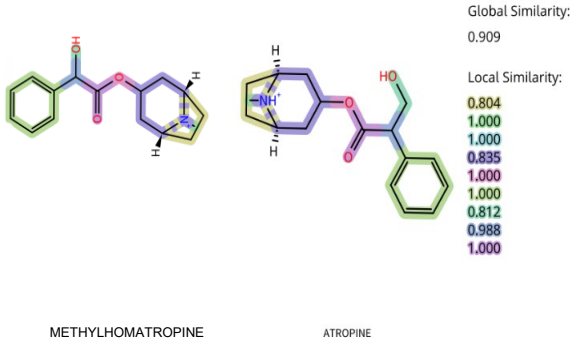
Analogue of amphetamine




## METHYLHOMATROPINE

1943

Analogue of atropine




## HUMAN IMMUNOGLOBULIN G

1944

Endogenous-based biopharmaceutical

## UNDECYLENIC ACID

1945

"A new therapeutic principle was introduced in 1938 by Peck and Rosenfeld, who found that organic fatty acids occurring in sweat have considerable fungicidal action without any irritating effect. They found that the sodium salt of undecylenic acid has the strongest fungicidal action of all tested fatty acids and their salts(*61*)."

From the discovery paper cited in the previous quotation:

"The interest of the authors in the fungicidal properties of the fatty acids and their salts was aroused during the investigations which

are being conducted on sweat. It was observed that sweat had fungicidal properties which were probably due to a certain extent to some of the fatty acids. […]

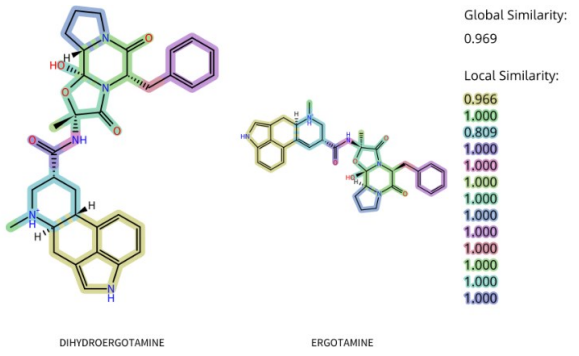
The importance of this approach to the problem of the treatment of fungous infections does not lie in the discovery of any startlingly new fungicidal agents but in the concept that the use of some of these products approaches a more physiologic method of therapy. It is probably for this reason that this form of herapy causes very little irritation and thus tends to decrease the incidence of trichophytids which very often are sequelae of more irritating methods of treatment.

*Organisms Investigated.* The effects of the fungicidal activities of the various substances was tested on *Trichophyton Gypseum*, *Epidermophyton Inguinale* and *Monilia Albicans*(*62*)."

DIHYDROERGOTAMINE

1946

Analogue of ergotamine

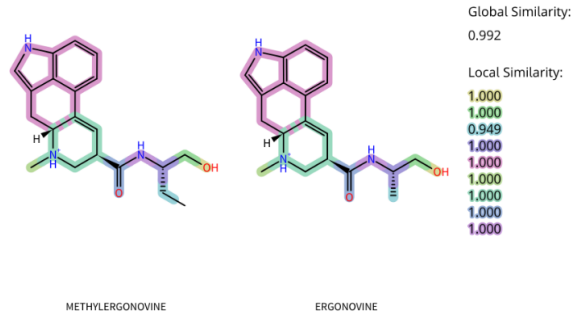



"DHE was developed in 1943 and tried in migraine on the basis of the belief that migraine headache resulted from an increase in sympathetic activity. Accordingly, DHE was expected to be more efficacious than ergotamine in treating migraine, since it possesses greater α-adrenoceptor activity. However, early clinical experience showed that DHE, although effective in the acute treatment of migraine, must be given in higher doses than ergotamine(*63*)"

METHYLERGONOVINE

1946

Analogue of ergonovine




Also see the oxytocin entry

"Once a dreaded poison, ergot has changed its role over the centuries to become a rich treasure house of valuable pharmaceuticals. In the Middle Ages it was the cause of epidemics of ergotism, which cost tens of thousands of people their lives. Ergot was first mentioned by the German physician *Lonitzer* in 1582 as a remedy used by midwives for quickening childbirth. The isolation of pharmacologically useful alkaloids started in 1906 with the discovery of ergotoxine and its adrenolytic activity by *Barger, Carr and Dale*. In 1918, Stoll isolated ergotamine, the first chemically pure ergot alkaloid, which found widespread therapeutic use in obstetrics and internal medicine. In 1935 the specific oxytocic principle of ergot, ergonovine, was discovered simultaneously in four separate laboratories(*64*)."

DIMERCAPROL

1946

Chelating agent

TETRADECYL HYDROGEN SULFATE

1946

Surfactant

FOLIC ACID

1946

Vitamin $B_9$

## STREPTOMYCIN

1946

Following the path of the previous successful quests for antibiotics in bacteria, Waksman initiated his for antibiotics in a group of soil bacteria, Streptomycetes. The screenings were performed on organisms like *M. smegmatis*(*10*).

From the discoverer(s):

"Suffice to say that streptomycin pointed the way, both through the planned screening programs and through its specific activity against the gram-negative bacteria and tuberculosis, to many of these antibiotics(*65*)."

## DIPHENHYDRAMINE

1946

Staub and Bovet synthesized many compounds and tested them in these assays: protecting guinea pigs against lethal doses of histamine, and antagonizing the effect of histamine on uterine and intestine smooth muscles of guinea pig(*66*).

"The evidence assigning histamine an active role in allergy and anaphylaxis prompted scientists to attempt methods of reducing histamine manifestations.

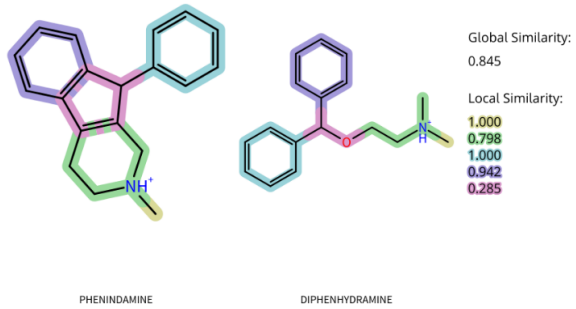
The systematic search for compounds having the specific property of counteracting the physiological effects of histamine began in the Pasteur Institute in the 1930s. The parent compound of the first antihistamines was thymoxyethyldiethylamine first synthesized as early as 1911. In 1933 Fourneau and Bovet reported that certain phenolic ethers had the property of inhibiting or counteracting the action of histamine; the most effective of these was 2-isopropyl-5-methyl phenoxyethyl diethylamine (929 F). This is the parent compound of the ethanolamine series. Staub and Bovet demonstrated that 929 F could protect guinea-pigs from histamine-induced anaphylaxis but its toxicity precluded its clinical use. Because of this toxicity Staub went on to investigate a series of Fourneau compounds of the general phenoxyethylamine type. She showed that substitution in the benzene ring played a critical role.

Staub had produced and tested highly active potent antihistamines of which the new compound (1571 F) was out-standing but the toxicity of these compounds precluded their use in man. Antihistaminic research continued separately in France and North America during the war years of the early 1940s. In France, Rhone Poulenc patented RP 2339 in May 1941. This compound antergan ($N_1N$ dimethyl-$N_1$-benzyl-N-phenyl-ethylenediamine), described by Halpern in 1942 was the first antihistamine used clinically in man. Many new antihistamines followed in rapid succession including diphenhydramine in 1945, and RP 3277 (Phenergan) in 1948. Huttrer's review of 1950 lists 20 clinically available antihistamines(*67*)."

## PHENINDAMINE

1947

Analogue of diphenhydramine




## METHADONE

1947

Analogue of meperidine

"Methadone, the first of the open-chain analgesics, was discovered at I.G. Farbenindustrie at Hoechst-am-Main in Germany during World War II in the course of work on spasmolytic compounds.

Its narcotic-type analgesic activity was unexpected, since it lacked any obvious

resemblance to previously known compounds. Despite the fact that there was a morphine shortage at the time of its discovery, methadone was not used as an analgesic until after the war(*68*)."

From the discovery paper cited in the previous quotation:

"In der vorliegenden Abhandlung bringen wir eine Fortsetzung der Arbeiten unseres Werkes, welche seinerzeit ihren Anfang mit der Gewinnung spasmolytisch wirksamer Verbindungen nahmen und welchen das im Jahre 1939 von Eisleb und Schaumann aufgefundene morphiumartig wirkende Dolantin zugrunde liegt. Bei der neben diesen Arbeiten von uns s. Z. gewählten zweiten Forschungsrichtung handelt es sich weniger um die Nachbildung irgendeines Strukturgliedes der Morphiummolekel, vielmchr ist bei der neuen, im folgenden geschilderten Klasse von Verbindungen lediglich der Umstand von Beachtung, daß diese ebenso wie das Morphium und Dolantin ein quartäres C-Atom tragen. Das Vorhandensein eines solchen quartären C-Atoms in der Morphiumstruktur hat bei den Synthesen der neueren Literatur bereits starke Beachtung gefunden). […]

Eine orientiernde pharmakologische Untersuchung einiger Ketone der besprochenen Konstitution zeigte nämlich, daß wir es hier mit zum Teil ganz ausgezeichnet analgetisch wirkenden Substanzen zu tun haben. Und zwar ist der morphinartige Wirkungshabitus, gemessen an den üblichen pharmakolog. Testen, ein ganz ähnlieher wie der der Dolantin-Gruppe. Auch die in der Morphin-Reihe von Straub-Herrmann festgestellte Reaktion an weißen Mäusen (katatonische S-förmige Schwanzhaltung über dem Rücken), die bereits bei der Dolantin-Gruppe beschriebcn wurde, finden wir hier wieder. Gegenüber der stark ausgeprägten zentralanalgetischen Eigenschaft tritt die Bedeutung der daneben auftretenden, am Nerven- und Gefäßmuskelpräparat festgestellten spasmenlösenden Wirkung in den Hintergrund und soll hier unbeachtet bleiben oder nur in den Tabellen kurz notiert werden(*69*)."

Translation from Google Translate:

"In the present treatise we bring a continuation of the work of our work, which began at the time with the extraction of spasmolytic compounds and which is based on the morphine-like acting Dolantin discovered in 1939 by Eisleb and Schaumann. The second research direction chosen by us in addition to this work is not so much the reproduction of any structural member of the morphine molecules, but rather the fact that the new class of compounds described below is merely the fact that these, like morphine and Dolantin carry a quaternary carbon atom. The presence of such a quaternary carbon atom in the morphine structure has already attracted considerable attention in the syntheses of the more recent literature. […]

An orienting pharmacological investigation of some ketones of the constitution discussed showed that we are dealing here with substances that have an excellent analgesic effect. And that is the morphine-like habitus, measured against the usual pharmacological. Testing, very similar to that of the Dolantin group. The reaction found in the Straub-Herrmann morphine series in white mice (catatonic S-shaped tail posture above the back), which was already described in the Dolantin group, is found here again. Compared to the strongly pronounced central analgesic property, the importance of the spasm-relieving effect found on the nerve and vascular muscle preparation takes a back seat and should be ignored here or only briefly noted in the tables(*69*)."

## FLAVIN MONONUCLEOTIDE

1947

A form of vitamin $B_2$ used to restore riboflavin in anemia, migraine, alcoholism, and

hyperhomocysteinemia(*2*).

PROPYLTHIOURACIL

1947

"The thionamide antithyroid drugs were discovered in large part following serendipitous observations by a number of investigators in the 1940s who found that sulfhydryl-containing compounds were goitrogenic in animals. […]

In 1942, Astwood treated the first hyperthyroid patient with thiourea, in whom there was a remarkable clinical improvement. At the same time, he initiated a series of studies of over 100 synthetic thiourea analogs as potential goitrogens in rats, and came upon one compound, 2-thiouracil, that was particularly potent. […]

In 1946, after studying more than 300 compounds for their 'antithyroid' effect, the more potent 6-n-propylthiouracil (PTU) was introduced and approved by the U.S. FDA in 1947. Methimazole (MMI) was discovered to be an even more potent and less toxic thiourea analog in 1949. Subsequently, carbimazole, a 'prodrug' for methimazole was introduced in 1953, in the unrealized hope that it would have less toxicity than methimazole(*70*)"

VITAMIN A

1947

ASCORBIC ACID

1947

Vitamin C

PROGUANIL

1947

"Proguanil was the first reported antimalarial antifolate agent and was discovered as a result of an intensive British research programme, led by Imperial Chemical Industries (ICI) on synthetic antimalarials, which started during the Second World War. The first report on proguanil was in 1945, and the drug was found to be more active than quinine against avian malaria and to have a better therapeutic index in animal models, prompting its use in humans. After this discovery, studies demonstrated that, in fact, proguanil is a prodrug and metabolizes to its triazine form chlorcycloguanil, an inhibitor of the parasite DHFR(*71*)"

From the discovery paper:

"**SUMMARY**

l. The chemical considerations which led to the discovery of some biguanide substances as antimalarial drugs are outlined.

2. Our working hypotheses concerning the life-cycle of the malarial parasite in the vertebrate host, and their bearing on the chemotherapy of malaria, are described.

3. The results we have achieved with 4430 and 4888 in various tests against various species of *Plasmodium* in birds are given. Both drugs exert a causal prophylactic action and a therapeutic action against different bird infections, but, whereas 4430 is a causal prophylactic only against *P. gallinaceum* and is without an action on the blood forms of *P. cathemerium* (*P. relictum* not tested), no definite failure either in causal prophylactic action or in therapeutic action has been encountered with 4888 in the infections used (*P. cathemerium*, *P. gallinaceum*, *P. lophurae*, *P. relictum*).

4. Our results have been such that we considered that both 4430 and 4888 should be tried in causal prophylactic experiments and therapeutically with all types of human malaria(*72*)."

THIAMINE ION

1947

Vitamin $B_1$

PYRIDOXINE

1947

Vitamin $B_6$

NIACINAMIDE

1947

Vitamin $B_3$

CYANOCOBALAMIN

1947

Vitamin $B_{12}$

BIOTIN

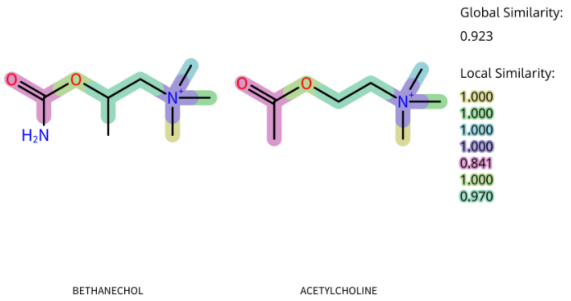
1947

Vitamin $B_7$

BETHANECHOL

1948

Analogue of acetylcholine




HEXACHLOROPHENE

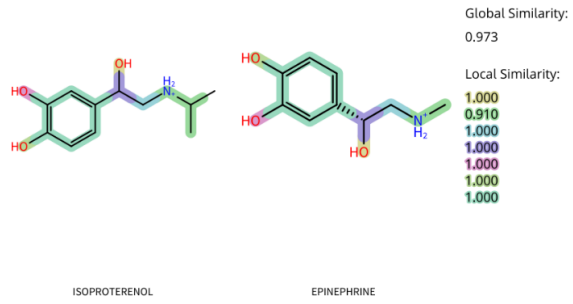
1948

"The discovery of salicylanilides as anthelmintic agents owes its origin to research for new antiseptics. Following the demonstration of pathogenic effects of microorganisms by Pasteur, Koch and others, Lister was able to show in 1867 the germicidal power of phenol (then called carbolic acid). This observation led to the introduction of several phenol derivatives with marked antibacterial properties as disinfectants, many of which were used for several decades. In a further probe to the development of better disinfectants derived from phenols, it was found that compounds containing two phenolic nuclei, linked directly or through a bridge, possessed higher antibacterial activity. Some of these carrying a hydroxy group at 2,2'-positions also exhibited promising activity against liver flukes. The most effective anthelmintics thus discovered were bithionol and hexachlorophene. Both these drugs were later used to eradicate tapeworms and liver flukes from humans and domestic animals(*73*)."

ISOPROTERENOL

1948

Analogue of epinephrine




From the discoverer(s):

"**The Konzett-Rössler method for recording pharmacological effects on bronchial muscle**

The many different methods in vitro and in vivo for recording effects on bronchial muscle described in the literature proved to be either unphysiological or unreliable or too complicated for the equipment available to us. After some unsuccessful attempts, a satisfactory solution to the methodological problem was found mainly through the ingenuity and experimental skill of R. Rössler. With such simple apparatus as a Starling respiration pump, a mercury manometer, a piston recorder, a gas-washing flask and glass and rubber connections, a functional machine was built which allowed us to measure bronchoconstrictor and bronchodilator effects quantitatively in vivo. By means of the adapted technique, changes in the distensibility of the lungs at constant pressure are continuously registered by means of an overflow. Excess air provided by the respiration pump during the inflation phase which does not

enter the lungs displaces a piston carrying a lever which writes a vertical line on the kymograph. A decrease in the volume of air entering the lungs due to bronchoconstriction causes the lever to rise farther; an increase in the volume of air entering the lungs due to bronchodilatation causes the lever to rise less. Volume calibrations of the ventilation overflow can easily be made.

For registration of a relaxation of bronchial muscles it was necessary first to elicit a bronchoconstriction. Pilocarpine was chosen from a great number of possible candidates as a suitable, long lasting bronchoconstrictor agent for these experiments which were mostly performed on dogs with open thorax. Preliminary experiments, inducing bronchoconstriction in this way and bronchodilatation mainly by epinephrine, were performed to become familiar with the peculiarities of the new set-up. […]

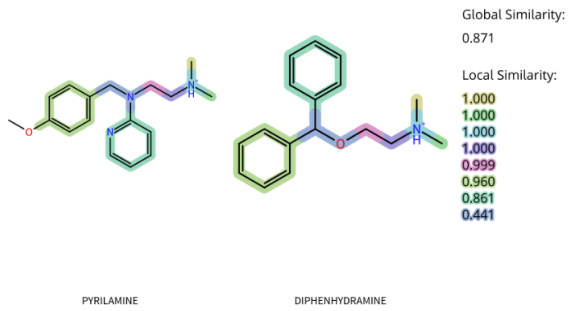
The compounds propyl- and butyl- norepinephrine were as effective as epinephrine with regard to bronchodilatation, but they completely lacked its pressor activity; both were depressor agents.

On 18 November, 1938 we carried out the first experiment with the isopropyl analogue of epinephrine. We recognized its powerful bronchodilator action straightaway. The compound was about as active as epinephrine in tenfold lower doses. Its strong bronchodilator effect could also be confirmed on cats and guinea pigs using the method described above for measurement and using histamine as a bronchoconstrictor agent. A further careful pharmacological analysis mainly regarding its cardiovascular effects showed that isopropylnorepinephrine had pronounced chronotropic and positive inotropic effects on the heart, accompanied by a remarkable increase in coronary blood flow. It produced a fall in blood pressure by vasodilatation and an inhibition of movement of the isolated rabbit intestine. Its acute toxicity in mice was much less than that of epinephrine(*74*).”

## PYRILAMINE

1948

Analogue of diphenhydramine(*21*)




## CHLORTETRACYCLINE

1948

“Duggar was world renowned for his extensive knowledge and study of soil fungi; he collected soil samples from all over the world sent to him by friends from sites he instructed would yield actinomycetes soil bacteria, or ‘ultra-molds’ as he called them, those with ground coverings left undisturbed and natural. The samples were subjected to culture and broth dilution assays performed by his technicians, in which the microorganisms were plated, and the colonies assayed for antibiotic activity against a panel of Gram-positive and Gram-negative bacteria. Although many soil organisms were known to produce antibiotics, most were toxic or had undesirable properties, and the team encountered many false leads.

One sample, however, drew their attention early on. It was marked A-377 and sent by William Albrecht, dug from Plot 23 on Sanborn field, a dormant timothy hayfield on the University of Missouri campus, outside Columbia, Missouri. It yielded an unusual yellow-colored colony that inhibited the growth of all their strains in an initial panel of bacteria, and produced remarkably large zones of growth inhibition in agar. This was

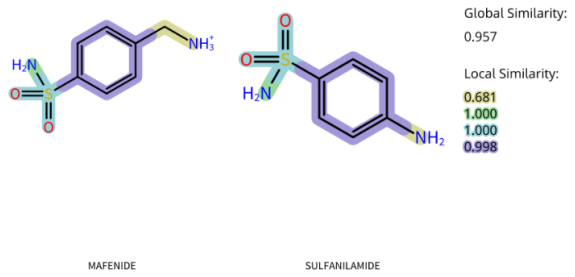
an unheard-of property at this point, as compared to the few antibiotics available for comparison. They further found that even crude extracts of the colony retained remarkable antibacterial activity against lethal scrub typhus and the rickettsias, such as Rocky Mountain spotted fever, an infection for which there was no cure. […]

This established Aureomycin as a new and potent broad-spectrum antibacterial agent that was safe and effective, although its exact chemical structure had yet to be determined(*75*).”

## MAFENIDE

1948

Analogue of sulfanilamide




## ERGOTAMINE

1948

“In 1906 Dale, Nobel Prize winner of 1936, showed that a liquid extract of ergot inhibited the pressor response to adrenaline in anaesthetized cats […]

Ergot treatment had been unreliable because of varying alkaloid content, but in 1918 Stoll at Sandoz in Basel isolated ergotamine from ergot. The pharmaceutical product was called Gynergen, since it was envisaged that the drug should be used in gynaecology and obstetrics for its uterotonic effect. Migraine was believed to be due to vasospasm because of the pale face of most migraineurs during attacks. Rothlin at Sandoz thought that the adrenolytic properties of ergotamine would counteract the sympathotonic mechanism of migraine, and his colleague Maier in Zürich did a successful study in 1925, which was confirmed by Trautmann in Germany in 1928, using placebo controls. The effect of ergotamine in migraine was also investigated in an open study in 1928 France(*63*).”

## LIDOCAINE

1948

During the investigations of the chemical relationships between genes and enzymes, from a mutant barley, an indole alkaloid, gramine, was isolated and analyzed. Afterwards, 2-dimethyl-aminomethylindole, isogramine, was synthesized. The chemist performing the synthesis, had the habit of testing the chemicals on his tongue. After testing this comound he found his tounge anesthesized, which was contrary to his testing gramine on his tongue. After some years and testing different compounds, LL30 was found active in self-experiment.

“Lidocaine was discovered from systematic investigations at the Institute of Chemistry at Stockholm University, Stockholm. In the early 1930s, Hans von Euler Chelpin, Ph.D. (1873–1964, Nobel Prize winner in 1929 for studies on the fermentation of alcohols), wanted to investigate how genes and enzymes were chemically related and to map out the actual process of inheritance in purely chemical terms. He tried to find chemical differences between normal barley and some chlorophyll-defective mutants resistant to certain pests. From the mutants he had obtained from the famous Swedish plant geneticist, H. Nilsson-Ehle, Ph.D. (1873–1949), von Euler-Chelpin *et al.* isolated an alkaloid, an indole, that they named gramine after the Latin name of the grass family Gramineae. They made a correct elemental analysis ($C_{11}H_{14}N_2$).

In von Euler-Chelpin’s laboratory, Holger Erdtman, Ph.D. (1902–1989), was given the task to synthesize 2-dimethyl-aminomethyl-indole, which was not identical to gramine;

instead, it was an isomer, called isogramine. As usual, he tested the substance on his tongue, which he found anesthetized. Gramine was inactive in this respect. Erdtman, in association with a young chemistry student, Nils Löfgren, Ph.D. (1913–1967), prepared several analogs, working with the starting material for the synthesis of isogramine, dimethylamino acetotoluidide. Pharmaceutical tests of these compounds were performed in von Euler-Chelpin's laboratory with the assistance of his son, Ulf von Euler (1905–1983, Nobel Prize winner in 1970 for the discovery of noradrenalin and prostaglandins). None of the compounds was considered able to compete with procaine, and the investigations were discontinued.

**Discovery of a Potent Anesthetic, Initially Labeled LL30**

After some years, Löfgren continued the interrupted work. Early in 1943, he gave one compound to his assistant, Bengt Lundqvist (1922–1953), who, in self-experiments, found it was active and had a longer duration of action than procaine. It was originally labeled LL30 after the initials of the two main coworkers. It differed from one of the compounds prepared by Erdtman and Löfgren only by the addition of an extra methyl group in the 6 position of the benzene ring(*76*)."

AMINOSALICYLIC ACID

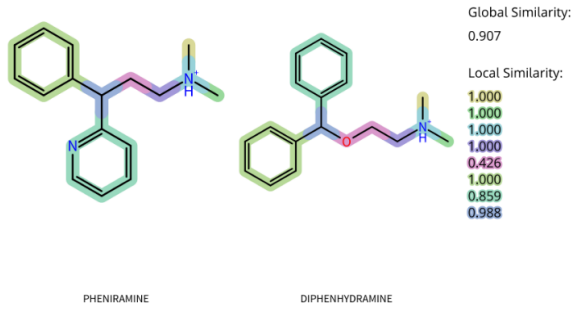
1948

"Because sodium salicylate (o- hydroxybenzoate) and sodium benzoate increased the oxygen uptake of tubercle bacilli, Lehman, a master of competitive inhibition who discovered the antagonism between dicoumarol and vitamin K, postulated that antagonists of salicylate and benzoate should decrease the oxygen uptake and have an antituberculosis activity. Synthesized in 1943 by K.G. Rosdahl in Sweden, PAS demonstrated antituberculosis activity in guinea pigs and in the first 20 patients who received 10– 15 g/day in Sweden(*77*)"

PHENIRAMINE

1948

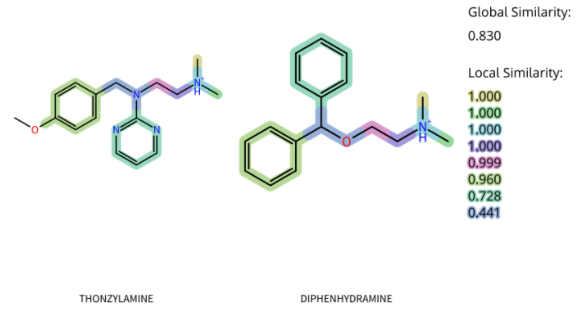
Analogue of diphenhydramine(*21*)




THONZYLAMINE

1948

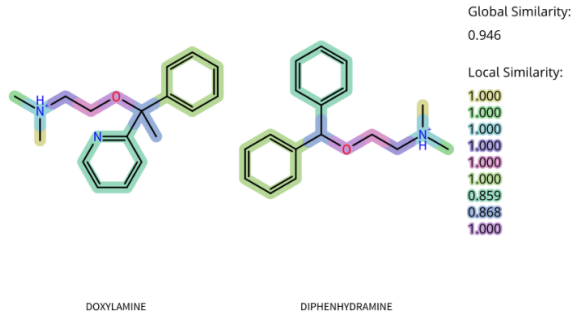
Analogue of diphenhydramine




DOXYLAMINE

1948

Analogue of diphenhydramine(*21*)




POLYSORBATE 80

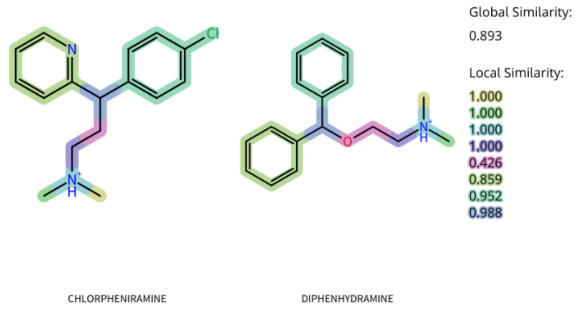
1949

"Polysorbate 80 is a nonionic surfactant and emulsifier often used in foods and cosmetics(*1*)."

## CHLORPHENIRAMINE

1949

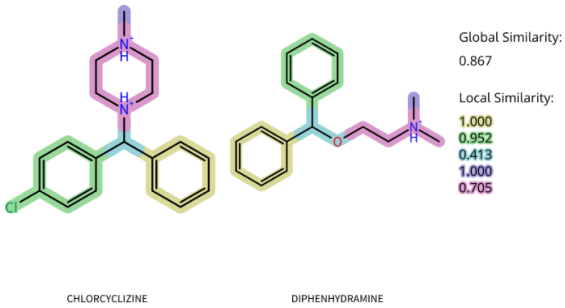
Analogue of diphenhydramine(*21*)




## CHLORCYCLIZINE

1949

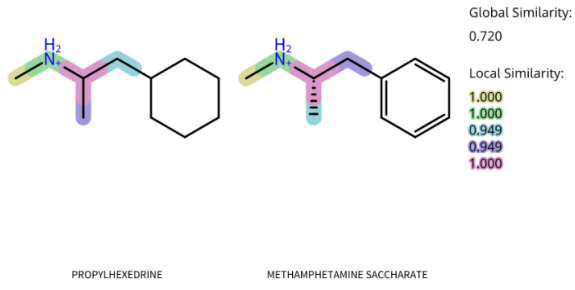
Analogue of diphenhydramine




## PROPYLHEXEDRINE

1949

Analogue of methamphetamine




"Propylhexedrine is a cycloalkylamine structurally similar to methamphetamine, the primary difference being the salicylic cyclohexyl group is present in lieu of an amphetamine's aromatic phenyl group. Like its amphetamine cousins, propylhexedrine is a chiral compound such that two stereoisomers are possible. The levorotatory isomer is the more active releaser of norepinephrine and dopamine in the central nervous system, and currently levopropylhexedrine is in fact synthesized from dextromethamphetamine. The propylhexedrine contained in the Benzedrex inhalers is racemic D, L-propylhexedrine. Though the exact mechanism of action is unknown, propylhexedrine indirectly stimulates an adrenergic receptors of the sympathetic nervous system and exerts a minor stimulant effect on b adrenergic receptors(*78*)."

## MECHLORETHAMINE

1949

"During World War II, naval personnel who were exposed to mustard gas during military action were found to have toxic changes in the bone marrow cells that develop into blood cells. During that same period, the US Army was studying a number of chemicals related to mustard gas to develop more effective agents for war and also develop protective measures. In the course of that work, a compound called nitrogen mustard was studied and found to work against a cancer of the lymph nodes called lymphoma(*79*)."

"Nitrogen mustards were first synthesized in the 1930s. These compounds were modifications of sulfur mustard and were found to have greater systemic toxicity than sulfur mustard. Particularly potent was the effect of nitrogen mustard on cells that are actively proliferating, including the lymphoid tissue, bone marrow, and certain cells lining the gastrointestinal tract. During WWII, the Committee on the Treatment of Gas Casualties authorized a contract between the Office of Scientific Research and Development and Yale University. Under this contract, Louis C. Goodman headed a group that was responsible for the study of the pharmacologic effects

of nitrogen mustards. The group, including Alfred Gilman, Frederick Philips, and Roberta Allen, focused its efforts on the study of the cytotoxic properties of nitrogen mustard. Enlisting the help of anatomist Thomas Dougherty, the group expanded its work to examine the effect of nitrogen mustard on experimental tumor cells in mice. It was found, but not published until later, that systemic administration of nitrogen mustard caused dramatic regression of these mouse tumors. These data formed the experimental basis of the first clinical trials of nitrogen mustard as a cancer chemotherapy agent(*80*)."

## CROTAMITON

1949

"Domenjoz reported on the parasiticidal action of a new synthetic compound, N-ethyl-o-crotono-toluidide. The antiparasitic action of this chemical was discovered during a systematic investigation of more than 1100 newly synthesized compounds which were initially tested on *Psoroptes cuniculi*, the cause of scabies in rabbits. […]

In the original investigations of Domenjoz and his associates, N-ethyl-o-crotono-toluidide proved to be relatively nontoxic and nonirritating to rabbits, guinea pigs, rats, and mice, with similar results later in man. […]

The scabicidal action of N-ethyl-o-crotono-toluidide was demonstrated by its lethal action in concentrations of 5 and 10 per cent on *Psoroptes cuniculi* within 10 minutes after exposure, while a 2 per cent concentration killed this organism in 10 to 30 minutes. Comparative studies with other scabicides, including benzyl benzoate, showed N-ethyl-o-crotono-toluidide to be superior to these in its lethal action on *Psoroptes cuniculi*. Studies on the bacteriostatic effect of this substance on staphylococci and streptococci shows it to be definitely inhibitory to the growth of these microorganisms, but not to E. coli(*81*)."

I could not find the discovery paper: PMID: 20296711

## DICYLOMINE HYDROCHLORIDE

1950

"Dicyclomine was evaluated and compared with atropine for its effect on dose-response curves of ACh, bradykinin, and histamine which were obtained by the cumulative dose-response technique in the isolated guinea-pig ileum(*82*)."

From the earliest paper reporting the antispasmodic activity of the structure:

"In the search for new compounds having antispasmodic and antihistamine activity, a series of aminoesters of substituted cycloalkanecarboxylic acids was investigated. The substituents attached to the ring were aryl, aralkyl, and cyclo-alkyl. All of these aminoesters are new compounds except β-diethylaminoethyl 1-pheriylcyclohexanecarboxylate which has been reported recently. […]

The pharmacological activities of the compounds of this study are listed in Table I. The most active compounds are 1-substituted cyclo- alkanecarboxylates having 4-6 carbon atoms in the alicyclic ring. Further substitution by a methyl group in the 2-position decreases activity; however, a methyl group in the 3-position of the cyclobutane derivative enhances activity(*83*)."

The reported activity indexes in Table I(*83*):

- ✓ "Dilutions in million parts of water that gave a minimal but definite relaxation of the normal isolated rabbit jejunum."
- ✓ "Dilutions in million parts of water that gave complete relief of spasm on isolated rabbit jejunum induced by a 1 to 1 million concentration of acetyl choline."
- ✓ Dilutions in million parts of water that gave complete relief of spasm on isolated

rabbit jejunum caused by a 1 to 10 thousand concentration of barium chloride.

- ✓ Minimal dose of test compound necessary to antagonize 0.1 γ/cc. of histamine diphosphate on isolated guinea pig intestine.

## SODIUM COPPER CHLOROPHYLLIN

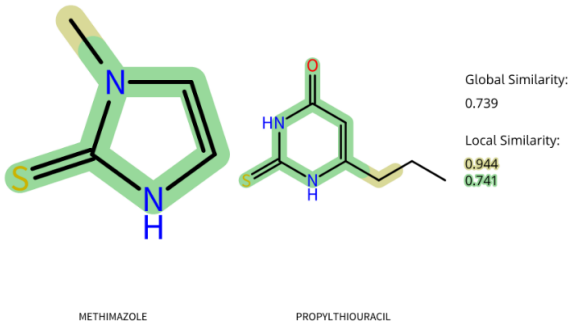
1950

"Chlorophyllin is a water soluble derivative of chlorophyll. It has chemopreventive properties and forms a non-covalent complex with many mutagenic/carcinogenic molecules(*1*)."

## METHIMAZOLE

1950

Analogue of propylthiouracil




## SULFASALAZINE

1950

From the discoverer(s)(*84*):

"For about four years I have been engaged in experiments on the treatment of rheumatic polyarthritis with combinations of sulfanilamide and salicyl preparations. As I have several times pointed out, the earlier known sulfanilamide preparations are active in the so-called septic forms of arthritis, but not in the common rheumatic forms.

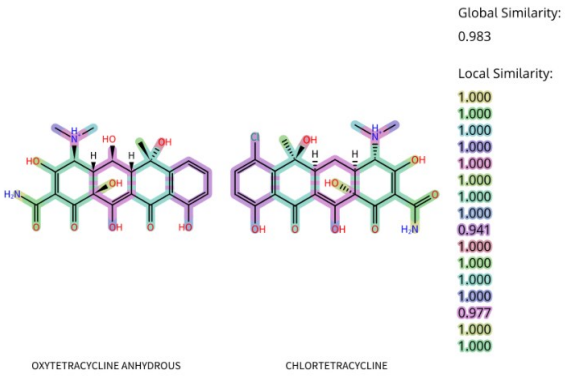
At first my experiments concerned the question of whether medication with both salicyl and sulfanilamide preparations at the same time affects rheumatic polyarthritis. These experiments yielded no tangible results, however.

The nest phase in the series of investigations consisted of attempts to produce chemical compounds between salicyl preparations on the one hand and sulfanilamide or sulfapyridine on the other. These experiments were first conducted by the writer alone, but later in collaboration with A. B. Pharmacia, where the chemists, Civil Engineer E. Askelof and Dr. Phil. H. Willstaedt produced different combinations of salicyl and sulfanilamide preparations for the later investigations. One of these preparations, *salicylazosulfapyridine* or acidum p- (benzolsulfonyl-[amino- a-pyridine1)-azo-salicylicum, was found to possess remarkable qualities. It is now in the market under the name *salazopyrin*(*85*)."

## OXYTETRACYCLINE

1950

Analogue of chlortetracycline




## CHLORAMPHENICOL

1950

From the discovery paper(*86*):

"From a soil sample collected in a mulched field near Caracas, Venezuela, a *Streptomyces* sp. was isolated. Agar streak cultures were found to inhibit adjacent inocula of *Bacillus mycoides*, *B. subtilis*, *Mycobacterium tulerculosis* var. *hominis* (ATCC 607 and H37Rv), *Staphylococcus aureus*,

*Streptococcus*, *pyogenes, Brucella abortus*, *Escherichia coli*, *Klebsiella pneumoniae, Salmonella schottmuelleri*, and *Shigella paradysenteriae* (Sonne). When the organism was grown in liquid media in shaken flasks, filtrates of these submerged aerated cultures proved to possess marked antibacterial activity in broth-dilution assays against several gram-negative bacteria, notably *S. paradysenteriae* (Sonne), and indications of antirickettsial activity. From these filtrates a crystalline antibiotic has been isolated(*87*)"

ACETAMINOPHEN

1950

"**1. Discovery by error and serendipity**

**1.1 Acetanilide**

In 1884, an important discovery took place in Strasbourg. At that time, the medical clinic of Strasbourg was headed by the famous professor Adolf Kussmaul. Two young assistants, A. Cahn and P. Hepp, asked his advice on how to treat a patient who suffered from many ailments, among those fever and worm infestation. Kussmaul suggested to try naphthalene, which had been recommended as an intestinal antiseptic. The two young physicians followed the advice and were disappointed by the result – most ailments remained, including the worms. Much to their surprise, they observed, however, that the fever of the patient fell shortly after the administration of the putative naphthalene. The two physicians wondered why the antipyretic effect had not been described before. Researching the source of the 'naphthalene', they learnt that (the local) pharmacy had provided them with acetanilide instead of naphthalene – an error with long-lasting consequences!

Consequently, Cahn and Hepp tested acetanilide in rabbits and dogs (at that time, an animal ethics request was not needed). They observed reliable but short-lasting antipyretic activity. Both species did not suffer from (visible, acute) toxicity. The young physicians then dared to try acetanilide in 24 patients (certainly without informed consent). They were excited as all of them showed a reduction of fever. […]

**1.2 Phenacetin**

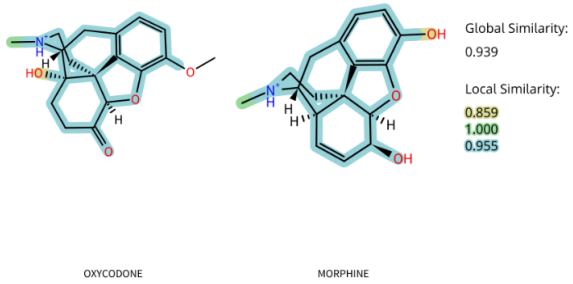
It is to be credited to O. Hinsberg (1913) to have synthesized phenacetin. Together with a pharmacologist from Freiburg, A. Kast, he showed that the new compound worked as acetanilide but was less toxic. […]

Bayer and other companies tried to find more drugs with an even better effect/side-effect profile; one was paracetamol (synthesized by Bayer). From the beginning, it was suspected to be a metabolite of phenacetin(*88*)."

OXYCODONE

1950

Analogue of morphine(*21*)




NOREPINEPHRINE

1950

Analogue of epinephrine

MANNITOL

1950

"Mannitol is an osmotic diuretic that is metabolically inert in humans and occurs naturally, as a sugar or sugar alcohol, in fruits and vegetables. Mannitol elevates blood plasma osmolality, resulting in enhanced flow of water from tissues, including the brain and cerebrospinal fluid, into interstitial fluid and plasma(*2*)."

CORTICOTROPIN

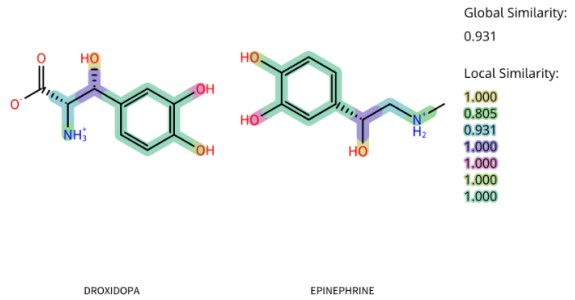
1950

Endogenous-based biopharmaceutical

DROXIDOPA

1950

Analogue of epinephrine




CORTISONE

1950

"During World War II, it was believed that German pilots were enabled to fly at higher altitudes and for longer periods without oxygen supplementation than the Allied airmen because they had been conditioned for higher performance by injections of adrenal extracts. This 'rumour' subsequently proved ill-founded but it did stimulate a massive effort by a consortium of American chemists to synthesise active principles from these glands. The biological test for efficacy was improvement in the work capacity of rats compromised by adrenalectomy. The principle active steroid in this bioassay was cortisone, 17α21-dihyroxypregn-4-ene,3,11,20-trione. Paradoxically, this particular hormone is not synthesised by the rat adrenal and it is actually inactive until the 11-keto group is stereospecifically reduced to the 11β-ol, cortisol, (hydrocortisone) *in vivo*.

Cortisol is the principal steroid secreted by the human adrenal cortex: in rats it is corticosterone, 17-desoxycortisol. The first major synthesis of cortisone required desoxycholic acid from ox bile as the starting material and a complex series of reactions to remove the 12-hydroxy group and insert the 11-keto function. The overall yield in this first commercial 30-step synthesis by Merck & Co was approximately 0.2 per cent. However this was sufficient for Hench to initiate clinical trials in 1948 at the Mayo Clinic for treating rheumatoid arthritis. This breakthrough in therapeutics was rapidly recognised in 1950 by the award of the Nobel Prize for Physiology or Medicine to Hench, E.C. Kendall and also T. Reichstein for his pioneering studies of adrenal steroids. […]

Ironically the two primary tests for detecting anti-inflammatory activity in young rats were de facto toxicity studies involving measurements of (i) involution (shrinkage) of the thymus gland, a key component of the immune system; and (ii) reduction of granuloma formation (a type of scar tissue) around implanted foreign objects e.g. small pieces of plastic sponge or even lengths of string! These bioassays were deceptively simple and only involved weighing the thymus or implanted tissue from groups of untreated animals, for comparison with the reduced thymus mass or granulomae in steroid-dosed rats(*89*)."

But how adrenal gland extracts were discovered to have therapeutic effects on rheumatism?

From 1949 article of two of the discoverers, Philip Hench and Edward Kendall:

"Since 1929 one of us (Hench, 1933, 1934, 1935, 1938a, b, c, 1940, 1949) has studied the beneficial effects of pregnancy and jaundice on rheumatoid arthritis. Results of these and other studies led us to the following conclusions. Even though the pathologic anatomy of rheumatoid arthritis is more or less irreversible, the pathologic physiology of the disease is potentially reversible, sometimes dramatically so. Within every rheumatoid patient corrective forces lie dormant, awaiting proper stimulation. Therefore, the disease is not necessarily a relentless condition for which no satisfactory method of control

should be expected. The inherent reversibility of rheumatoid arthritis is activated more effectively by the intercurrence of jaundice or pregnancy than by any other condition or agent thus far known. Regardless of the supposed 'validity' of the microbic theory, rheumatoid arthritis can be profoundly influenced by phenomena which are primarily biochemical.

It became increasingly difficult to harmonize the microbic theory of the origin of rheumatoid arthritis with the phenomenon of relief of the disease by jaundice or pregnancy. It became easier, rather, to consider that rheumatoid arthritis may represent, not a microbic disease, but some basic biochemical disturbance which is transiently corrected by some incidental biologic change common to a number of apparently unrelated events. It seemed logical to suppose that what causes relief of rheumatoid arthritis in pregnancy is closely related to, if not identical with, that which relieves the same disease in jaundice; if so, it could be neither hyperbilirubinaemia nor a unisexual (female) hormone since neither of these is common to both pregnancy and jaundice. It was believed that the discovery of some biochemical denominator common to various agents or states beneficial in rheumatoid arthritis, but common especially to jaundice and pregnancy, would provide us with an improved treatment or control of the disease.

Finally, it was conjectured that the hypothetic common denominator or 'antirheumatic substance X' was not a disintegration product from a damaged liver, but probably was a biologic compound specific in nature and function, a compound which was normal to the human organism (Hench, 1935, 1949). But if this was true, we had no certain clue as to its chemical nature or the organ of its origin.

In an attempt to reproduce the effects of jaundice or pregnancy we and others used more or less empirically, many agents and measures, some related to jaundice, some to pregnancy. These included the transfusion of blood from jaundiced or pregnant donors, the administration of female hormones and various biliary products, the production of experimental hyperbilirubinaemia and of induced jaundice by means of toluylene diamine, icterogenic serum, or lactophenin. The latter two agents produced articular remissions, but the mechanism of relief was not apparent.

In time we conjectured that the antirheumatic substance X might be an adrenal hormone. This conjecture was strengthened by the knowledge that temporary remissions of rheumatoid arthritis are frequently induced by procedures which are now known to be capable of stimulating the adrenal cortices, such as general anaesthesia or surgical operation. In 1938 we administered to several rheumatoid volunteers lecithin separated from the adrenal gland, not as an adrenal product *per se*, but in an attempt to induce hyperlipaemia such as may occur in association with pregnancy and jaundice. In January 1941 we recorded our interest in adrenal cortical fractions in general and in Kendall's compound E in particular, and we used briefly Kendall's cortical extract(*90*)."

From an earlier paper of one of the discoverers, Philip Hench:

"When patients with rheumatoid (atrophic, chronic infectious) arthritis or with primary fibrositis become definitely jaundiced a notable event usually occurs: their rheumatic symptoms are rapidly, markedly, and generally completely alleviated for some weeks or months. My first observations on this phenomenon were reported in 1933 and later. This phenomenon was unmentioned in the modern literature on rheumatic diseases, but was casually noted by Still in 1897, by Wishart in 1903, and in three recent discussions, not on arthritis but on cinchophen toxicity. More recently further observations on the phenomenon were reported by Sidel and

Abrams (1934), and by Borman (1936)(*91*)."

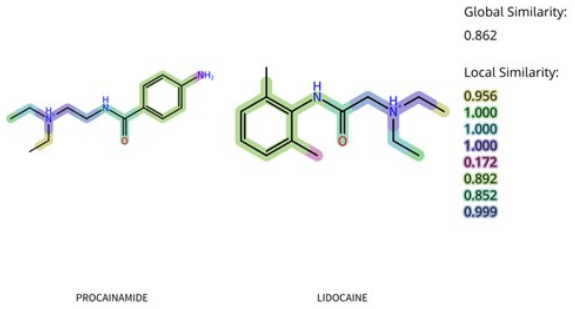
From the earliest article mentioning the relationship, published in 1896:

"Curiously enough, some accidental complications have been followed by marked improvement; thus I have known measles, scarlet fever, and catarrhal jaundice, to be each followed by distinct improvement of the joint symptoms(*92*)."

PROCAINAMIDE

1950

Analogue of lidocaine




SORBITOL

1950

Isomer of mannitol: Only the orientation of the second carbon's hydroxyl is different.

LINDANE

1951

"Benzene hexachloride, more accurately described as hexachlorocyclohexane, was probably first made by Michael Faraday in 1825 by bubbling chlorine through benzene in sunlight, which gave what he described as 'a tenacious triple compound of chlorine, carbon and hydrogen'. […]

Samples of BHC were sent to Hawthorndale in the mid-1930s. The earliest record of any tests on BHC at Jealott's Hill appears to be in an internal report issued in March 1937 which records the results of a test for repellency to clothes moths. This was a multiple-choice type of test, in which the BHC-treated samples of cloth showed no repellent activity as measured by the number of moth eggs laid on the treated samples. It was noted, however, that all the adult moths were killed by exposure to the batch of test substances, any of which could have been responsible in this type of experiment. BHC, sample No. PC 135, next appears in work reported by F J D Thomas and G H Stock.

Issued in July 1942, this report gathers together the results of insecticide screening test on some 75 different chemical samples, as part of a programme seeking possible substitutes for derris, imports, of which were becoming difficult due to war conditions and the Japanese occupation of Malaya. Pesticide chemistry was then in its infancy, and there was a tendency for those at Widnes to regard the pesticide tests at Hawthorndale which no other use could be envisaged. Thomas remembered some of the earlier materials in this context and requested various samples from Widnes; BHC was included in the samples sent because, according to Tanner, 'there was a lot of it in the Widnes store'. Thomas and Stock included in their tests two different samples and five formulations of BHC as dusts or sprays. The test species were various caterpillars and aphids, together with locusts and red spider-mites. They were treated in the laboratory. On small potted plants or on detached shoots or leaves, by dusting with a hand dust-gun or by spraying with a hand-held atomiser spray. BHC killed high proportions of most of the insects in the test, and the report concludes that it 'possesses considerable toxicity to many species of aphids and caterpillars and also to locusts. Against red spider it appears less promising'.

Results of the initial screening tests had been made known to Plant Protection Ltd at Yalding, and a report by Ordish, also issued in July 1942, summarised a series of field experiments in Kent against raspberry beetle (*Byturus tomentosus*) and caterpillars on raspberry and cultivated blackberry, against

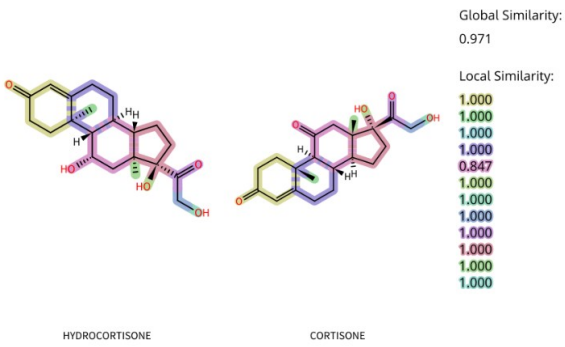
flea beetles (*Phyllotreta* spp) on swedes and turnips and against aphids on hops, which fully confirmed the promise of the laboratory experiments. […]

There is also a US patent filed in July 1933 by H Bender, whose work appears to have been concerned primarily with uses for chlorine. Bender chlorinated benzene in sunlight by adding benzene a little at a time to liquid chlorine, the operation being conducted, in the absence of suitable fume-cupboard space, in the middle of a field. He noted that the white crystalline product of this reaction killed flies and bees when left around exposed, and on this basis claimed insecticidal activity in the patent(*93*).”

## HYDROCORTISONE

1951

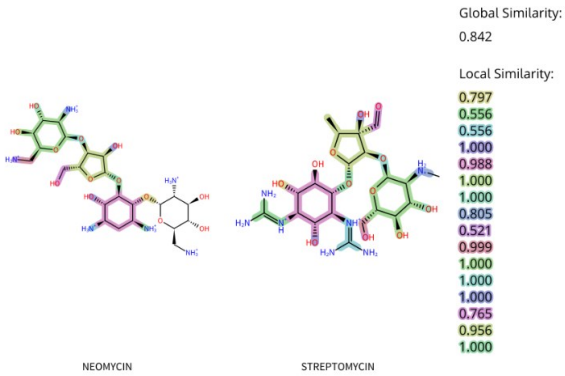
Analogue of cortisone




## NEOMYCIN

1951

Analogue of streptomycin




## PROBENECID

1951

“Probenecid, *p*-(di-*n*-propylsulfamyl)-benzoic acid, was initially known as Benemid (brand name) and was synthesized by Miller et al. (1949). It was first introduced by Beyer et al. in the Federation Proceedings for the explicit purpose of decreasing the renal clearance of penicillin. It was initially studied because of its similarity to drugs that were developed during the second world war including carinamide, diodrast, benzoic acid, sodium benzoate, and para-aminohippuric acid (PAH). These had been proven to increase serum levels of penicillin and para-aminosalicylic acid (PAS), but their clinical application was limited due to undesirable side effects, or the need to be administered via constant intravenous drip or at extremely high oral doses. A lower dose of probenecid was found to be as effective as carinamide and was used as adjunct therapy with penicillin. Subsequent studies revealed that probenecid was also effective in enhancing the retention of other antibiotics as well.

These early studies also led to the serendipitous finding that both carinamide and probenecid enhanced the renal excretion of urate by inhibiting its tubular reabsorption. Clinical studies confirmed probenecid’s effectiveness in decreasing serum uric acid levels and improving symptoms in patients with gout, and quickly became the standard of therapy(*94*).”

## POLYMYXIN B

1951

The first polymyxin antibiotic reported is polymyxin A, reported in 1947(*95*). From the discovery paper of polymyxin A:

“A BACTERIUM isolated from the soil of a market garden in Surrey during February 1946 and afterwards from a Yorkshire soil and from the air has been found to produce an

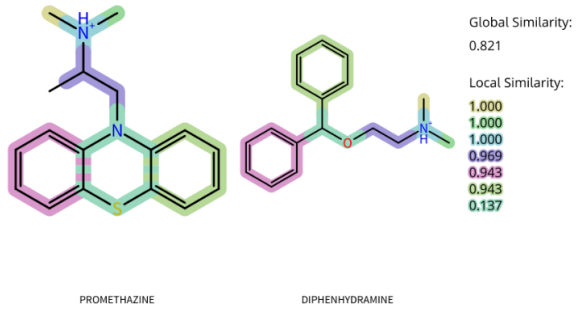
antibiotic of possible therapeutic importance for which, as it appears to be hitherto undescribed, the name 'Aerosporin' is proposed. […]

aerosporin is active against Gram-negative organisms, and the routine method for its assay has been a dilution method using Escherichia coli as the test organism. Two variants of the test have boon used. In one the tests are read after approximately three hours incubation at 37°C.; in the other, after incubation overnight at 28°C(*96*)."

PROMETHAZINE

1951

Analogue of diphenhydramine(*21*)




DISULFIRAM

1951

"The Nobel Laureate Dr. Albert Szent-Gyorgyi stated that '*discovery is said to be an accident meeting a prepared mind.*' The story of disulfiram illustrates the fantastic journey of a molecule from being discovered accidentally, going into obscurity due to lack of indications, bounced back due to the bravado of a few determined researchers and stood the test of time.

The first reports of synthesis of disulfiram as a compound dates back to 1881 when a German Chemist M. Grodzki synthesized it like many of other newer compounds during that time. The then apparently insignificant discovery made it back to the limelight by finding its use in rubber industry in order to hasten vulcanization. It was here that the watchful eyes of E. E. Williams caught the distress among the workers involved in the processing of the substances after ingesting alcohol.

However, the lead character of the disulfiram story was Dr. Erik Jacobsen (1903-1985) who was a Professor of Pharmacology at the University of Copenhagen. In the 1940s, he along with Dr. Jens Hald started working on the copper metabolism of the intestinal parasites, which is the prime metal in the respiratory pigment in the helminthes. They discovered that disulfiram could form chelates with copper leading to the death of the organisms. During these years Dr. Jacobsen assumed the post of head of the Biochemistry Laboratory of a Danish Pharmaceutical Company Medicinal Co. Inc., which took an immediate interest in these results. At that time, courtesy of the damage due to the Second World War, Scabies and intestinal worm infections were major public health problems and thus, disulfiram was rapidly hoisted to the peak of popularity.

Then came the positive results of its vermicidal action in rabbits, and Dr. Jacobsen, with a habit of trying out the new drugs on himself, decided to expose himself to disulfiram. Very quickly, he could realize that 'disulfiram tablets really changed the effect of alcohol in a most unpleasant direction.' When similar results also came from his partner Dr. Hald, they thought of using the substance in treating patients with alcohol use disorder. However, the idea received lukewarm interest because alcohol dependence was not considered to be a big enough problem!(*97*)"

SELENIUM SULFIDE

1951

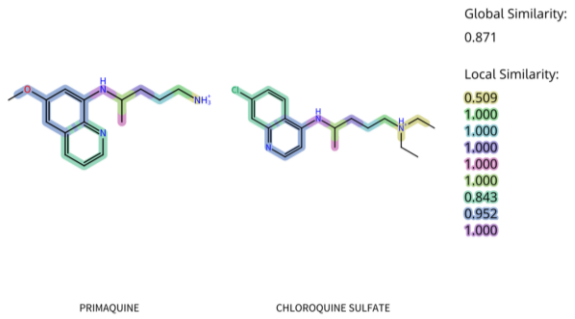
IODIDE ION I-131

1951

PRIMAQUINE

1952

Analogue of chloroquine




ISONIAZID

1952

From the discoverer(s):

"In 1951 it was demonstrated simultaneously and independently in 3 different laboratories that a remarkably simple chemical compound, isoniazid, first synthesized some 40 years previously, had a high degree of antituberculous activity in the test tube and in laboratory animals(*98*)."

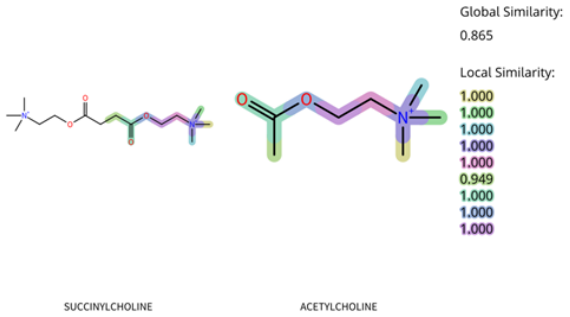
SUCCINYLCHOLINE

1952

"The history of neuromuscular blocking agents starts with curare, a substance which Koelle calls 'a drug with a long and romantic history'. Curare, a complex group of competitive neuromuscular blocking agents, has been used for centuries to kill wild animals by tribes in South America, Borneo, and other aboriginal cultures. It is prepared as a crude extract of one or more of a variety of plants. […]

Curare was known to western medicine in the nineteenth century. […]

Modern clinical use of curare began in 1932, when Ranyard West employed curare-based preparations in the treatment of tetanus and spastic disorders. However, it was the introduction of electric shock therapy (ECT) for the treatment of depressive illness that was to provide the main impetus for curare's widespread use. Indeed, the entire ECT technique would have been abandoned had not an American psychiatrist, Abram Elting Bennett, advanced the idea of using curare to block neuromuscular transmission, thus preventing the disturbing occurrence of fractures and dislocations due to massive contraction of skeletal muscles during treatment(*99*)."




ERYTHROMYCIN

1952

"The first macrolide antibiotic was isolated from a *Streptomyces* strain in 1950 and was named pikromycin due to its bitter taste(*100*)."

From the discovery paper of pikromycin cited in the previous quotation:

"Zur Isolierung des Antibioticums wurde der Stamm 326 im Submers-Ver-fahren mit Glycerin und Glykokoll als Kohlenstoff- bzw. Stickstoff- Quelle kultiviert, wobei die gegen *Staphylococcus aureus* getestete antibiotische Wirksamkeit der Nahrlosung nach 6-8 Tagen ihr Optimum erreichte(*100*)."

Translation from Google Translate:

"To isolate the antibiotic, strain 326 was cultivated in the submerged method with glycerine and glycocoll as a carbon or nitrogen source, the antibiotic effectiveness of the nutrient solution tested against *Staphylococcus aureus* after 6-8 days reached optimum(*100*)."

CYCLOSERINE

1952

"During the laboratory investigation of this drug there developed a discrepancy between

its relatively weak *in vitro* antibiotic activity and its virtual ineffectiveness in treatment of induced disease in animals, especially as regards tuberculosis. However, cycloserine has been shown to have rather satisfactory clinical activity in tuberculosis, and in a variety of urinary infections."

From its patent:

"This new antibiotic is formed during the cultivation under controlled conditions of a novel strain of the known species of microorganism, *Streptomyces levendulae.* This strain which we have isolated from soil, and which we designate as culture number 8197-20, appears to be very similar in cultural characteristics to a strain of *S. lavendulae* obtained from Dr. Selman Waksman […]

Cycloserine shows considerable activity against a number of different gram-negative and gram-positive micro-organisms, and notably against the mycobacteria. It is effective in human therapy for bacterial infections and tuberculosis. With certain other microorganisms, such as *Monilia albicans* and *Trichophyton gypseum,* its activity has not yet been proven in therapy. It has unusually low toxicity as an advantageous accompaniment to its generally high activity. For instance, 100 mg. of the crude preparation described in the table below may be injected(*101*)."

## LEVOLEUCOVORIN

1952

Analogue of folic acid and methotrexate(*2*)

See the methotrexate entry.


## PHENTOLAMINE

1952

From the first published report (as sympathicolytic 7337)(*102, 103*):

"The series of aromatic imidazolines which have been investigated for about ten years in our laboratories has offered special possibilities for the systematic variation of pharmacological effects. This is due to the fact that, in this group, substances are found with a specific effect in several directions(*104*)."

Bioassays reported for the series in this paper(*104*):

- ✓ Toxicity (LD50) in Rabbit
- ✓ Spasmolysis histamine test in Guinea pig
- ✓ Protection *in vitro* Schultz-Dale
- ✓ Protection of Guinea pig against anaphylactic death
- ✓ Number of lethal IV histamine doses (20 mg/kg.cc in Guinea pig
- ✓ Comparison of the pressor effect, respiration, and blood pressure of adrenaline and Privine, before and after the test compound
- ✓ "Effect of pretreatment with Priscol and sympathicolytic imidazoline 7337 on the adrenaline effect on blood pressure and the perfusion of different arterial areas on the cat. 1-blood pressure of the carotid artery; 2-perfusion pf the mesenteric artery; 3-perfusion of the renal artery; 4-perfusion of the femoral artery"
- ✓ "action of a series of substances with specific and nonspecific effect on":
  - "perfused isolated blood vessels of the rabbit"
  - "the seminal vesicle and the isolated intestine of the guinea pig"
- ✓ antagonistic effect of different drugs to adrenaline on different test objects:

- "antagonistic effect on isolated pefused hindleg of the rabbit (inhibition of adrenaline contraction)"
- "antagonistic effect on isolated seminal vesicles of the guinea pig"

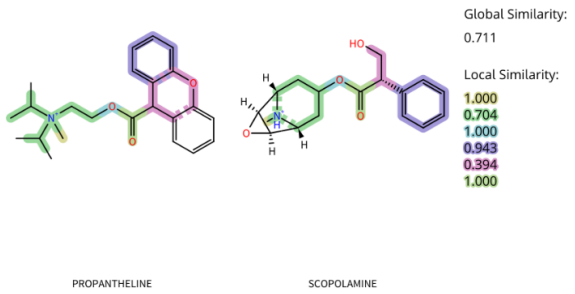
✓ "antagonistic effect of different drugs to histamine on the isolated intestine of the guinea pig"

✓ "antagonistic effect of different drugs to acetylcholine on the isolated intestine of the guinea pig"

PROPANTHELINE

1953

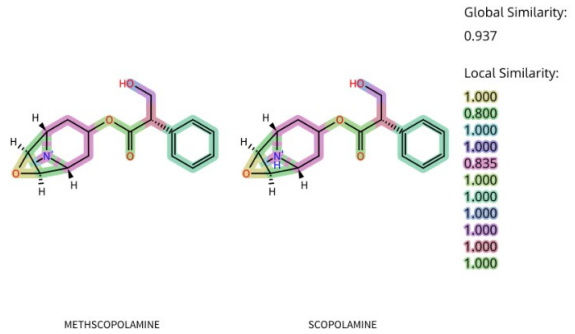
Analogue of scopolamine




METHSCOPOLAMINE

1953

Analogue of scopolamine




NITROFURANTOIN

1953

Not found

PRAMOXINE

1953

From the discovery paper:

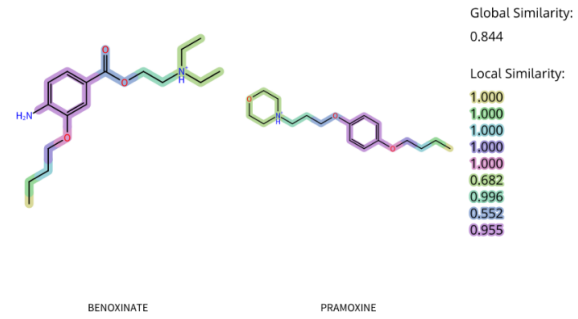
"Sixty-four 4-morpholinylalkyl aryl ethers have been prepared and tested for local anesthetic activity. The method of synthesis has been described in previous papers. The compound 4-n-butoxyphenyl -y-4'-morpholinylpropyl ether seems to combine maximum anesthetic efficiency with minimum toxicity. […]

Replacement of the ethoxy group of compound 3 with methoxy in compound 7 reduced the anesthetic activity but did not change the toxicity. Shifting of the propenyl group from position five to four reduced activity practically to zero (compound 14). In compound 12, the propenyl group has been replaced with allyl and shifted to position four with no change in activity. The 4-phenyl derivative, 9, and the 4-butoxy derivative, 6, seemed to give maximum topical anesthetic activity and minimum toxicity(*105*)."

BENOXINATE

1953

Analogue of pramoxine




ERGOLOIDS

1953

Not found

EDETATE CALCIUM DISODIUM

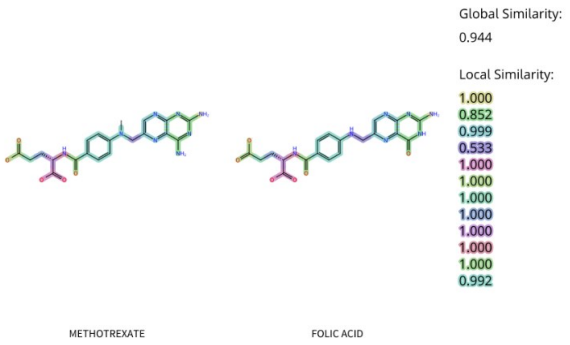
1953

Chelating agent

## METHOTREXATE

1953

Analogue of folic acid

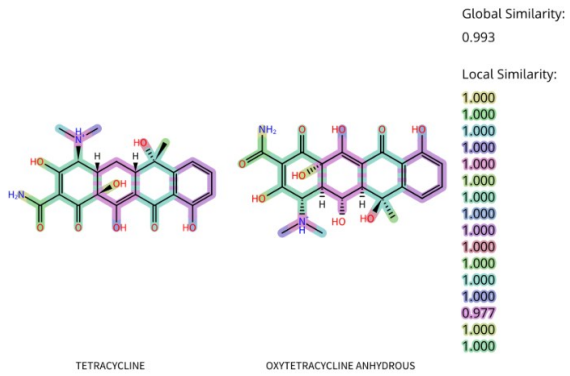



“Sidney Farber, a pathologist at Boston's Children’s Hospital, with an interest in the treatment of childhood leukemia, was aware of a medical tragedy that had occurred in New York. In the early 1940s cancer researchers at Mount Sinai Hospital in New York were involved in an extensive screening program to find compounds that could cause regression of tumors. They were aware of the work of Subbarow on the liver extract that was used for extracting folic acid and purportedly contained folic acid. However, when given intravenously to tumor-carrying mice this preparation inhibited the tumor cells. This observation was perplexing and contrary to the hypothesis that starving the tumor cells for folic acid would lead to suppression of cell growth. The workers were unaware that the preparation that they had given to mice had contained a slightly different compound that was an antagonist of folic acid and led to the deprivation of folic acid for tumor cells, disrupting their DNA synthesis, causing tumor regression. Erroneously they believed that folic acid was the cause of tumor regression. By then, Subbarow at Lederle had already synthesized various forms of folic acid. Farber and colleagues quickly organizsed its clinical trials in patients with advanced cancer and leukemia with the hope of curing them. The results were devastating. There was massively accelerated growth of the tumor cells, a situation that Farber called ‘acceleration phenomenon’. However, Farber converted this tragedy into opportunity by clever thinking. If folic acid caused acceleration of tumor growth, then depriving them of folic acid might arrest their growth, he argued. With much encouragement from Farber, Subbarow and colleagues synthesised two important molecules namely, 4-aminopteroylglutamic acid (aminopterin) and amethopterin that competitively inhibited folic acid synthesis, a key molecule in the synthesis of DNA and RNA. Farber used these compounds successfully in treating childhood leukemia by ‘starving’ them of folic acid and thus disrupting the ‘synthesis phase’ of the rapidly dividing leukemic cells and published this landmark paper in the year 1948, the same year in which Subbarow passed away. This was one of the very first drugs to be developed as a cancer chemotherapy agent. However, the molecule aminopterin was rather unstable and difficult to synthesize. Therefore, its analogue amethopterin became the popular drug in clinical medicine. It was later re-named methotrexate(*106*).”

## TETRACYCLINE

1953

Analogue of oxytetracycline(*21*)




## THONZONIUM

1953

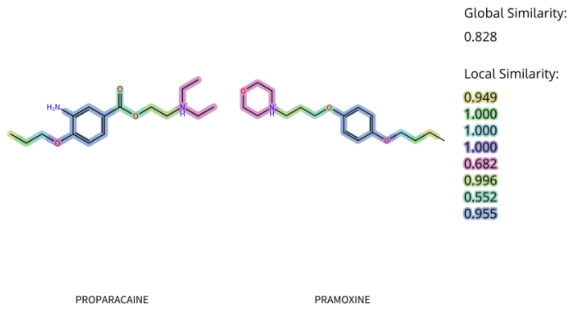
“Thonzonium Bromide is a cationic surface-active compound. As an additive to

pharmacologic formulations, thonzonium bromide causes dispersion and penetration of cellular debris and exudate, thereby promoting tissue contact of the administered medication(*1*).”

## PROPARACAINE

1953

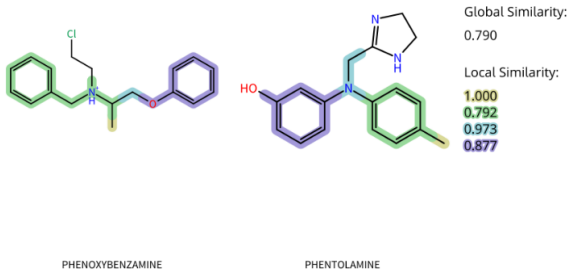
Analogue of pramoxine




## PHENOXYBENZAMINE

1953

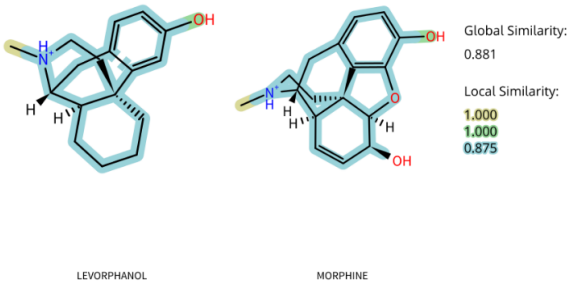
Analogue of phentolamine




## LEVORPHANOL

1953

Analogue of morphine



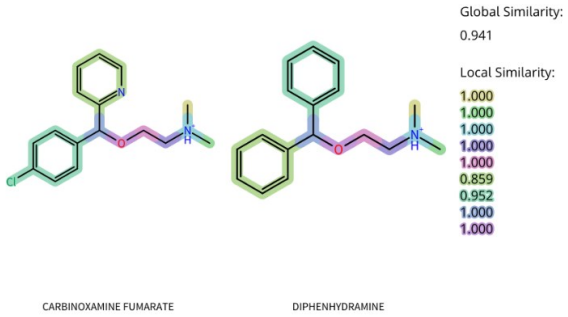

## MONOFLUOROPHOSPHATE ION

1953

## CARBINOXAMINE FUMARATE

1953

Analogue of diphenhydramine(*21*)




## LEVOTHYROXINE

1953

“Levothyroxine (T4) is a synthetically prepared levo isomer of thyroxine, the major hormone secreted from the thyroid gland(*1*).”

“San Si Miao (AD 623–682) from China first administered the organ extracts of deer and sheep thyroid to patients with goiter and observed beneficial effects(*56*).”

From a pioneering article published in 1981:

“MIYXŒDEMA has until recently been considered an incurable disease. Since the pathology of this remarkable condition, however, has become more fully understood, hopes of the possibility of greatly relieving the symptoms, if not of curing the disease entirely, have been entertained. The observations of the symptoms which followed the removal of the thyroid gland in man made by Professor Kocher, of Berne, and the results of the experimental removal of the gland in monkeys obtained by Mr. Victor Horsley have firmly established the view that this disease is due to the loss of function of the thyroid gland. It was found by Dr. von Eiselsberg that if the thyroid gland was successfully transplanted from the neck of an animal to some other part of the body, it was capable of continuing its functions, and so preventing the onset of the symptoms which would otherwise have followed its removal from the

neck. Mr. Horsley then suggested that grafting a healthy sheep's thyroid gland into a patient suffering from myxœdema should be tried as a means of arresting the progress of the disease. This suggestion has since been carried out. Bettencourt and Serrano, of Lisbon, introduced one half of the thyroid gland of a sheep beneath the skin of the inframammary region on each side in a woman of 36, suffering from myxœdema. The operation was followed by an immediate improvement. […] authors considered that as the improvement commenced the day after the operation, it could not be due to the gland becoming vascularised and so functional, but suggested that it was due to the absorption of the juice of the healthy thyroid gland by the tissues of the patient. […]

If we consider that myxœdema and cachexia strumipriva are due to the absence from the body of some substance which is present in the normal thyroid gland, and which is necessary to maintain the body in health, it is at least rational treatment to supply that deficiency as far as possible by injecting the extract of a healthy gland. G. Vessale has made intravenous injections of an extract of the thyroid gland in dogs after thyroidectomy with beneficial results. As far as I am aware this means of treatment has not before been tried in the human subject. Since suggesting this treatment at the February meeting of the Northumberland and Durham Medical Society, I have been able to carry it out in a well-marked case of myxœdema. Such decided improvement has resulted that the details of the method of treatment employed and the results obtained are worth recording(*107*)."

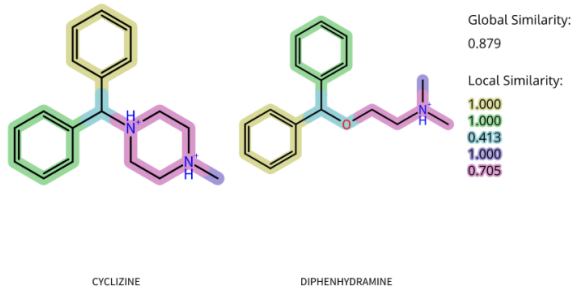
"In 1895 Adolf Magnus-Levy (1865–1955) introduced the experimental method of determining thyroid disturbances. He fed dried animal thyroids to normal men and made the fundamental observation that their metabolic rate was considerably increased. He also produced the first systematic study of the basal metabolism of normal individuals from childhood to old age and established that the function of the thyroid is to maintain the proper level of metabolism. The following year, Eugen Baumann (1846–1896) demonstrated the presence of iodine in an organic compound, which he called "Thyrojodin" (iodothyrin), as a normal constituent of the thyroid. This substance was effective in relieving the symptoms and signs of myxedema in patients with the spontaneous disease and in thyroidectomized animals. […]

Studies on the chemistry of the thyroid gland prompted the extensive biochemical investigations that led to Edwin Calvin Kendall's (1886–1972) isolation of crystalline thyroxine in 1914(*108*)."

## CYCLIZINE

1953

Analogue of diphenhydramine(*109*)




## MERCAPTOPURINE

1953

Discovered in the knowledge-based and systematic search of Hitchings, Elion and their colleagues for drugs against infections and cancers. This search was inspired by the success of sulfonamide antimicrobials and mainly used the inhibition of the growth of bacteria like *Lactobacillus casei* or tumours as the screening assay(*110-112*).

From the discoverer(s):

"In studies of a large number of pyrimidine derivatives, we have found an inhibition of the growth of *Lactobacillus casei* with PGA in the absence of purine to be a property of

nearly all 2,4-diaminopyrimidines and their condensed systems(*110*)"

From the discoverer(s):

"The effects of some of the 6-substituted purine on *Lactobacillus case*; have been reported. While 6-mercaptopurine inhibits growth, 6-methyl- aminopurine can satisfy the purine requirement of this microorganism. The biological activities of these purines on Sarcoma 180 will be reported elsewhere(*111*)."

"SINCE 1942 the relationship between the chemical structure of the purines and pyrimidines and their role in the biosynthesis of nucleic acids has been undergoing systematic examination by Hitchings and co-workers. An experimental screening program for testing compounds for antitumor activity has been in operation for the past seven years at the Sloan-Kettering Institute. Because of the importance of nucleic acids in normal and abnormal cell growth a cooperative project was set up between these two groups. The purposes of this program were two fo1d: (1) to obtain fundamental knowledge of the roles of pyrimidine and purine bases in growth and of the part played by folic acid in the synthesis of these bases and (2) to uncover effective chemotherapeutic agents against neoplastic disease.

Since qualitative differences had been demonstrated in the ability of various bacterial and mammalian tissues to incorporate and utilize preformed purines and pyrimidines, it was postulated that purine and pyrimidine antagonists might prove to be effective chemotherapeutic agents against neoplastic disease because of possible differences in the metabolism of neoplastic and normal tissue."

"The most effective of the purines and pyrimidine derivatives against transplanted mouse tumors thus far uncovered in the experimental tumor screening program is 6-mercaptopurine (6MP). This compound has also been given the proprietary name Purinethol. In microbiologic studies 6MP acts as a purine antagonist in the wild strain of *L. casei*, where its toxicity can be reversed by adenine, guanine, xanthine, or hypoxanthine. The original studies on this compound against Sarcoma 180, reported by Clarke et al., demonstrated that it not only inhibited the growth of this tumor but also caused a significant percentage of the developed tumors to regress permanently(*112*)."

From the discoverer(s):

"It was the microorganism *Lactobacillus casei* upon which we mainly relied. This organism could grow on adenine, guanine, hypoxanthine, or xanthine, provided the pyrmidine thymine was added. It could also synthesize purines and thymine, if given a source of folic acid in the form of liver powder. [The structure of folic acid was not elucidated until 1946 by the Lederle group]. Hitchings and Falco had devised a screening test in which it was possible to determine whether a compound could substitute for thymine or a natural purine or inhibit its utilization, and they could also determine whether a compound was a folic acid antagonist(*113*)."

PYRIMETHAMINE

1953

It was also discovered by Hitchings and his team.

From the discovery paper(*71*):

"It was found by Hitchings, Elion, VanderWerff, and Falco (1948) that many 2: 4-diaminopyrimidines are powerful antagonists of pteroylglutamic acid in cultures of *Lactobacillus casei*. The formal analogy between 2: 4-diamino-5-p-chlorophenoxypyrimi-dine and proguanil ('Paludrine'), and the finding that proguanil was also an antagonist of pteroylglutamic acid, suggested that the pyrimidine compound might have

antimalarial activity.

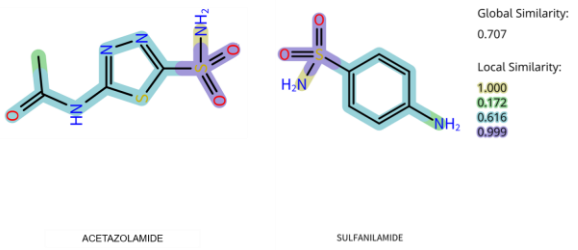
A large number of derivatives of 2: 4-diaminopyrimidine substituted in the 5- and 6-positions has now been prepared and tested against laboratory plasmodial infections. The results obtained upon 158 of these substances are recorded in the present paper.

Preliminary 'screening' tests were carried out against blood-induced infections of *Plasmodium gallinaceum* in chicks and *P. berghei* infections in mice. The more active substances were then assayed against standard antimalarials such as proguanil and quinine. Further tests were carried out with selected compounds against sporozoite-induced infections of *P. gallinaceum* in chicks and against trophozoite and sporozoite infections of *P. cynomolgi* in monkeys.

Acute and chronic toxicity tests and full pharmacological investigations have been made with the more active compounds, and will form the substance of a separate report(*114*)."

ACETAZOLAMIDE

1953




"The era of carbonic anhydrase inhibitors began to emerge in the mid-1930s, when it was discovered that the antimicrobial agent sulfanilamide increased bicarbonate excretion and caused metabolic acidosis. These effects were attributed to inhibition of carbonic anhydrase, an enzyme that was found to be abundant in the kidney. These facts and conceptualizations started a long series of experimental investigations that led to the era of modern oral diuretics. In 1949, for the first time, sulphanilamide was given to a woman with congestive heart failure and edema who was refractory to mercurial diuretics. An unexpectedly high rate of urine excretion was observed. This finding was followed by the synthesis of several sulfonamide derivatives which inhibit carbonic anhydrase, the prototype of which was acetazolamide(*115*)."

HYDRALAZINE

1953

"Originally developed in the 1950s as a malaria treatment, hydralazine showed antihypertensive ability and was soon repurposed(*2*)."

RIBOFLAVIN

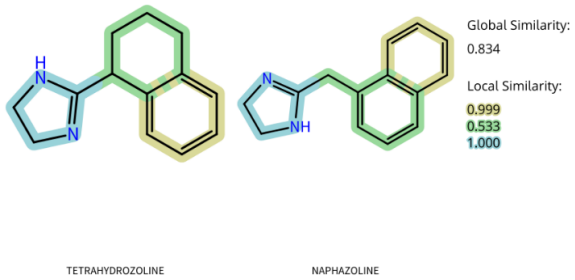
1953

Vitamin $B_2$

TETRAHYDROZOLINE

1954

Analogue of naphazoline




BUSULFAN

1954

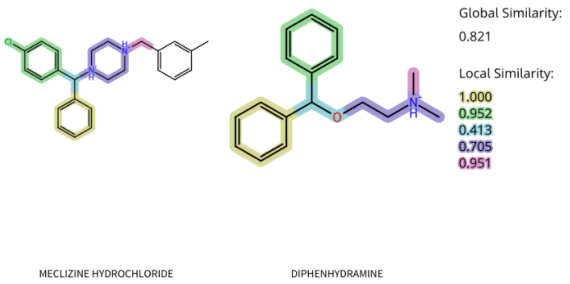
"G.T.41 is a dimesyloxyalkane, its formula being $CH_3OSO_2(CH_2)SO_2OCH_3$. Though the drug is not a nitrogen mustard, its action is similar. The substance is one of a long series of nitrogen mustards and related compounds the biological properties of which have been the subject of experiment for several years. G.T.41 and other associated substances have from time to time been selected for clinical trial by oral administration in cases of advanced malignant disease, since they have an inhibitory action on the growth of certain

tumours. The inhibition is not exerted against the malignant cells specifically, and various normal tissues are also affected(*116*)."

MECLIZINE HYDROCHLORIDE

1954

Analogue of diphenhydramine




DIGOXIN

1954

"**C**ardiac glycosides have played a prominent role in the therapy of congestive heart failure since William Withering codified their use in his classic monograph on the efficacy of the leaves of the common foxglove plant (*Digitalis purpurea*) in 1785(*117*)."

Regarding the monograph of William Withering:

"In 1775, Withering started collecting case histories on the effects of digitalis in dropsy and ascites (accumulation of fluid in the abdomen). But what had led him to start using internal applications of digitalis at a time when it was little used because of reports of toxic effect? Withering himself explained this in his account.

'In the year 1775, my opinion was asked concerning a family receipt for the cure of dropsy. I was told it had long been kept a secret by an old woman in Shropshire, who had sometimes made cures after the more regular practitioners had failed and was informed that the effects produced were violent vomiting and purging; for the diuretic effects seemed to have been overlooked. The medicine was composed of 20 or more different herbs.

He examined the dried leaves microscopically. (His botanical volume contained an account and a picture of the microscope he had designed for the study of botany.) In this way, he noted that the foxglove leaf was present, writing 'It was not very difficult for one conversant in these subjects, to perceive, that the active herb could be no other than the foxglove'(*118*)."

"Ointments containing digitalis are mentioned in the Welsh pharmaceutical book *Meddygon Myddmacn* around 1250, as being good for headaches and spasms. Digitalis pills are described in Hieronymus Bock's Book of herbs (1546). In England, digitalis was recommended by John Parkinson (1567-1650) and William Salmon (1644-1713) for treatment of epilepsy, goitre, and tuberculosis, and as an expectorant and an emetic. Salmon published several works on medicinal plants and in one mentioned digitalis as providing therapy for dropsy, a disease involving a generalized accumulation of fluid now regarded as a symptom of heart failure. It was included in the *Pharmacopoeia Londinensis*(*118*)."

METHOXSALEN

1954

Methoxsalen (Oxsoralen) was isolated in 1947 from the plant *Ammi majus*, bishop's weed, which had traditional use in treating vitiligo(*119, 120*).

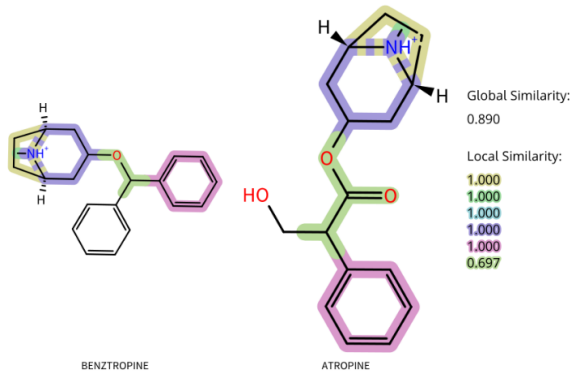
"The use of fruits of *A. majus* in treating vitiligo has a long tradition. Medicinal virtues of this species were known to the ancient Egyptians (and were first mentioned in Ebers' papyrus). Most of the preparations whose photosensitizing properties are currently used in dermatological treatment methods have been developed on the basis of *A. majus*. These are, among others, such preparations as

Meladinine; Oxsoralen; and Ammifurin(*120*)."

## BENZTROPINE

1954

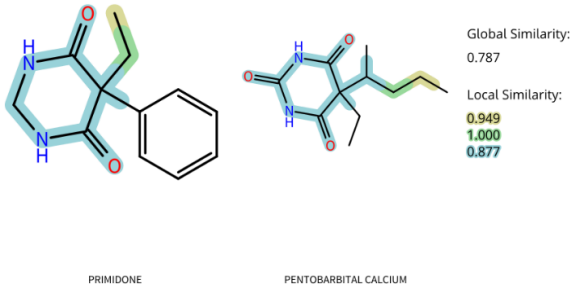
Analogue of atropine




## PRIMIDONE

1954

Analogue of pentobarbital




## WARFARIN

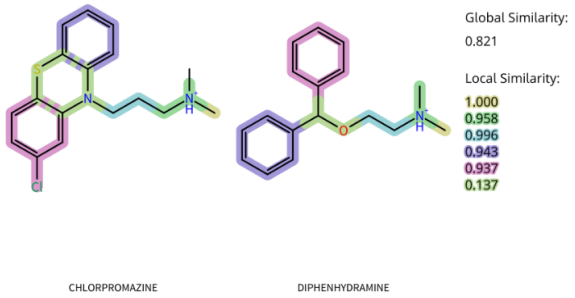
1954

"In the 1920s cattle in the Northern USA and Canada were afflicted by an outbreak of an unusual disease, characterised by fatal bleeding, either spontaneously or from minor injuries. Mouldy silage made from sweet clover (*Melilotus alba* and *M. officinalis*) was implicated, and L M Roderick in North Dakota showed that it contained a haemorrhagic factor that reduced the activity of prothrombin. However, it was not until 1940 that Karl Link and his student Harold Campbell in Wisconsin discovered that the anticoagulant in sweet clover was 3,3′-methylenebis(4-hydroxy coumarin). Further work by Link led in 1948 to the synthesis of warfarin, which was initially approved as a rodenticide in the USA in 1952, and then for human use in 1954. The name warfarin is derived from *WARF* (Wisconsin Alumni Research Foundation) and –*arin* from coumarin(*121*)."

## CHLORPROMAZINE

1954

First synthesized as an analogue of diphenhydramine




In 1951, Henri Laborit, surgeon of a military hospital, had received a newly introduced antihistamine drug, chlorpromazine, that was supposed to potentiate anesthesia and lower body temperature during surgery with the purpose of reducing the shock after surgery. Yet he observed that it caused a calmness and indifference that continued even after surgery. After validating this alongside army psychiatrist on more-agitated patients, he went to Paris and persuaded a psychiatrist to test it intravenously on himself and report its subjective effects. After initially reporting "no effects worthy of mention, save a certain sensation of indifference," the psychiatrist fainted because of the antihypertensive effects of chlorpromazine. Laborit convinced another psychiatrist to test it on their psychotic patients. On January 19, 1952, Jacques, a 24-year-old severely agitated schizophrenic, was given 50 mg chlorpromazine intravenously. The calming effect was immediate. After three weeks of treatment, Jacques was back to normal life. The first antipsychotic was born(*10, 122, 123*).

"The discovery of the first family of antipsychotic agents was made within the context of widespread research on antihistaminic substances in France after World War II, and more specifically in that of the work being carried out on phenothiazines. These substances had been known of since the late nineteenth century, having been used by the dyeing industry. Later, in the early 1930s, they were employed as antiseptics and antihelminthics. Finally, in the second half of the 1940s, their antihistaminic properties were studied, though their toxicities made clinical use impossible. Thus, their application to patients with mental illnesses was never directly sought; rather, as Lickey and Gordon so rightly put it, 'their introduction in therapeutic use is more like the story of a drug in search of an illness.' […]

### *Phenothiazines as Antihistamine and Anti-shock Agents: The Contributions of Henri Laborit*

The early use of phenothiazine compounds as neuroleptic agents resulted from the research of Henri-Marie Laborit. This French army surgeon, working in 1949 at the Hôpital Maritime in Bizerte (Tunisia), was interested in finding a pharmacological method for preventing surgical shock. According to one of the prevailing hypotheses at the time, proposed by Canadian endocrinologist Hans Selye and defended by French surgeon René Leriche, surgical shock was due to an excessive defensive reaction of the organism to stress, so that a peripheral and/or central inhibition of the autonomic nervous system would be a highly advantageous alternative anti-shock therapy. Thus, Laborit studied from 1947 the ganglionic blocking effect of curare, with the aim of achieving chemical sympathectomy. His idea was received with scepticism by the scientific community at the time, though it did prove successful later on, with the incorporation into the anaesthetic techniques of another ganglioplegic substance, tetraethylammonia. Subsequently, Laborit continued to test different substances endowed with inhibitory effects of the visceral vasomotor reactions of the vegetative system – substances that included antihistamines then available. This 'Laborit's idea' was described by Leriche, in 1952, in the preface to a book by Laborit, as 'revolutionary, fascinating and extremely promising.'

Among the antihistamine drugs of the era under study, Laborit found that promethazine, whose capacity for prolonging the sleep induced by barbiturates had been demonstrated in rodents, had acceptable anti-shock activity, so that he added it to another, morphine-type substance, dolantine (Dolosal®), creating the so-called 'lytic cocktail,' a landmark in the history of anaesthesia in that it constituted the origin of neuroleptoanalgesia. This early cocktail was widely used in Tunisian women affected by eclampsia. Laborit himself actually predicted the potential psychiatric implications of these agents, and, recalls, in an interview recounted by Swazey, that 'I asked an army psychiatrist to watch me operate on some of my tense, anxious Mediterranean-type patients. After surgery, he agreed with me that the patients were remarkably calm and relaxed. But I guess he didn't think any more about his observations, as they might apply to psychiatric patients.'

Subsequently, Laborit's cocktail would undergo numerous modifications, including the addition of diethazine (Dip-Dol cocktail, Diparcol-Dolosal), or even, later, chlorpromazine. The Dip-Dol cocktail was introduced by a colleague of Laborit, Pierre Huguenard, anaesthetist at the Hôpital de Vaugirard in Paris, who in a nostril operation on a highly agitated patient, to whom he was unable to apply the ether or chloroform mask, administered diethazine mixed with dolantine. The patient underwent general relaxation while remaining conscious, even being capable of answering questions from hospital staff – a result that some authors described as 'pharmacological lobotomy.' However, despite

the success of the intervention, this cocktail was not applied in psychiatric practice, possibly due to fears that the opiate nature of its formula would create dependence.

### *The Synthesis of Chlorpromazine and Its Initial Clinical Applications*

In the light of these discoveries, Specia Laboratories at Rhône-Poulenc (Vitry-sur-Seine, France), the company that synthesized and commercialized promethazine, undertook to continue the line of research opened up by Laborit and, in 1950, attempted to find a lytic agent that would prevent surgical shock, through depressant actions on the central nervous system. Thus, Simone Courvoiser analyzed all the phenothiazines synthesized by Paul Charpentier since 1944 as antihistaminic agents. Of these, promazine appeared to be the best option, despite its low antihistaminic activity, so that Charpentier synthesized various derivatives of it. A chlorinated derivative (RP-4560), produced in December 1950, displayed, according to Courvoisier's test, extraordinary activity, not only of an antihistaminic nature, but also of a parasympathetic and adrenolytic character, capable of cancelling out, and even of inverting (at higher doses), the effect of adrenalin on blood pressure. Furthermore, it was demonstrated in experiments with rats, such as tests of conditioned avoidance, that RP-4560 was capable of extinguishing conditioned reflexes without modifying the animal's strength. Similarly, RP-4560 was capable of prolonging the sleep induced by barbiturates in rodents and preventing the emesis induced by apomorphine in dogs. Although the pharmacology of the new product was studied by Courvoisier and Pierre Koetschet in 1951, the first data were not published until 1953, after the publication of the first clinical experience with the substance.

The following year, between April and August, RP-4560 was tested by numerous doctors, both French and from other countries. Among those who received samples was Laborit, now working at the Physiology Laboratory of the Val-deGrâce Military Hospital in Paris, and who confirmed that this could be the lityc agent he had been seeking for so long. After the statutory studies with experimental animals, Laborit tried the new drug on patients undergoing surgery, at endovenous doses of 50-100mg. The results as an anaesthetic booster were striking. However, Laborit observed that not only did these patients feel much better during and after the operation, due to the anti-shock action, but they also felt much more relaxed and calm (*désintéressement*) in the pre-operative period, a time associated with intense stress and high levels of anxiety. Another interesting property of the product was its hypothermic effect, which allowed reduction of the body temperature to 28-30º C. This effect, attributed by Laborit to a fall in basal metabolism and oxygen consumption, together with the hypnotic properties of the new drug, allowed Laborit and Huguenard to propose, in 1951, the concept of 'artificial hibernation,' a technique that would make possible greater efficacy of certain types of operation, such as cardiac surgery. Indeed, as Jacobsen relates, the 'artificial hibernation' technique was applied on a large scale by Laborit and Huguenard in 1953 in Vietnam, during the French campaign in IndoChina, and permitted the m to save the lives of hundreds of soldiers. […]

The new drug, described by numerous authors at the time as 'Laborit's drug,' was called chlorpromazine, and was commercialized in France by Rhône-Poulenc in 1952. Its commercial name, Largactil® ('Large' = broad; 'acti*' = activity), was designed to reflect its wide spectrum of pharmacological activities; gangliolytic, adrenolytic, antifibrillatory, antiedema, antipyretic, antishock, anticonvulsant, antiemetic, and so on.

## *PERIOD OF CLINICAL PSYCHIATRIC INTRODUCTION OF CHLORPROMAZINE IN EUROPE (1952-1955)*

Laborit's observations allowed him to hypothesize other therapeutic uses for the new drug, which he called a 'vegetative stabilizer', including in addition to the boosting of anaesthesia, the management of surgical stress, serious burns, cardiovascular disorders and psychiatric disorders. Thus, in November 1951, Laborit and Montassut administered a dose of chlorpromazine intravenously to Cornelia Quarti, a fellow psychiatrist acting as a healthy volunteer at the Villejuif mental hospital. Although there were no effects worthy of mention, save a certain sensation of indifference, on getting up to go to the toilet, Quarti fainted; as a result, the head of the hospital's Psychiatric Service decided to discontinue experimentation with the substance.

In spite of these events, in one of his first publication on the surgical results obtained with RP-4560, in early February of 1952, Laborit argued that the observation made 'may anticipate certain indications for the use of this compound in psychiatry, possibly related to sleep cures with barbiturates.' Thus, during a meal in the canteen at Hôpital Val-de-Grâce, he persuaded his colleagues from the Neuropsychiatry Service, headed by Joseph Hamon, to test the drug in psychotic patients, though, as Swazey recounts, the psychiatrists were not initially enthusiastic about Laborit's proposal. On January 19, 1952, it was administered for the first time, as an adjunct to an opiate (petidine), a barbiturate (pentotal) and electroconvulsive therapy, to Jacques Lh., an extremely agitated manic patient aged 24, who rapidly began to calm down, maintaining a state of calm for several hours. By February 7, Jacques had calmed down sufficiently to be able to play bridge and carry out normal activities, though he maintained certain hypomanic attitudes. Finally, after a 3-week treatment, with a total quantity of 855 mg of RP-4560 administered, the patient was discharged from hospital. Colonel Jean Paraire presented these data on February 25, at a meeting of the *Société Médico-Psychologique in Paris*, and they were published in March of that same year of 1952. In prophetic tone, he said: 'We have quite probably introduced a series of products that will enrich psychiatric therapy'. This event marked the culmination of what may constitute one of the most important landmarks in the history of psychopharmacology, since this was the first time chlorpromazine had been administered in the field of psychiatry(*123*)."

ETHIODIZED OIL

1954

Contrast agent

DIATRIZOATE MEGLUMINE

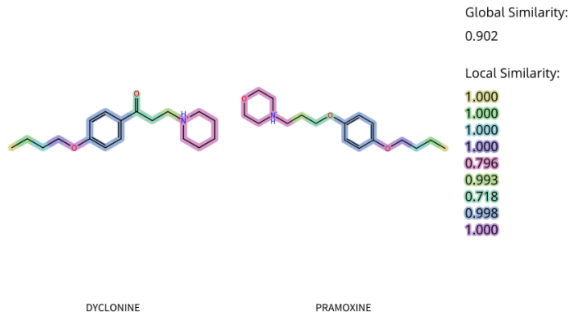
1954

Contrast agent

DYCLONINE

1955

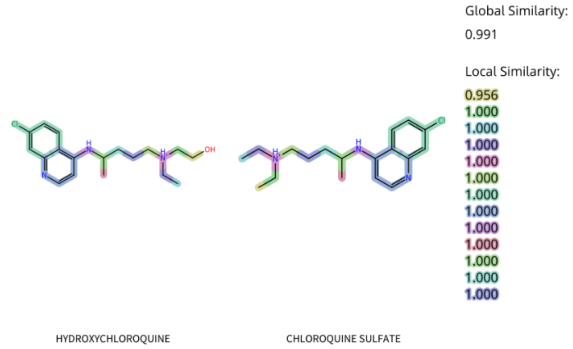
Analogue of pramoxine




HYDROXYCHLOROQUINE

1955

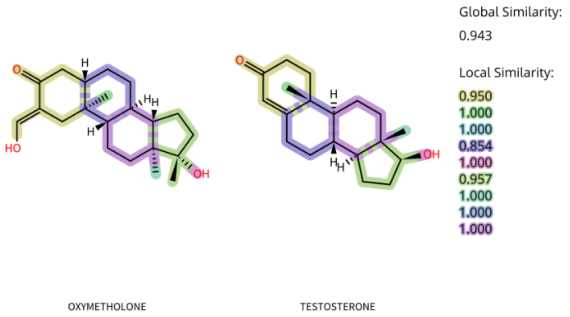
Analogue of chloroquine



## OXYMETHOLONE

1955

Analogue of testosterone(*1*)




## METHYLPHENIDATE

1955

"Methylphenidate was first synthesized from benzyl cyanide and 2-chloropyridine in Basel, Switzerland in 1944 by Ciba chemist Leandro Panizzon. After he synthesized the compound, Panizzon's wife Marguerite, who had low blood pressure, would take methylphenidate as a stimulant before playing tennis. Panizzon named the substance Ritaline after his wife, whose nickname was Rita. […] Methylphenidate was first used to reverse drug-induced coma. Ritalin was approved by the Food and Drug Administration (FDA) in 1955 and introduced in the United States in 1956 for several conditions including depression, senile behavior, lethargy, and narcolepsy.

[…] The use of methylphenidate for treating ADHD is based on work originating in the 1930s that demonstrated amphetamines were eff ective in treating hyperactive and impulsive behavior. Hyperactive children were first treated with stimulants in 1937. Since methylphenidate first appeared on the market, its use for treating ADHD has steadily increased(*124*)."

From the discovery paper of Panizzon:

"Nell'intento di approfondire lo studio di queste sostanze a carattere aromatico-eterociclico, si andò alla ricerca di una reazione che potesse servire come base di partenza per la, preparazione di sostanze presentanti diversi gruppi interesssnti dal punto di vista fisiologico. Una tale reazione la trovammo infine nella condensazione di un nitrile arilacetico con una cloropiridina, il gruppo nitrilico offrendo già di per sè molte possibilità di trasformazione.

In questa prima parte comunichiamo la preparazione dei nitrili misti, la loro trasformazione in amidi ed esteri, e la riduzione del gruppo piridinico a quello piperidinico.

L'esame farmacologico di alcuni derivati qui riportati ha rivelato azioni fisiologiche veramente degne di nota sulle quali sarà comunicato in una prossima pubblicazione(*125*)."

Translation from Google Translate:

"In order to deepen the study of these aromatic-heterocyclic substances, we went in search of a reaction that could serve as a starting point for the preparation of substances presenting different groups of interest from a physiological point of view. We finally found such a reaction in the condensation of an arylacetic nitrile with a chloropyridine, the nitrile group already offering many possibilities of transformation.

In this first part we communicate the preparation of mixed nitriles, their transformation into starches and esters, and the reduction of the pyridine group to the piperidine one.

The pharmacological examination of some derivatives reported here revealed truly noteworthy physiological actions on which will be communicated in a forthcoming publication(*125*)."

From an early paper reporting its pharmacological activities:

"Im Hinblick auf die bisher angenommene Beschränkung der Verknüpfung von zentralerregenden und sympathicomimetischen Eigenschaften auf einige Phenylisopropylamine war es daher von besonderem Interesse,

als bereits vor Jahren in unseren Laboratorien bei der Untersuchung von durch Panizzon hergestellten Piperidinessigsäureestern Verbindungen aufgefunden wurden, die am Tier Wirkungen hervorufen, wie sie bisher nur vom Amphetamin oder ähnlichen Stoffen bekannt waren, sich daneben aber auch in typischer Weise von diesen unterscheiden. [...]

Die *Anregung der Psychomotorik* durch Ritalin ist am nichtnarkotisierten Tier (Maus, Ratte, Kaninchen, Hund) bei parenteraler und peroraler Verabreichung nachweisbar. Neben allgemeiner Unruhe zeigen die Versuchstiere koordinierte Motilitätssteigerung, besonders in Form von Bewegungs- und Laufdrang, und einen Freß- oder Nagetrieb, ohne daß sie gleich-zeitig bissig oder angriffslustig werden. Abhängig von Tier- und Verabreichungsart ist diese zentralerregende Wirkung bei 0,5-1-5 mg/kg nachweisbar, hält mehrere Stunden an und klingt unter Ermüdungserscheinungen ab. Höhere Dosen von Ritalin bewirken ataktischen Gang sowie klonisch-tonische Krämpfe(*126*).”

Translation from Google Translate:

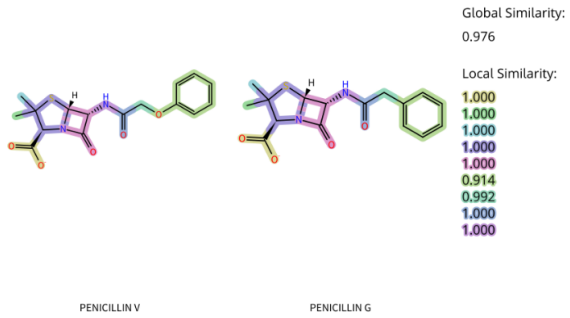
“In view of the previously assumed restriction of the linkage of central excitation and sympathomimetic properties to some phenylisopropylamines, it was of particular interest when, years ago in our laboratories, when investigating piperidine acetic acid esters produced by Panizzon, compounds were found that produce effects on animals, such as they were previously only known from amphetamines or similar substances, but also differ from these in typical ways. [...]

The stimulation of psychomotor functions by Ritalin can be demonstrated in non-anesthetized animals (mouse, rat, rabbit, dog) with parenteral and peroral administration. In addition to general restlessness, the test animals show a coordinated increase in motility, especially in the form of an urge to move and run, and an urge to eat or gnaw, without being biting or aggressive at the same time. Depending on the type of animal and the type of administration, this central stimulating effect is detectable at 0.5-1-5 mg / kg, lasts for several hours and subsides with symptoms of fatigue. Higher doses of Ritalin cause atactic gait and clonic-tonic convulsions(*126*).”

## PENICILLIN V

1955

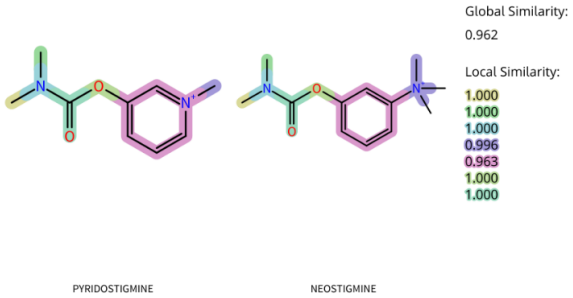
Analogue of penicillin G




## PYRIDOSTIGMINE

1955

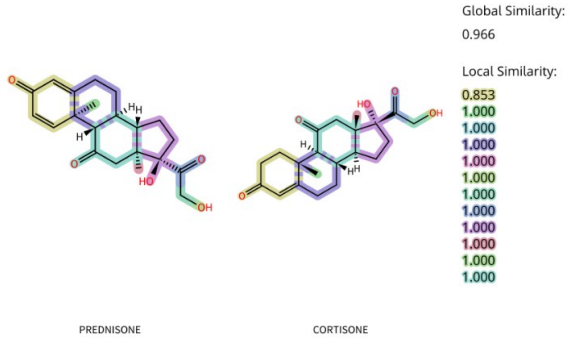
Analogue of neostigmine(*21*)




## PREDNISONE

1955

Analogue of cortisone(*21*)



## MEPROBAMATE

1955

"The synthesis and development of meprobamate began with mephenesin because it was the result of an effort to find a superior compound. Berger and Bradley were a chemist-pharmacologist team that was engaged in the development of a new synthetic antibacterial agent that would be effective in destroying gram-negative bacteria unresponsive to penicillin. There was, at the time, a disinfectant on the market in Great Britain that was believed to be effective in combating gram-negative rods. This compound was phenylglycerol ether called phenoxetol. Bradley believed that lengthening its carbon chain would produce a compound with a definitive desired antibacterial effect. This expectation bore out to a certain extent so Berger decided to determine its toxicity on mice to establish safety. To his surprise, the mice developed a reversible flaccid paralysis of the voluntary skeletal muscles.

In graduated doses, mephenesin produced muscle relaxation and paralysis of all voluntary muscles in mice, rats and other small laboratory animals but remained conscious, responded to painful stimuli and their corneal reflex was preserved. The autonomic nervous system appeared to be unaffected and the recovery from the drug was spontaneous and complete in an hour. Unlike barbiturates, the compound had a quieting effect on the demeanor of animals without a stage of initial excitement. This effect was termed 'tranquilization' by the team in their first publication of this finding in 1946.

Mephenesin was first introduced in clinical practice as an agent for producing muscle relaxation during light anesthesia by Mallison in 1947 as an alternative to tubocurarine. Its anti-anxiety effect was recognized only in brief case reports but its use as such was limited by its three significant drawbacks—a very short duration of action, greater effect on the spinal cord than on supra-spinal structures and a weak action so that large doses were required. Thus an extensive laboratory search began to overcome these disadvantages. Berger and his colleagues felt that understanding the metabolism of mephenesin would help them find ways to alter or delay its rapid breakdown. They found that the short duration of action was due to the rapid oxidation of its primary hydroxyl group so they synthesized various ester derivatives that had a terminal hydroxyl group less susceptible to enzymatic attack. They also tested a number of related compounds in the hope of finding ones with more potent muscle relaxant action and those that would exercise a stronger inter-neuronal blocking action of supra-spinal structures. The latter was measured by the ability of such compounds to counteract pentylenetetrazol-induced convulsions. The tranquilizing effect was measured primarily by the ability of drugs to produce the loss of righting reflex without significant initial excitement and the potency of the drugs was measured by their ability to produce reversible paralysis of voluntary muscles.

This was a tedious process. Finally, in 1951, Ludwig and Piech reported that meprobamate was the compound with the potential to overcome the drawbacks of mephenesin(*127*)."

## DAPSONE

1955

"On 15 June 1908, Eric Fromm and J. Wittmann, chemists at the University of Freiburg, published a paper announcing the synthesis of dapsone. While the pair considered their discovery applicable to the booming German dye industry, neither chemist thought it important enough to take out a patent on the product. They saw their discovery as purely an advance in the field of chemistry and had no reason to look for any clinical significance. For almost three decades thereafter, the therapeutic potential of dapsone lay

unknown and untapped until the rise of sulfa drugs shifted scientific attention toward the medicinal properties of sulfur-containing compounds. The development of antimicrobial sulfa drugs generally and Prontosil specifically in 1935/36 created what historian John Lesch has called 'the first miracle drugs.' These sulfas provided the only broad-spectrum action against bacterial infections. Researchers quickly looked to chemically analogous compounds, like dapsone, as possible additions to this class of medications.

Early animal tests of dapsone showed promising antibacterial potential, but severe hematological side effects appeared to preclude its use in humans. In 1937, G. A. H. Buttle, one of the leading British sulfa researchers, conducted the first trials of DDS in guinea pigs. His laboratory found the drug one hundred to one thousand times more potent than the sulfanilamide Prontosil; however, the new drug was also twenty-five times more toxic, causing anemia and methaemoglobinaemia in his laboratory animals. Other laboratories quickly confirmed Buttle's results, agreeing that DDS had the greatest therapeutic potency of any agent tested, but that its toxicity negated any possibility of using it in humans. Pharmaceutical giant Parke–Davis Company refused to relinquish such a potentially efficacious (and profitable) drug and worked to reduce toxicity by chemically modifying the compound. By 6 August 1937, they succeeded in producing a non-toxic derivative that they called Promin.

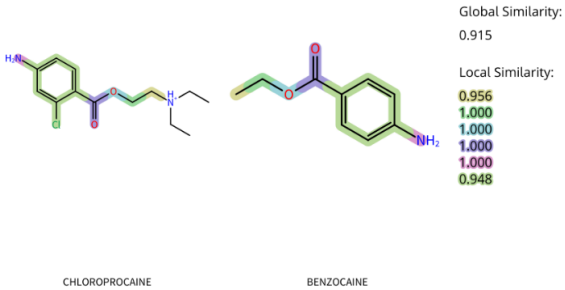
After Promin proved safe, investigators pursued its medicinal possibilities. Encouraged by a 1938 article suggesting the potential for sulfa drugs to fight tuberculosis, three researchers at the Mayo Clinic decided to test Promin against the disease. Given that tuberculosis was the second leading cause of death in the United States in the early twentieth century, this research had substantial societal implications. In Rochester, Minn., William H. Feldman, Corwin H. Hinshaw, and Harold E. Moses administered Promin to tuberculosis-infected guinea pigs; almost half of the experimental animals lived through the trial, whereas none of the control subjects survived. This outcome led to the cautious conclusion: 'the results of this experiment suggest the possible effectiveness of promin in combating tuberculosis in guinea-pigs.' The trio tested Promin in different doses and in different animals over the next four years and consistently remarked on the drug's successful inhibition of tuberculosis with only minimal side effects such as hemolytic anemia. The possibility of a cure for TB generated enough interest and hope to garner an article in the New York Times. Although Promin appeared promising, the new antibiotic streptomycin (1943) quickly eclipsed the sulfa-based drug as the preferred treatment for tuberculosis by the late 1940s. However, physicians continued to investigate the potential of sulfones to cure other diseases. They soon observed the spectacular effects the drug had in reversing the course of one of the world's most notorious afflictions: leprosy. […]

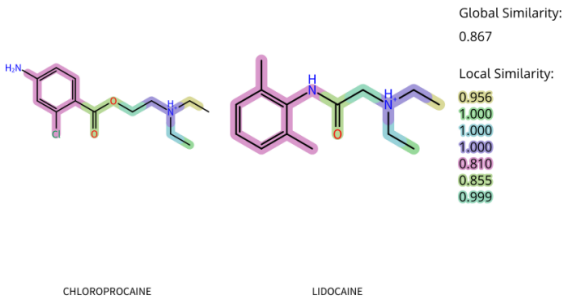
Faget read Feldman and Hinshaw's article regarding the activity of Promin against tuberculosis in 1940 and wrote Parke–Davis to see if anyone had tried the drug against leprosy. Since the bacteria that cause leprosy and tuberculosis belong to the same family and are both acid-fast, it seemed plausible that drugs affecting one disease might also work against the other. Parke–Davis directed Faget to Edmund V. Cowdry, a physician at Washington University in St. Louis who was researching the effect of Promin on rat leprosy. Since the drug appeared to cure the rodents without causing severe side effects, on 10 March 1941, Faget began clinical trials of Promin on human patients in Carville(*128*)."

CHLOROPROCAINE

1955

Analogue of benzocaine and lidocaine

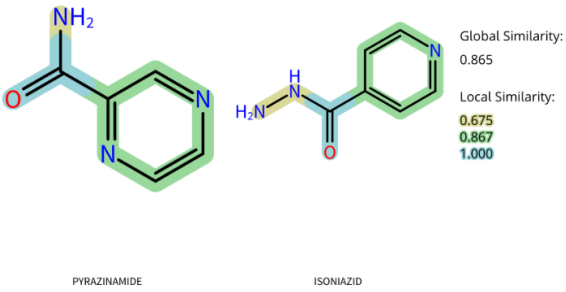



## PYRAZINAMIDE

1955

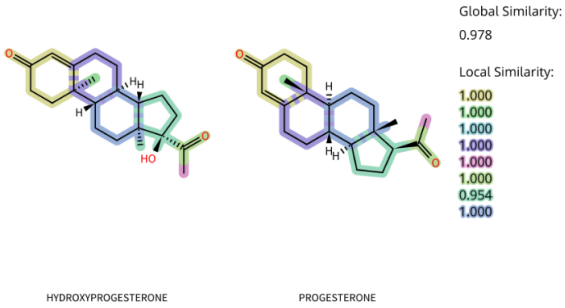
Analogue of isoniazid




## HYDROXYPROGESTERONE

1956

Analogue of progesterone




## MECAMYLAMINE

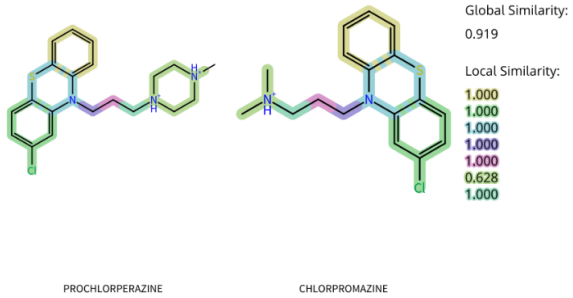
1956

Not found

## PROCHLORPERAZINE

1956

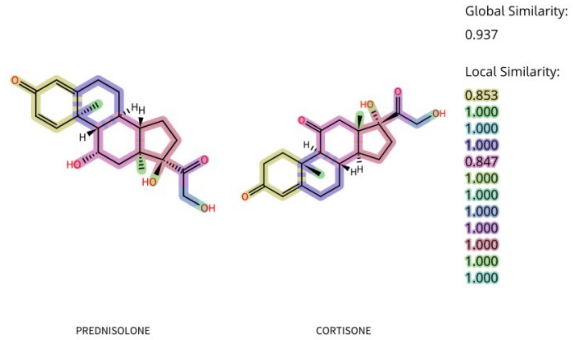
Analogue of chlorpromazine




## PREDNISOLONE

1956

Analogue of cortisone(*21*)




## LIOTHYRONINE

1956

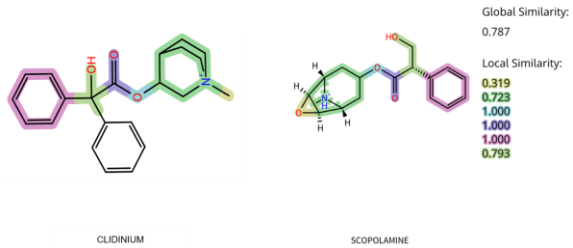
See the levothyroxine entry.

"It was later discovered that the thyroid is able to synthesize a second hormone more active than thyroxine(*108*)."

## CLIDINIUM

1956

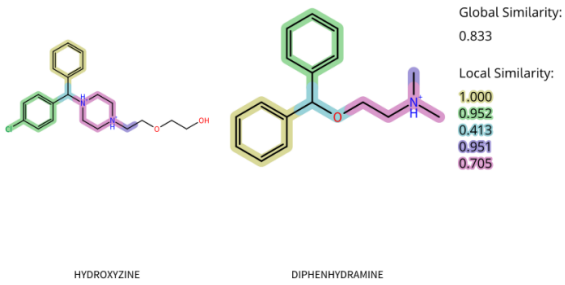
Analogue of scopolamine



## HYDROXYZINE

1956

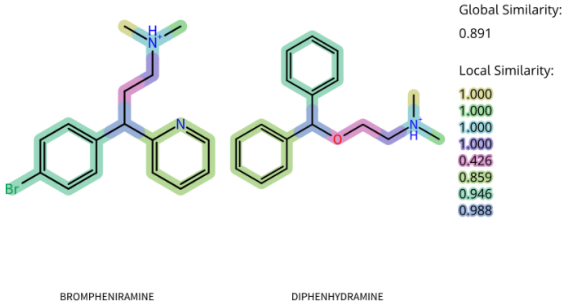
Analogue of diphenhydramine




## BROMPHENIRAMINE

1956

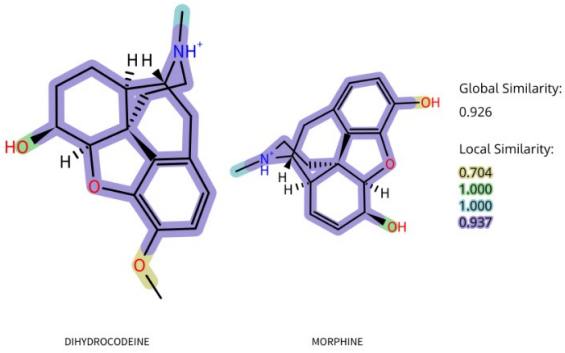
Analogue of diphenhydramine(*21*)




## DIHYDROCODEINE

1956

Analogue of morphine(*21*)




## FLUOXYMESTERONE

1956

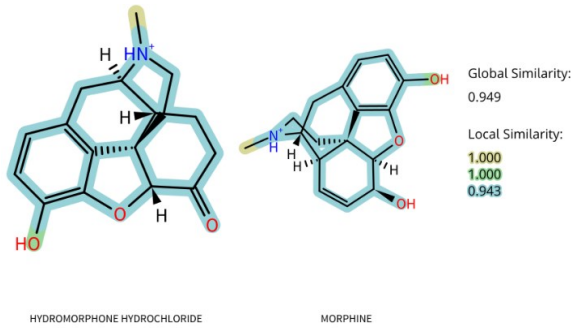
Analogue of testosterone(*2*)

Error in similarity calculation by FTrees

## HYDROMORPHONE HYDROCHLORIDE

1956

Analogue of morphine(*21*)




## TRIAMCINOLONE ACETONIDE

1957

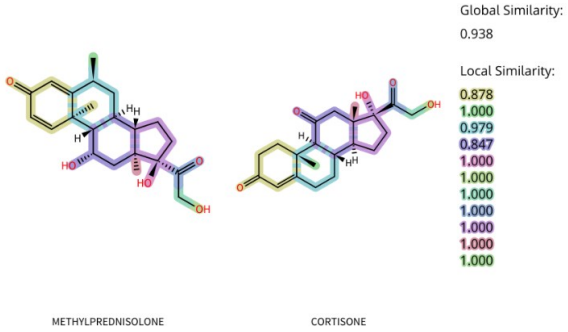
Analogue of cortisone(*21*)

Error in similarity calculation by FTrees

## METHYLPREDNISOLONE

1957

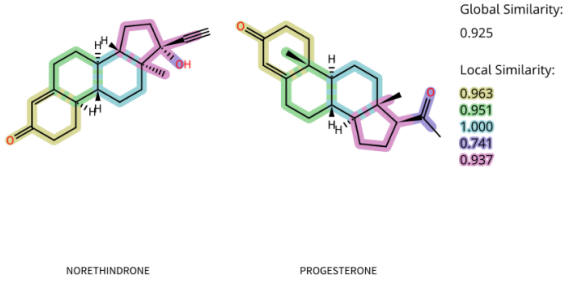
Analogue of cortisone(*21*)




## NORETHINDRONE

1957

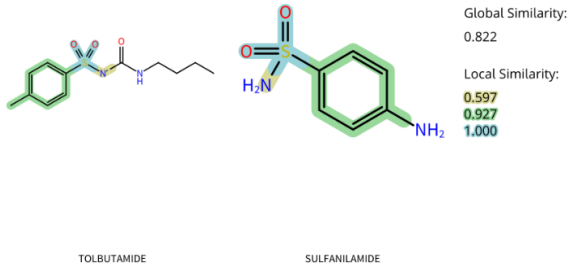
Analogue of progesterone(*2*)



## TOLBUTAMIDE

1957

Analogue of sulfanilamide




Tolbutamide, like carbutamide, is an analogue of the sulfonamide antibacterials whose glycemic effects where observed numerously after the initiation of their prevalent use(*129*).

"Gerhard Domagk had discovered Prontosil in 1932, and from then on sulfa (sulfanilamide) antibiotics flourished. In 1942, France was under Nazi occupation. Janbon, professor of pharmacology at the University of Montpellier, gave a sulfa antibiotic drug to soldiers to alleviate their typhoid fever. Some patients who took this drug felt tired and dizzy, an indication of a drop in blood glucose levels. Three patients subsequently died of hypoglycemia. Janbon infused glucose into some of his patients, who promptly recovered. He made an astute hypothesis that some sulfa antibiotics, namely sulfonylureas, could be used in the treatment of diabetes(*130*)."

"The toxicity of the sulfonamides was studied by a number of investigators in the late 1930's. Even earlier (1930), Ruiz and colleagues in a little-read Argentinian journal, reported several sulfonamide compounds as having a hypoglycemic effect. […]

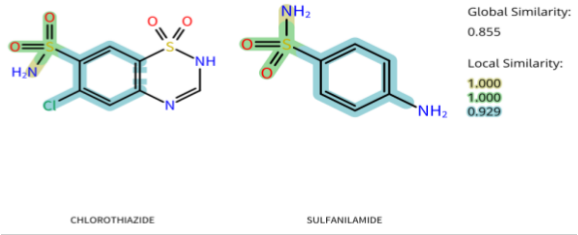
Loubatieres, in studies from 1942 to 1946, also at Montpellier, suggested the use of hypoglyc emic sulfonamides in diabetes and described their mechanism of hypoglycemic action. He also found that some sulfonamides were hypoglycemic some were hyperglycemic and that others had little or no effect on 'blood sugar' levels. […]

Logically, those studies of the sulphonamides causing hypoglycemia were the first to be exploited, resulting eventually during 1954-1957 in highly useful agents in the treatment of diabetes after earlier agents had been found too toxic. Tolbutamide and chlorpropamide are representatives of this class(*129*)."

## CHLOROTHIAZIDE

1957

Analogue of sulfanilamide




See the acetazolamide entry.

"The decisive breakthrough to the new-type diuretics was achieved by structural variations of sulfanilamide and by the introduction of a chlorine atom in the ortho position of the sulfonamide structure, whereby the inhibition of carbonic anhydrase was still present, although less prominent. The carbonic anhydrase inhibitory activity of the new diuretic chlorothiazide (6-chloro-7-sulfamoyl-2*H*-l,2,4-benzothiadiazine 1,1-dioxide) was only about l00th that of acetazolamide; however, chlorothiazide produced a remarkable sodium and chloride excretion with relatively little bicarbonate output(*115*)."

## METHSUXIMIDE

1957

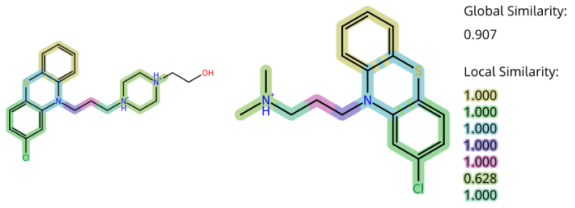
"The discovery of ethosuximide was the result of a systematic search for new antiepileptic drugs. Because trimethadione has a marked ability to protect experimental animals against pentylenetetrazol-induced

seizures and is specifically effective against absence seizures, the subcutaneous pentylenetetrazol seizure threshold has become a popular test for screening new compounds for potential usefulness in the treatment of absence seizures. The search for structurally related anti-pentylenetetrazol agents that were less toxic than trimethadione and paramethadione led to the investigation of the succinimides: first phensuximide, then methsuximide, and finally ethosuximide. Of these, ethosuximide had the greatest anti-pentylenetetrazol action and turned out to be the most selective for absence seizures(*131*)."

## PERPHENAZINE

1957

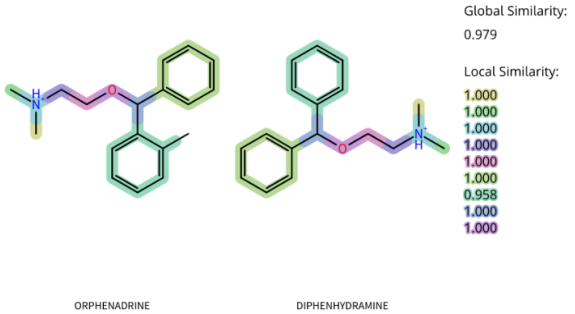
Analogue of chlorpromazine




## ORPHENADRINE

1957

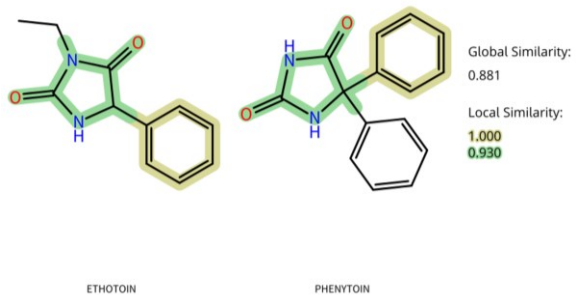
Analogue of diphenhydramine(*109*)




## ETHOTOIN

1957

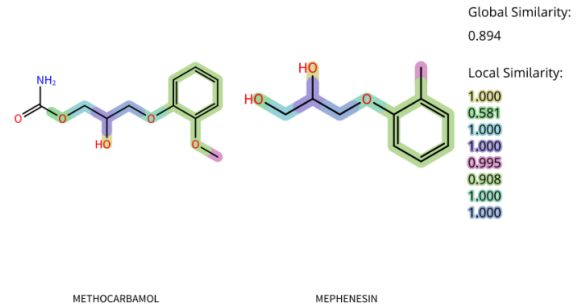
Analogue of phenytoin




## METHOCARBAMOL

1957

Analogue of mephenesin(*132*)




Mephenesin had been previously discovered serendipitously(*127*). See the meprobamate entry.

From the discovery paper:

"Mephenesin monocarbamate is reported to show the same pharmacological activities as mephenesin itself and sometimes slightly prolongs the duration of the action. The fact was examined together with the syntheses and examination of pharmacological activities of mephenesin carbanilate and the carbamates and carbanilates of 3-(o-methoxyphenoxy) propane-1, 2-diol (I) and 3-(1, 2, 3, 4-tetrahydro-7-naphthyloxy) propane-1, 2-diol (II). The muscle relaxing action of these compounds is weaker than that of mephenesin but the monocarbamate of (II) showed stronger anticonvulsant action against pentetrazol than mephenesin, and about equal anticonvulsant action against electric shock as mephenesin. The safety margin, $LD_{50}/MED_{50}$ and $LD_{50}/EED_{50}$, of these compounds was greater than that of mephenesin. The

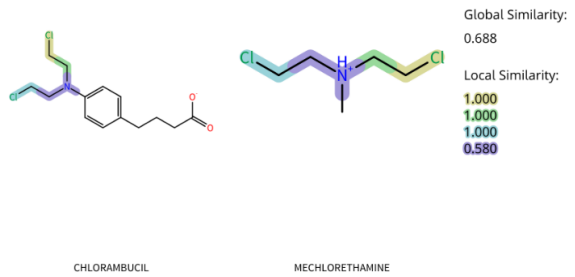
monocarbamates of both (I) and (II) showed longer duration of action than mephenesin in paralysis and protection against electric shock seizure(*132*).”

The tests were performed on mice(*132*).

## CHLORAMBUCIL

1957

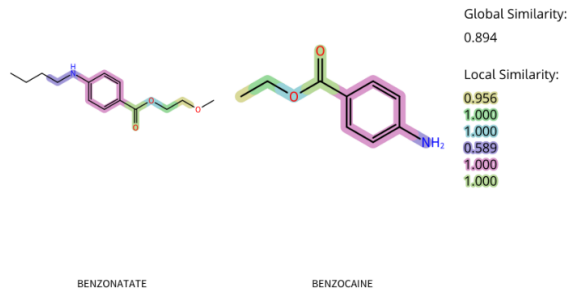
Analogue of mechlorethamine




## BENZONATATE

1958

Analogue of benzocaine




## AMPHOTERICIN B

1958

Analogue of nystatin(*21*)

Error in similarity calculation by FTrees because of the unsupported macrocycle

“The broad screening of Streptomycete cultures for antifungal activity was therefore continued. In January of 1953, culture M 4575, an isolate from soil obtained in the Orinoco basin in Venezuela, was ‘fermented’ and found to produce considerable antifungal activity. Concentration and partial chemical purification of the active material permitted preliminary characterization. Although the antifungal spectrum and general chemical properties of this concentrate were similar to those of nystatin, several pronounced differences were apparent. The bioassays showed that this substance, even though only partially pure, was much more active *in vitro* than was pure nystatin(*133*).”

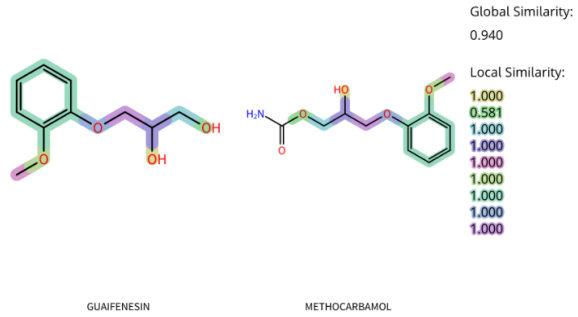
Discovery of nystatin:

“Hazen, a bacteriologist, and Brown, a chemist, as a team were able to identify, characterize, and purify nystatin following its detection in cultures of *Streptomyces noursei* (named after William Nourse, the farm’s owner) near the barn of a dairy farm in Fauquier County, Virginia. The screening of soil samples for antifungal actinomycetes was conducted by a selective plating technique in which *C. albicans* and *C. neoformans* served as the screen fungi. Brown and Hazen also demonstrated the in vitro and in vivo activity of nystatin in laboratory (experimental) animal studies(*134*).”

## GUAIFENESIN

1958

Analogue of methocarbamol




## VANCOMYCIN

1958

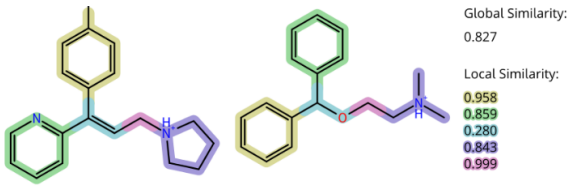
“In the 1950s, with few options available to treat penicillin-resistant staphylococcal infections, Eli Lilly and Company initiated a program aimed at discovering antibiotics with activity against these pathogens. In 1952, a missionary in Borneo sent a sample of dirt to his friend Dr. E. C. Kornfield, an

organic chemist at Eli Lilly. An organism isolated from that sample (*Streptomyces orientalis*) produced a substance ('compound 05865') that was active against most gram-positive organisms, including penicillin-resistant staphylococci. Some anaerobic organisms, including clostridia, were also susceptible to compound 05865, as was *Neisseria gonorrhoeae*. In vitro experiments were initiated to determine whether the activity of compound 05865 would be preserved despite attempts to induce resistance. After 20 serial passages of staphylococci from Eli Lilly laboratories, resistance to penicillin increased 100,000-fold, compared with only a 4–8-fold increase in resistance to compound 05865(*135*)."

## TRIPROLIDINE

1958

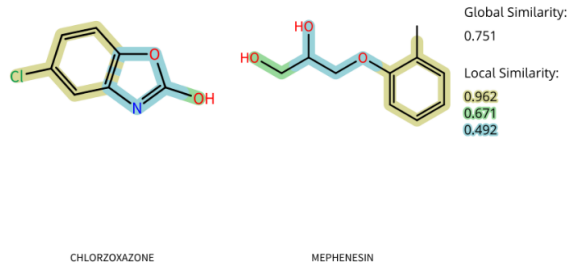
Analogue of diphenhydramine(*21*)




## CHLORZOXAZONE

1958

Analogue of mephenesin




## DEXCHLORPHENIRAMINE

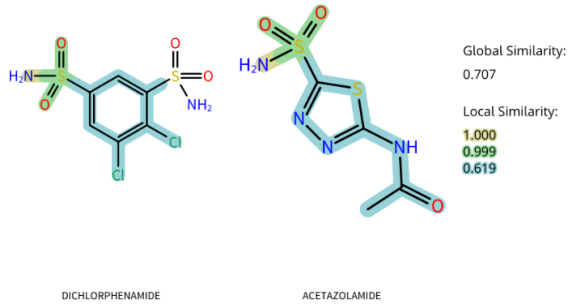
1958

Enantiopure chlorpheniramine

## DICHLORPHENAMIDE

1958

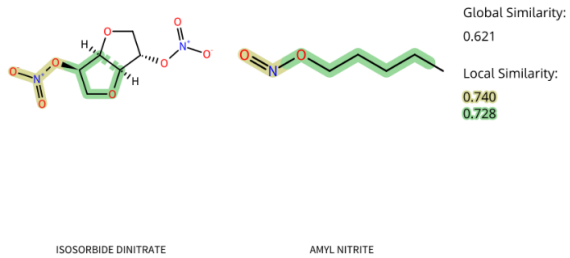
Analogue of acetazolamide




## ISOSORBIDE DINITRATE

1959

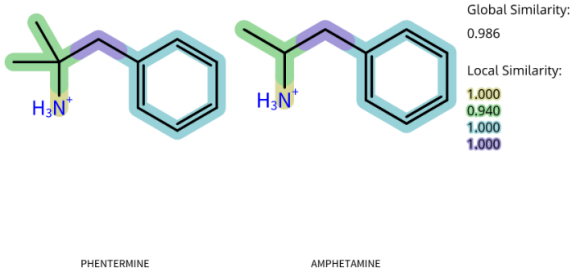
Analogue of isoamyl nitrite(*21*)




## PHENTERMINE

1959

Analogue of amphetamine




## THIOTEPA

1959

"Molecules that bore structural resemblance to the mustards were explored. Triethylenemelamine (TEM) was one such compound. It contains aziridine groups, structures similar to the 3 membered rings that HN2 and HN3 display when they react. Two or more

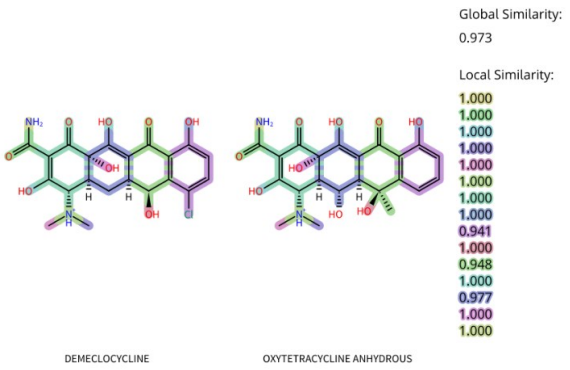
aziridine moieties were necessary for a drug to be biologically active. Possessing three of these moieties, TEM was found to be efficacious against various mouse cancers. TEM was shown to induce less nausea and vomiting than HN2 and patients tolerated higher doses. Like HN2 and HN3 before it, TEM went to human trial. Unlike HN2/HN3, intravenous administration of TEM caused no thrombophlebitis. TEM was also effective orally, making it possible to treat on an outpatient basis. Like HN2 and HN3 however, TEM was limited by its toxic effect on the bone marrow. […]

1,1',1''-phosphorothioyltriaziridine (thioTEPA), and its synthesis, were patented in 1952 by the American Cyanamid Company. It was intended for use in the textile industry and in the production of plastics. However, it went on to see heavy use in the medical field. It disrupts the functionality of nucleic acids like HN2 and HN3 before it. Similar to TEM and TEPA, thioTEPA contains aziridine moieties(*136*)."

## DEMECLOCYCLINE

1959

Analogue of oxytetracycline(*2*)




## TRIMETHOBENZAMIDE

1959

Not found

## DEXBROMPHENIRAMINE

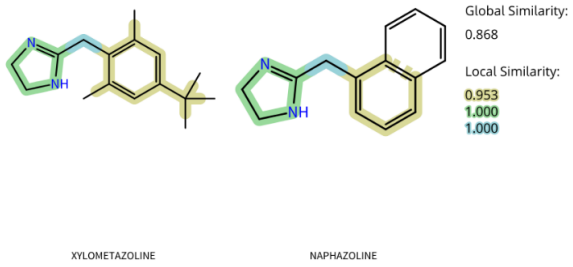
1959

Enantiopure brompheniramine

## XYLOMETAZOLINE

1959

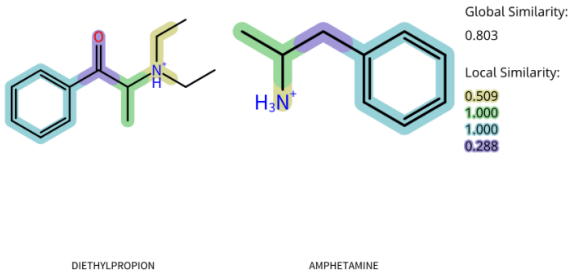
Analogue of naphazoline




## DIETHYLPROPION

1959

Analogue of amphetamine




## CHLORHEXIDINE

1959

"THE occurrence of antimalarial activity in certain substituted diguanides stimulated the search for other therapeutically useful members of this series, and in due course led to the discovery of high antibacterial activity, more especially amongst a series of bisdiguanides. One such compound, 6-di-(*N*-*p*-chlorophenyl-$N^1$-diguanido)hexane has recently been introduced into medical and veterinary practice under the common name chlorhexidine B.P.C. […]

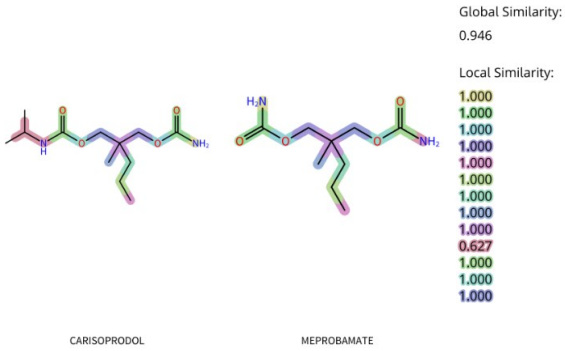
The original observation of marked bacteriostatic action was made with the mixture of polymeric diguanides that resulted from the fusion of 1:6-di-($N^3$-cyano-$N^1$-guanidino)-hexane with hexamethylenediamine dihydrochloride. Attempts to determine actual chain

lengths, or to separate the mixture into homogeneous fractions, were unsuccessful. Since, however, it was known that molecules carrying only one diguanide residue were but weakly antibacterial, it was clearly desirable to determine the degree of molecular complexity necessary for high antimicrobial potency. For this purpose the step-wise synthesis of polydiguanides was undertaken. In the event, full biological activity was reached immediately two diguanide systems were incorporated into each drug molecule, and effort was then concentrated on ascertaining the optimum distance which should exist between these two residues and the most effective types of end groupings-whether, for example, antibacterial activity was highest in bisdiguanides in which the terminal groups were aryl, alkyl, or heterocyclic(*137*)."

## CARISOPRODOL

1959

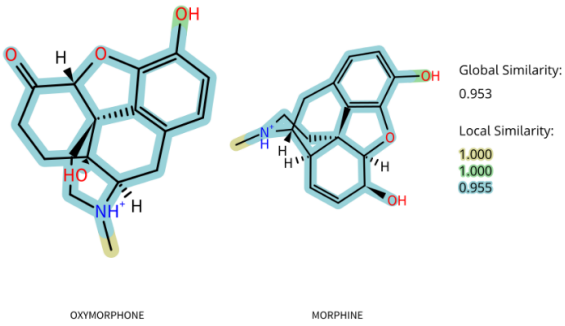
Analogue of meprobamate(*138*)




## OXYMORPHONE

1959

Analogue of morphine(*21*)




## ECHOTHIOPHATE

1959

"Anticholinesterase agents have been used for the control of intraocular pressure for many years. The first was physostigmine (eserine), an alkaloid obtained from the Calabar bean. In 1863 Fraser noted that physostigmine caused pupillary constriction, and Laqueur in 1875 employed it for the treatment of glaucoma. At that time it was noted that undesirable side-effects occurred with the drug. Ever since, an intermittent search for a more potent, less irritating anticholinesterase agent has been under way. A variety of cholinesterase agents have been tried. […]

Recently there has become available a tertiary and a quaternary form of an extremely potent thiophosphate anticholinesterase agent. The chemical structure of the tertiary form, 2-diethoxyphosphinylthio-ethyldimethylamine acid oxalate (217-AO; 217-acid oxalate), and that of the quaternary form, 2-diethoxyphosphinylthioethyltrimethylammonium iodide (217-MI; 217-methyl iodide) […]

These compounds were studied by Koelle and Steiner to determine central effects of these drugs after peripheral administration.

Following the intravenous administration of both forms to rabbits, the tertiary form produced 90% inactivation of the total brain acetylcholinesterase, while the quaternary derivative caused no measurable inactivation of the brain acetylcholinesterase. There was noted, however, a marked apparent inactivation of the acetylcholinesterase of the entire brain following the injection of 1/100 of the previous dose of 217-MI into the lateral ventricle. With this evidence that the quaternary agent is a potent anticholinesterase agent that does not permeate the blood-brain barrier and therefore has no central effects, the investigation of the miotic and antiglaucomatous

effects of this drug in the human eye was begun(*139*).”

From the discovery paper cited in the previous quotation:

“Following the intravenous administration to rabbits of the approximate LD50’s of 2-diethoxyphosphinylthioethyldimethylamine acid oxalate (217-AO; 0.32 micromol./kgm.) and the corresponding methiodide (217-MI; 0.087 micromol./kgm.), the tertiary compound produced 90 per cent inactivation of the total brain acetyicholinesterase (AChE), whereas the quaternary derivative caused no measurable inhibition. When the same dose of the latter was injected via a common carotid artery, slight inhibition of brain AChE resulted. However, marked apparent inactivation of the AChE of the whole brain followed the injection of one-tenth or one-hundredth this dose of 217-MI into a lateral ventricle. Thus, the blood-brain barrier limits the passage of the quaternary agent from the circulation to the cerebral AChE. Assay of the brain-halves separately following intraventricular injection of 217-MI showed that the agent wss fairly equally distributed between the two halves after three to four hours. The degree of inhibition of erythrocytic AChE at that time indicated that most of the 217-MI had passed into the circulation. However, traces of the free compound remained in the cerebrospinal fluid of some animals up to the second day after injection. From determinations of the AChE activities of the right brain-halves and of mixtures of the left halves with control homogenate, it was found that significant amounts of free 217-MI remained within the cerebral tissue of most animals(*140*).”

## FLUOROMETHOLONE

1959

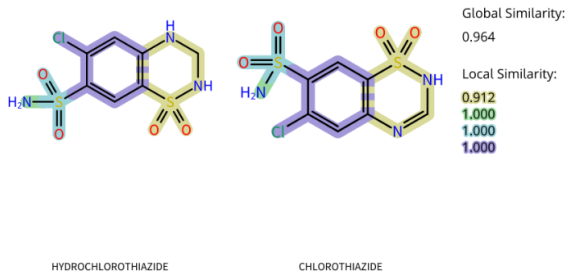
Analogue of cortisone

Error in similarity calculation by FTrees

## HYDROCHLOROTHIAZIDE

1959

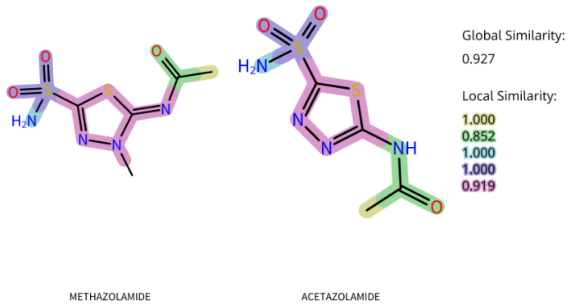
Analogue of chlorothiazide(*21, 115*)




## METHAZOLAMIDE

1959

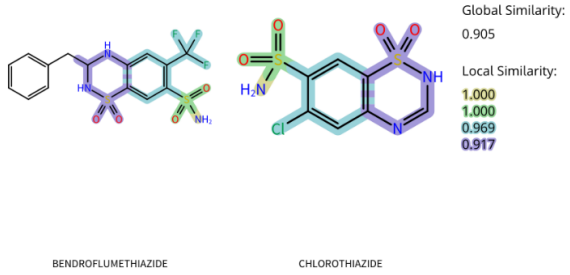
Analogue of acetazolamide




## BENDROFLUMETHIAZIDE

1959

Analogue of chlorothiazide(*21*)




## GRISEOFULVIN

1959

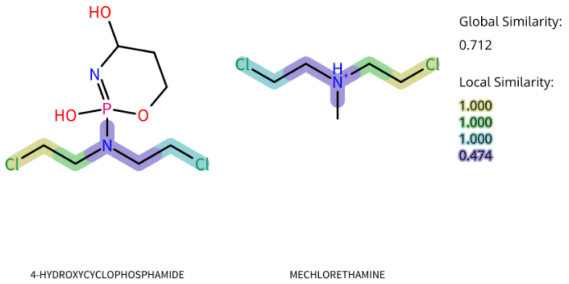
“The systemic antifungal antibiotic griseofulvin was first isolated from the mycelium of *Penicillium griseofulvum* Dierckx. In 1946, a compound named ‘curling factor’ was isolated from the mycelium and the culture filtrate of *Penicillium janczewskii* Zal. It caused

abnormal curling of the hyphae of *Botrytis allii* and later was identified as griseofulvin(*141*)."

## 4-HYDROXYCYCLOPHOSPHAMIDE

1959

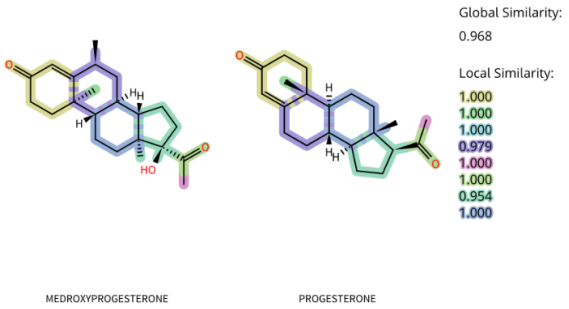
Analogue of mechlorethamine




## MEDROXYPROGESTERONE

1959

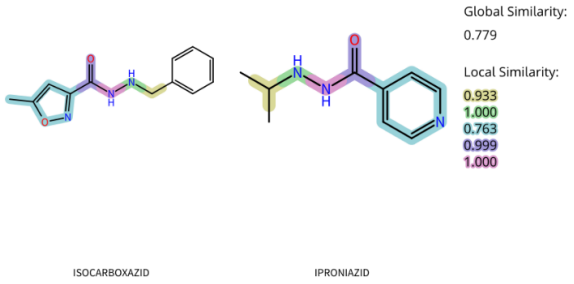
Analogue of progesterone(*21*)




## ISOCARBOXAZID

1959

Analogue of iproniazid




"The history of antidepressant pharmaceuticals dates back to the early 1950s when Irving Selikoff and Edward Robitzek noticed that clinical trial patients treated with the experimental antituberculosis agent iproniazid displayed gentle stimulation and renewed vigor(*142*)."

"From hydrazine hydrate, a powerful reducing agent, Hans Meyer and Josef Malley, of the German Charles-Ferdinand University in Prague, synthesized isonicotinyl hydrazine in 1912, as part of the work for their doctoral thesis. However, forgotten for almost 40 years, it would not be until the early 1950s that it was resynthesized and discovered, by chance, that the compound had, at any experimental level, powerful antitubercular properties. […]

The origin of the first specifically antidepressant drugs, the MAOIs, lies in the antitubercular hydrazide agents that had been used since the early 1950s. The enormous significance of the introduction of these drugs for the treatment of tuberculosis is reflected in the mortality data for this illness in the United States, which fell from 188 deaths per 100,000 inhabitants in 1904 to just 4 in 1952, 1 year after the introduction of isonicotinyl hydrazine or isoniazid.

It was precisely in 1952 that studies began, at the Sea View Hospital on Staten Island, NY, on the clinical effects of iproniazid, by Irving J. Selikoff and Edward Robitzek, who observed that when compared with isoniazid, this drug possessed greater power to stimulate the central nervous system, an effect initially interpreted as a side effect. The psychological changes observed in tuberculosis patients treated with iproniazid were especially striking; these patients showed greater vitality, to the point in some cases of wanting to leave the hospital, and a gradual increase in their social activity.

At this point of the story, serendipity came into play, when a few wise clinicians saw in the psychostimulant a 'side effect'—which had emerged by chance—a potential 'primary effect' that could be useful in psychiatric patients. These inspired individuals including Jackson A. Smith, of Baylor

University, Waco, TX, who in his analysis of iproniazid as a 'tranquilizer' observed some improvement in 2 depressed patients from a group of 11 treated over a period of 2 weeks, increased appetite, weight gain, increased vitality, and improved sleep(*143*)"

From the discovery paper cited in the previous quotation:

"During our original toxicological and pharmacological studies, the occurrence of toxic side-effects were recorded. Further experiences have confirmed these observations and have extended them. Toxic side-effects are qualitatively the same with iproniazid and isoniazid but are quantitatively different; they are much commoner and are more significant clinically with iproniazid.

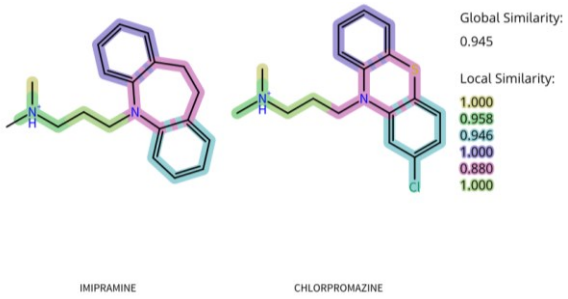
When toxic side-effects occur, they are principally noted in the central nervous system and, possibly, to a lesser extent, in the autonomic nervous system. Symptoms include hyper-reflexia, headache, involuntary muscle twitching, peripheral neuropathy, mild euphoria and excitability, constipation, vertigo, difficulty in initiating micturition, mouth dryness, minor difficulty in visual accommodation, and variations in sexual stimulation and activity. These symptoms, which are more frequent with iproniazid, occur at therapeutic dosage levels of 4 mg. per kilogram(*144*)."

## IMIPRAMINE

1959

First synthesized as an analogue of chlorpromazine(*10, 143*)

Four years after the discovery of chlorpromazine, the quest for its analogues was intense. Roland Kuhn, director of a psychiatric hospital on a tight budget, asked a drug manufacturer if they had any of these antipsychotics they would like to try out on their schizophrenic patients. After receiving and testing G22355, he observed that not only it had no antipsychotic effect, it even exacerbated the schizophrenia of patients who had been getting better by chlorpromazine. He then decided to test G22355 on his depressed patients. After three weeks, most of these patients were drawn out of their suffering. Imipramine was born(*10, 143*).




"In a climate of pessimism regarding present-day drug development, it may be instructive to look back at the research methods of 60 years ago, when a generation of groundbreaking psychotropic drugs was discovered. The study that identified the first antidepressant is a case in point. In 1955, Roland Kuhn, a 43-year-old Swiss psychiatrist, examined the antidepressant effects of an unknown Geigy compound designated G22355. Kuhn worked in a psychiatric hospital in the small, remote Swiss village of Münsterlingen. He was trained in psychodynamic psychiatry and had a scientific interest in existential psychoanalysis. At the same time, he had been caught up in the excitement surrounding the discovery, several years previously, of the antipsychotic effects of chlorpromazine. Drug companies, including Geigy, were collaborating with hospital-based psychiatrists like Kuhn to come up with other compounds that would have the antipsychotic effects of chlorpromazine. Working closely with Geigy scientists, Kuhn had tried a number of compounds bearing structural similarity to chlorpromazine in patients with schizophrenia. None of these compounds had much of an effect on psychotic symptoms. But Kuhn noted that although one of these compounds, G22355, did not reliably improve psychotic symptoms, some of the schizophrenia

patients became hypomanic from it. Furthermore, G22355 seemed to alleviate depression in the few schizophrenia patients who had prominent depressive symptoms. With the encouragement and support of Geigy, Kuhn then undertook a study of the antidepressant effects of G22355.

It is noteworthy that Kuhn trusted his initial observations and pursued this study despite the fact that in the prevailing psychiatric culture the idea that a drug alone could cure depression was implausible and despite his psychoanalytic perspective on psychopathology and its treatment.

Kuhn gave G22355, later named imipramine, to about 100 depressed patients and reported the results in a paper published in the August 31, 1957, issue of the Swiss Medical Weekly (1). The following week, he presented his results at The Second International Congress of Psychiatry in Zurich. There were about a dozen people in the audience who, in general, seemed oblivious to the fact that the quiet-spoken, dignified man at the podium was bringing them ground-breaking news.

Kuhn's original paper appeared in German. In its six pages, he provided, with notable thoroughness and accuracy, almost all the essential information about imipramine, including its clinical effects, the type of depression it most benefits, its delayed onset of action, and its anticholinergic and other side effects. He wrote nothing about his method for assessing patients, but in reminiscing about this study 40 years later, he pointed out that he eschewed rating scales, relying instead on close and frequent (sometimes daily) observation of his patients and that he also paid close attention to the comments of nursing staff(*145*)."

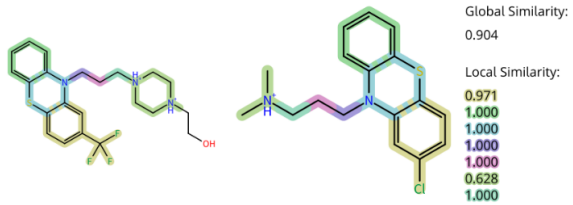
From the discoverer, Dr. Roland Kuhn, in his article, "Artistic imagination and the discovery of antidepressants":

"The psychopharmacological way of thinking and researching nowadays is based on the scientific principle of precision. Rating scales and statistics supply precise results obtainable at all times. The patient who is suffering is hardly ever mentioned and in a extreme case appears only under 'items'. These are then transformed into figures which are to be used in calculation and presented in the form of tables and curves. Research of this type bears no comparison with 'artistic imagination': consequently, the title of this article must seem absurd to today's researchers and clinical psychopharmacologists(*146*)."

## FLUPHENAZINE

1959

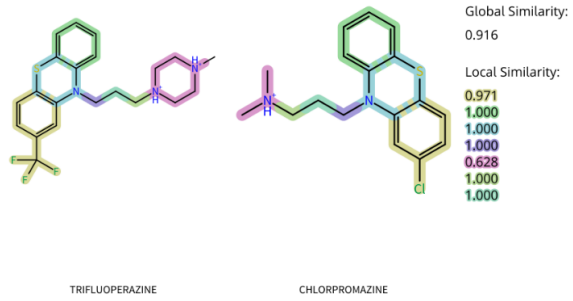
Analogue of chlorpromazine(*2*)




## TRIFLUOPERAZINE

1959

Analogue of chlorpromazine




## INDOCYANINE GREEN

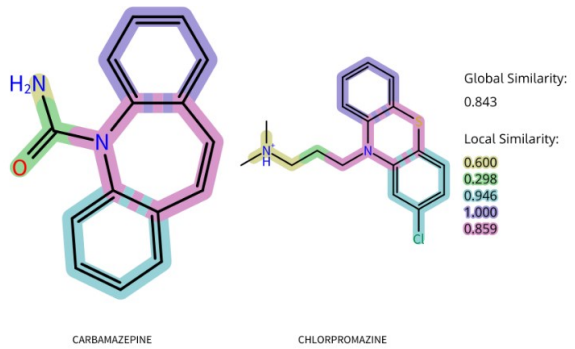
1959

Diagnostic

## CARBAMAZEPINE

1959

First synthesized as an analogue of chlorpromazine(*147*)




"Following the introduction of the antipsychotic drug chlorpromazine in the early 1950s, eager attempts were made to find further psychoactive substances with a more favourable side effect profile. By retaining the tricyclic structure and making some small changes to the molecule, both tricyclic antidepressants and carbamazepine were developed.

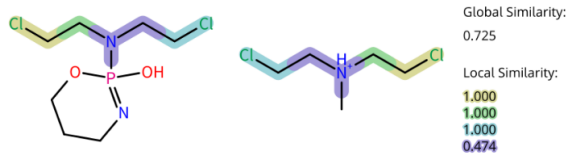
Carbamazepine was synthesised in 1953 but its efficacy against psychosis and depression was disappointing. On the other hand, it was found – somewhat surprisingly – that the drug worked well against trigeminal neuralgia. The drug's antiepileptic properties were discovered by chance a few years later. While chlorpromazine and tricyclic antidepressants lower the seizure threshold, carbamazepine has the opposite effect. Similarly-structured substances can thus have completely opposite effects on the central nervous system(*147*)."

"The development of carbamazepine was based on the neuroleptic drug chlorpromazine from Firma Rhône-Poulenc in Lyon. Jean Pierre and Pierre Deniker, French psychiatrists, used chlorpromazine in Centre Hospitalier Sainte Anne in Paris to treat patients with schizophrenia. However, research on neuroleptic drugs continued in Geigy labs; carbamazepine was synthesized by Schindler and Blattner at J. R. Geigy AG, Basel, Switzerland, 1953, in the course of development of another antidepressant drug imipramine. Initial animal screening showed that carbamazepine was effective against trigeminal neuralgia, which was confirmed by clinical trials. Antiepileptic effects were reported in 1963 and 1964. It was used as an anticonvulsant drug in the UK since 1965 and has been(*148*)."

## CYCLOPHOSPHAMIDE

1959

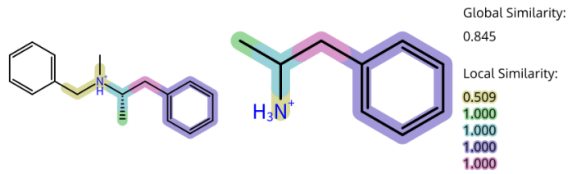
Analogue of mechlorethamine




## BENZPHETAMINE

1960

Analogue of amphetamine




## DIPHENOXYLATE

1960

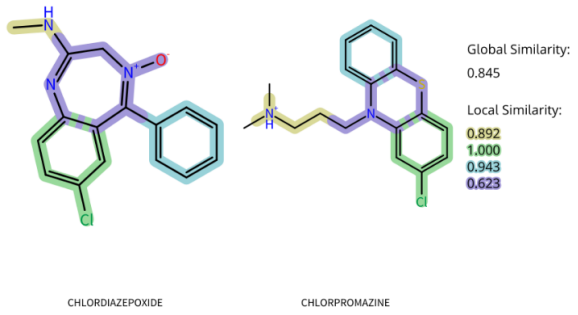
Meperidine (pethidine) was at first introduced as an anticholinergic synthesized based on atropine and scopolamine. In clinic, it had shown opium-like analgesic and antidiarrheal effects. In order to separate these activities, Paul Janssen used Straub mouse tail test for opiate activity and the electrically driven guinea pig ileum *in vitro* for

antispasmodic activity. He succeeded in invention of loperamide, diphenoxylate, and fentanyl(*149*).

## CHLORDIAZEPOXIDE

1960

First synthesized as an analogue of chlorpromazine




"As was the case with most of the psychotropic drugs discovered in the 1950s, scientific chance played a substantial role the development of the benzodiazepines […]

In 1954, he decided to continue his studies of some tricyclic compounds (heptoxdiazines) that he had synthsised at the University of Crakow 20 years previously, during his post-doctoral studies of colourings. The recent commercialization of chlorpromazine in France in 1952, and its tricyclic chemical structure, made Sternbach wonder whether some modifications to the lateral chains of his old compounds could endow them with properties similar to the new neuroleptic agent. To that end, he focused on a substance 'known as 4,5-benzo (hepto 1,2,6-oxdiazine) in the German literature' […]

Using this substance, the Hoffmann-LaRoche researcher developed 40 new compounds from the reaction of his key product, a haloalkane, with a number of secondary amines, selected to give them some structural similarity to the recently marketed tricyclic substances. However, when Lowell O. Randall, director of Pharmacological Research at Roche, studied the sedative, anticonvulsants and relaxant properties of these compounds, the results were negative (the first failure). Further chemical studies showed that the tricyclic system in the key intermediate product of synthesis was not benzoheptoxydiazine as previously believed, but was instead 3-oxidoquinazoline, and this appeared to be the reason for the lack of biological activity among the derivatives synthesised from the intermediate synthesis (the first error). However, the last of the analogues (Ro 5-0690) synthesised by Sternbach had not yet been studied, and a year and a half later (May, 1957), his colleague Earl Reeder (the first twist of chance) 'drew his attention to a few hundred milligrams of two products, a nicely crystallized base and its hydrochloride... Pharmacological tests had not been run on these products at the time, as we were busy with other problems... Instead of throwing them away, we submitted the water-soluble salt for pharmacological testing. We thought that the expected negative pharmacological results would cap our work on this series of compounds... We had no idea that this would be the start of a program that would keep us occupied for years to come.' Randall confirmed that this compound was superior to meprobamate in many trials in terms of anxiolytic activity and as a central muscle relaxant, and also had some sedative properties similar to chlorpromazine, and lacked any significant adverse effects (first success). Of particular interest was its calming effect, observed in a colony of wild monkeys whose level of alertness was not affected. On 26th July 1957, Randall wrote a few words that are today part of the history of psychopharmacology: "The substance has hypnotic, sedative, and antistrychnine effects in mice similar to meprobamate. In cats it is about twice as potent in causing muscle relaxation and ten times as potent in blocking the flexor reflex(*150*)"

From an interview with the discoverer, Leo Sternbach:

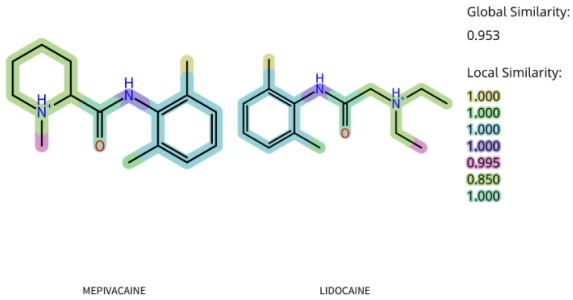
"In the 1950s and 1960s, when tinkering with new drugs, he tested them on himself. After

trying one particularly potent medicine, he had so much trouble walking that he asked colleagues to call his wife to pick him up. 'I got very disoriented and was half-conscious,' he recalls. 'For two days, I was not at all well.'(*151*)."

## MEPIVACAINE

1960

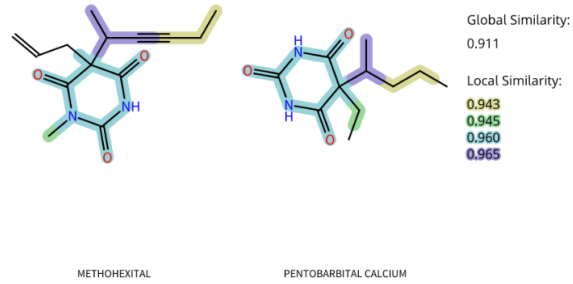
Analogue of lidocaine




## METHOHEXITAL

1960

Analogue of pentobarbital

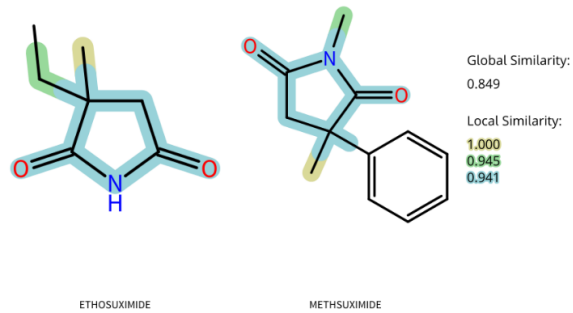



## ETHOSUXIMIDE

1960

Analogue of methsuximide

See the methsuximide entry.




"Ethosuximide has very definite effects in a variety of animal models but has failed to have any demonstrable action in most *in vitro* models. Indeed, ethosuximide even fails to prevent pentylenetetrazol-induced bursting in hippocampal slices despite its marked effectiveness against pentylenetetrazol *in vivo*(*131*)."

## VALPROIC ACID

1960

"valproic acid was thought to be pharmacologically inert and, being a liquid, was used as a solvent. It was only in 1963 that its anticonvulsant properties were serendipitously discovered(*152*)."

"Like many important discoveries in the history of pharmacology, valproate was not developed by any 'rational strategy,' but its anticonvulsant activity was serendipitously discovered by Pierre Eymard in France in 1962. Valproic acid was first synthesized in 1882, by Burton, but there was no known clinical use until its anticonvulsant activity was fortuitously discovered by Eymard. Because valproic acid is a liquid, it was used as a lipophilic vehicle to dissolve water-insoluble compounds during preclinical drug testing. As part of his thesis in 1962, Eymard had synthesized a number of khelline derivatives […]

Carraz proposed to test the most active derivative in the pentylenetetrazole (PTZ) seizure test. By doing this, the researchers found that the vehicle, valproate, alone exerted an anticonvulsant effect. Similarly, Meunier, by dissolving a coumarin derivative in valproate also found an anticonvulsant effect of the vehicle valproate alone in the PTZ test in rabbits(*153*)."

## MAGALDRATE ANHYDROUS

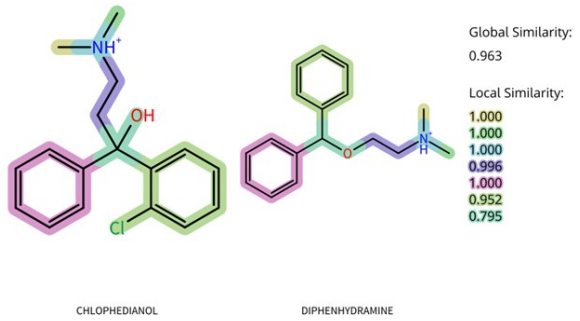
1960

Used because of its basic activity

## CHLOPHEDIANOL

1960

Analogue of diphenhydramine

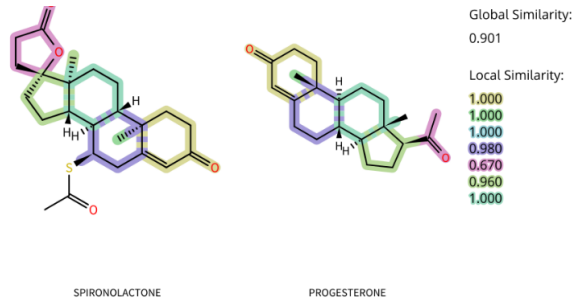



“Chlophedianol is an antitussive agent with antihistaminic and anticholinergic actions. It has no advantages over dextromethorphan. It has mild local anesthetic properties. It is structurally related to diphenhydramine. A cough syrup containing chlophedianol was approved in 1960 based only on safety data(*154*).”

SPIRONOLACTONE

1960

“It is a potent antimineralocorticoid which was developed as a progestational analog(*155*).”




Its antiandrogenic effect was later observed in patients receiving it:

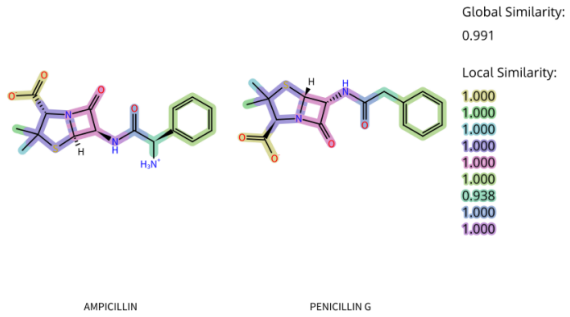
From a letter reporting gynecomastia in after prescribing spironolactone for one of his patients:

“I would be very interested to know whether any of your readers have encountered gynaecomastia during spironolactone (‘Aldactone’) treatment(*156*).”

AMPICILLIN

1960

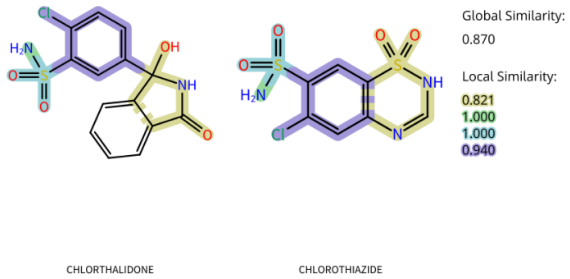
Analogue of penicillin(*21*)




CHLORTHALIDONE

1960

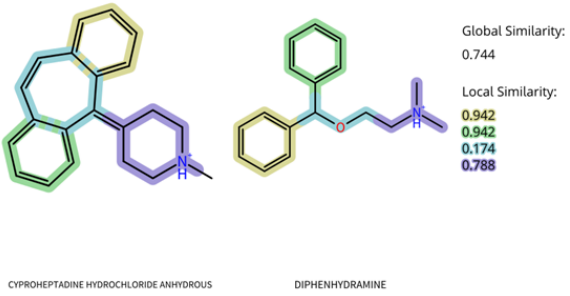
Analogue of chlorothiazide




CYPROHEPTADINE

1961

Analogue of diphenhydramine(*21*)




PROPYLENE GLYCOL

1961

Used for its physical properties

PSEUDOEPHEDRINE

1961

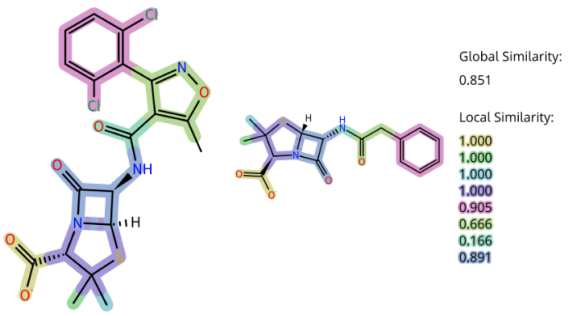
Naturally available in the Ephedra plant

which has been used in eastern traditional medicine and was first researched in west in 1889.

## DICLOXACILLIN

1961

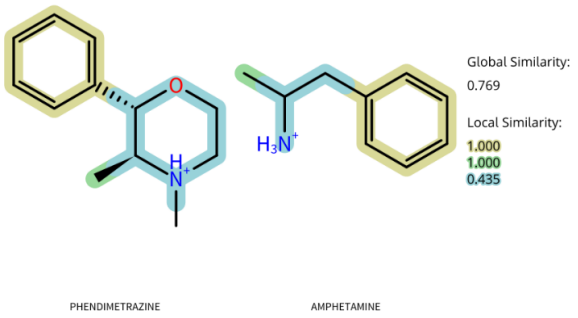
Penicillin analogue(*21*)




## PHENDIMETRAZINE

1961

Analogue of amphetamine




## COLISTIMETHATE

1961

"Colistimethate is a methanesulfonate of polymyxin antibacterial colistin. Colistimethate is a nonactive prodrug. In aqueous solutions, colistimethate is hydrolyzed and forms a complex mixture of partially sulfomethylated derivatives and colistin(*1*)."

## RACEPHEDRINE

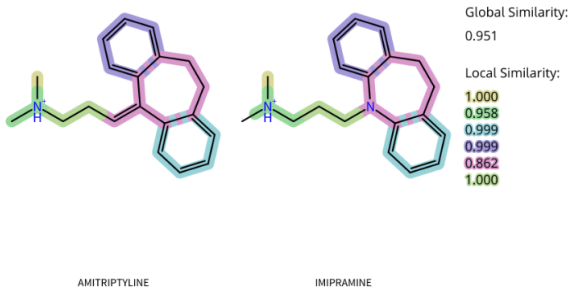
1961

Synthetic racemic ephedrine

## AMITRIPTYLINE

1961

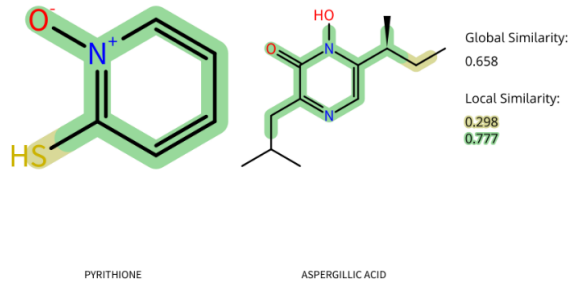
Analogue of imipramine




## PYRITHIONE

1961

Based on and synthesized from the natural antimicrobial aspergillic acid(*157*)




Discovery of aspergillic acid:

From the discovery paper:

"In 1940 one of us (White) reported that a strain of *Aspergillus flavus*, grown on certain liquid media, yielded filtrates that showed antibacterial activity against certain gram-negative as well as gram-positive bacteria. This was the second reported case of such behavior by a mold, the first being that of Fleming (1929) […] The present paper presents details of the isolation of an active crystalline substance from liquid cultures of our strain of *Aspergillus flavus*. […] We propose to call our substance 'aspergillic acid.' […]

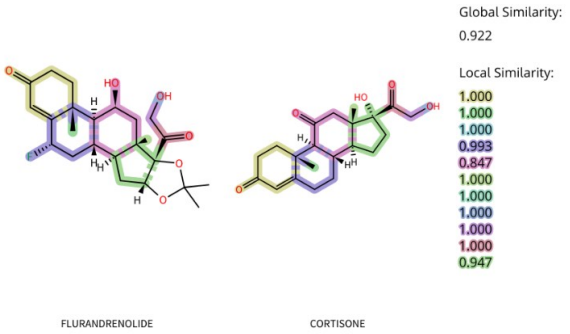
The filtrates have been tested against the following organisms: (a) *Pseudomonas aeruginosa*, (b) *Proteus*, (c) *Staphylococcus aureus*, (d) group A beta hemolytic

*streptococcus*, strain 203, (e) S*treptococcus fecalis*, (f) *Escherichia coli*, (g) *Aerobacter aerogenes*. No inhibition was noted in the case of the first two organisms, even with the dilute inoculum. The results with the other organisms were variable(*158*).”

FLURANDRENOLIDE

1961

Analogue of cortisone




FLUOCINOLONE ACETONIDE

1961

Analogue of cortisone(*21*)

Error in similarity calculation by FTrees

TRANYLCYPROMINE

1961

First synthesized in 1940, it was originally intended to become a nasal decongestant as an analogue of amphetamine. Yet, it failed as a decongestant(*159*). Its Monoamine oxidase activity was shown in rabbits, as producing central nervous system stimulation and marked rise in rectal temperature, and also by measuring the rate of disappearance of serotonin incubated with rat brain homogenates(*160, 161*). Because the antidepressant-like effect observed serendipitously from the antitubercular agent, iproniazid, was being attributed to its MAO inhibitor activity, it was postulated at the time that inhibiting this enzyme may be therapeutic for depression. As the MAO inhibitory activity of tranylcypromine had also been shown previously, it was suggested that like iproniazid, it may have some antidepressant effect. This was tested in a clinical trial in 1959(*143, 162, 163*).

METYRAPONE

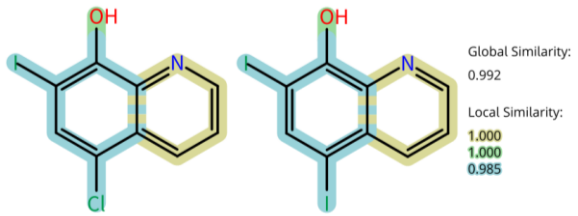
1961

Diagnostic

CLIOQUINOL

1961

Analogue of iodoquinol




From a 1931 article:

“Chiniofon, N. N. R., introduced commercially as “yatren”, and first tried clinically in amebiasis by Muhlens and Menk’ in 1921, has had some popularity as an amebicidal agent. Chemically chiniofon is sodium-iodoxy-quinoline-sulphonate, and is related to chinosol N. N. R. (oxyquinoline sulphate) and vioform N. N. R. (iodochloroxyquinoline) . Since chiniofon has been claimed to have amebicidal activity, we thought it might be of interest to study it from this standpoint in comparison with as many related compounds as we could secure. […]

These substances have been studied with respect to toxicity on oral administration to guinea-pigs, rabbits, and cats; balanticidal action in naturally infested guinea pigs; amebicidal action *in vitru*, and therapeutic effect in monkeys naturally infested with intestinal parasites(*164*).”

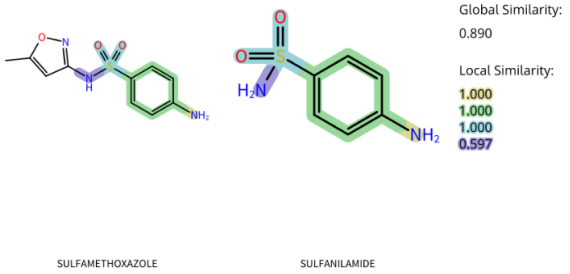
I could not find the paper of Mühlens and

Menk cited in the preivous quotation: Mühlens, P., and Menk, W., *Munch. Med. Tochnschr.*, 1921, 68, 802.

SULFAMETHOXAZOLE

1961

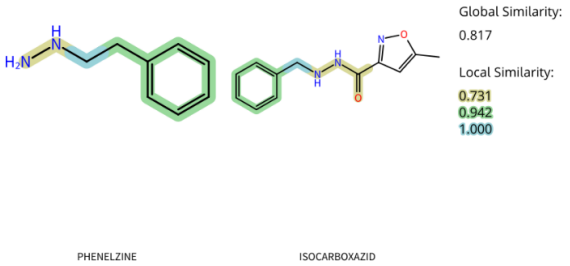
Analogue of sulfanilamide




PHENELZINE

1961

Analogue of isocarboxazid




ALLANTOIN

1961

"THE story of the development of this new tissue promoting substance, allantoin, seems to answer in the affirmative the question, 'Does man know by instinct what will cure his ills?' It is an interesting fact that for centuries European peasants have been healing ulcers with the root of a plant called comfrey, which is rich in allantoin. Of course, they did not know this plant contained allantoin. They discovered empirically the healing virtues of comfrey.

Ambrose Paré in 1652 observed unusually rapid healing in suppurating wounds in which blowflies had deposited their eggs. Larrey in 1829 observed that wounds infested with maggots healed rapidly. Malgaigne in 1847 made an observation concerning the action of maggots in the treatment of compound fractures. Similar observations were made during the Civil War by Keen and Zacharias who stated that maggots exerted a healing influence on infected wounds. However, it remained for Baer of Johns Hopkins Medical School, to make the first deliberate therapeutic application of this principle, with such results that this method of treatment has become an accepted procedure and numerous reports have appeared in medical literature amply confirming his results. […]

[M]aggots secrete a substance into the wound which directly stimulates the healing process, a theory frequently expressed in the literature.

Simmons showed that maggots excrete a bactericidal substance particularly potent to Staphylococcus aureus, Streptococcus hemolyticus and Clostridium Welchii. […]

Robinson has undertaken an investigation to determine the healing principle contained in the excretion of maggots. He demonstrated that allantoin was found in the crystals obtained from the excretions of maggots. Further experiments have established that allantoin possesses healing action upon chronic non-healing wounds with edamatous, indolent tissues lining the wounds and discharging pus, particularly when poor in circulation. […]

Twenty-four years ago, in 1912, Macalister found allantoin a very efficient cell proliferant. He tried pure allantoin solution in the treatment of chronic ulcers. He also used it internally in the treatment of gastric and duodena1 ulcers, with success(*165*)."

BETAMETHASONE

1961

Corticosteroid analogue(*21*)

Error in similarity calculation by FTrees

## VINBLASTINE

1961

"In March 1958, speaking on behalf of his small team, Noble read the original vinca paper with its master narrative at a cancer research symposium at the New York Academy of Science. He said the 'chain of events' began in 1949 when the Collip lab-ever devoted to endocrinology-was investigating the presence of hormone activity in 'various plant extracts to which historical hearsay had ascribed empirical uses by primitive peoples.' He continued:

'The disease of cancer was certainly far from our minds when we learned of a tea made from the leaves of a West Indian shrub that was supposedly useful in the control of diabetes mellitus. C.D. Johnston of Black River Jamaica, ... had been curious about the benefits of a tea made from ... periwinkle ... and he forwarded a supply of the material to us'

Researchers everywhere were keen to find a source of oral hypoglycemic agents that would eliminate the needle injections required by insulin. But oral administration of periwinkle extracts in rats had no effect on blood sugar or glucagon levels. Noble sent pediatrician John C. Rathbun and endocrinologist Hugh A. McAlpine to visit Johnston in Jamaica to find out more about the preparation of the tea. Much later the investigators learned that the antidiabetic potential of oral periwinkle had already been investigated and refuted by Australian researchers in the late 1920s.

Trying to improve on their own results, Noble's team decided to inject the water extracts of periwinkle into the rats. This time, he said, the animals were 'obviously affected but in an unexpected manner': they all died. Autopsy revealed multiple abscesses. The team noted that the offending bacteria (*Pseudomonas*) were the same as those 'isolated in rats . . . receiving large doses of cortisone.' Noble continued: 'Apparently some natural barrier to infection was being depressed by both types of treatment. Further studies readily localized the action of the V[inca] rosea extracts-a rapidly falling white blood count, granulocytopenia, and profoundly depressed bone marrow.'

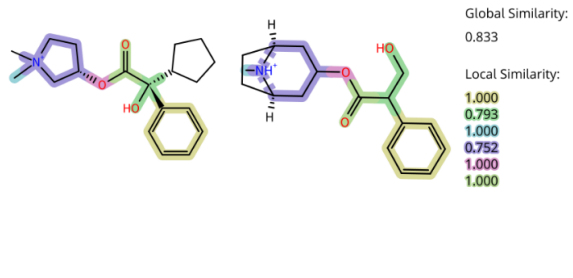
Noble's lab worked 'spasmodically' on the problem, he said, and 'an intensive study was not started until 1955.' He went on to explain the elegant biochemical work accomplished to isolate the active substance by extraction and chromatography, using the white blood count as an assay. Preliminary studies of the activity of the unpurified extracts were published in 1955 and 1957. A photograph of the crystalline product accompanied the 1958 paper. He concluded with a report of the effects on blood and bone marrow of healthy rats given the purified substance. Due to a lack of materials, only 'limited investigations for carcinostatic [anti-cancer] activity' had been made in vitro on a transplantable mammary adenocarcinoma of the mouse and a transplantable rat sarcoma(*166*)."

## GLYCOPYRROLATE

1961

Analogue of atropine

The tertiary amine in atropine is converted to quaternary ammonium to reduce CNS penetration




GLYCOPYRRONIUM ATROPINE

## DIPYRIDAMOLE

1961

"Here is where the discovery of antithrombotic properties of dipyridamole was made.

Mitchell observed in vivo (particularly intracerebral arteries investigated for other reasons) that dipyridamole treatment resulted in the prevention of thrombus formation. This finding was further investigated in vitro, but direct inhibition of platelet aggregation was only seen in supratherapeutic concentration(*167*)."

From Mitchell, one of the discoverers of dipyridamole's antithrombotic activity:

"Serendipity came to our aid, for three agents, widely used for other indications, and therefore of proven safety, were shown to modify platelet activities (the vasodilator, dipyridamole' 2; the uricosuric, sulphinpyrazone, and the panacea for all bodily ills, aspirin)(*168*)"

The experiments used in the paper discovering the antithrombotic effect of dipyridamole were done in Grey chin chilla rabbits.

"A new synthetic compound, Persantin (RA-8 or 2,6-Bis(diethanolamino)-4,8-dipiper-idino-pyTimido- (5,4-d) -pyrimidine), has recently been reported to produce coronary vasodilation without an associated increase in cardiac work. Although the mechanism responsible for the coronary vasodilation produced by Persantin has not been elucidated, there are some indications that an indirect action on myocardial nucleoside metabolism may be involved(*169*)."

## COPPER UNDECYLENATE

1961

"It should be borne in mind that the initial and principal object of the physician was the discovery of the cause and the control of epidemic scalp ringworm. In order to find the best topical medication for scalp ringworm, a number of chemicals already in use were tried. In addition, a number of representative chemicals with known fungicidal properties when used as mildew-proofing agents on fabrics, lumber, and other materials were tried.

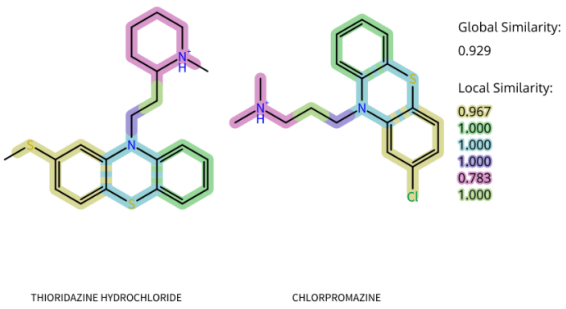
[…]

*Copper undecylenate*:-A special ointment prepared by the Dermatoses Section, containing a saturated solution of copper undecylenate in Carbowax 1500, was next to the most efficacious preparation tried(*170*)."

## THIORIDAZINE HYDROCHLORIDE

1962

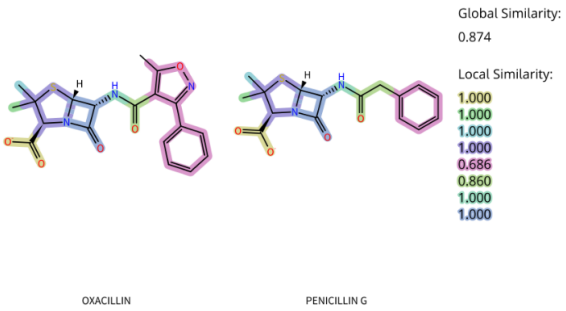
Analogue of chlorpromazine




## OXACILLIN

1962

Analogue of penicillin(*21*)




## COLISTIN

1962

Analogue of polymyxin B(*2*)

Error in similarity calculation by FTrees

## FLUOROURACIL

1962

From the discovery paper:

"**I**N view of the profound biological effects often obtained when fluorine is substituted for hydrogen in several classes of compounds

1 and because of the effectiveness, albeit limited, of various nucleic acid analogues in the treatment of human and animal cancer, it was felt that a fluorine-substituted purine or pyrimidine might display tumour-inhibitory activity. Attention was focused on the pyrimidines because of suggestions that uracil may be utilized preferentially for nucleic acid biosynthesis in tumours, and from the demonstration by Welch and his colleagues of tumour-inhibitory activity of 6-azauracil. Accordingly, we have synthesized a number of hitherto unknown 5-fluoropyrimidines and their 2-thio derivatives. 5-Fluorouracil (I Ro 2-9757) and 5-fluoro-orotic acid (II Ro 2-9945) exert considerable anti-tumour activity against transplanted tumours in rats and mice, whereas 5-fluorocytosine (III Ro 2-9915) and various 2-thio derivatives have been inactive. […]

To date, 5-fluoro-uracil and 5-fluoro-orotic acid have demonstrated growth-inhibitory activity against the following transplanted tumours in rats and mice: Flexner-Jobling carcinoma, Walker 256 carcino- sarcoma, Yoshida ascites tumour, Shay's chloroleukaemia, Sarcoma 180, Ehrlich ascites carcinoma, L-1210 leukaemia, E0771, mammary adenocarcinoma 755, and Sarcoma A-1 (a transplantable sarcoma derived from a dibenzanthracene-induced tumour ; Buck, unpublished) […]

In the work with solid tumours we have calculated their volumes, instead of weighing. This was done so that the determinations could be made repeatedly in order to assess the growth-rate of the tumours and the duration of effect of the drugs. It will be noted from Table 1 that in all cases in which they have been compared, 5-fluoro-uracil is more effective than 5-fluoro-orotic acid. A very significant inhibition of growth of all four tumours was produced by 5-fluoro-uracil, and a more pronounced effect was observed with repeated rather than with single doses. […]

With respect to *in vitro* anti-microbial activity, 5-fluoro-uracil is qualitatively different from 5-bromo- uracil. Whereas the latter has no significant activity, 5-fluoro-uracil in a cylinder-plate test procedure exerts a marked inhibitory effect on the following organisms three of which are Gram-negative: *Streptococcus faecalis, Bacillus simplex, E. bacillus, Sarcina lutea, Bacillus subtilis, Staphylococcus aureus, B. cereus, B. megatherium, Escherichia coli, Proteus vulgaris*, *Azotobacter vinelandii* and *Scopulariopsis brevicaulis*. The activity against *Proteus vulgaris* is half that of streptomycin. In addition, 5-fluoro-uracil has profound activity when tested in semi-synthetic media against *Lactobacillus leichmanii, Saccharomyces carlsbergensis, L. arabinosus, L. casei* and *S. faecalis.* […]

It is evident that 5-fluoro-uracil exhibits greater than 5,000 times the activity of 5-bromo-uracil, five times the activity of 5-fluoro-cytosine, and twenty-five times the activity of 5-fluoro-orotic acid. The thio compound is considerably less potent. With *L. leichmanii*, the inhibitory activity of 5-fluoro-uracil was reversed, in order of decreasing activity, by thymidine, thymine, 5-methyl-cytosine, uracil and cytosine(*171*)."

From another related paper from the discoverer(s):

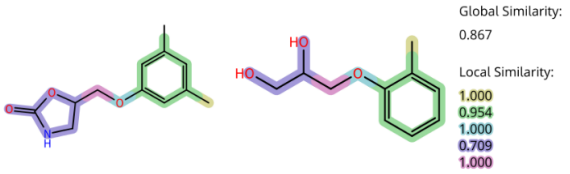
"Although it has been shown that the injection of $N^{15}$-labeled pyrimidines into normal adult rats does not lead to appreciable labeling of the total nucleic acids, Rutman et al. have made the interesting observation that uracil-2-$C^{14}$ is incorporated into the nucleic acids of rat hepatomas induced by 2-acetylaminofluorene to a considerably greater extent than into those of normal liver. Because of the possible chemotherapeutic implications of this finding and as a continuation of the work in this laboratory on the biosynthesis of nucleic acids, experiments were undertaken to determine whether uracil is also incorporated into the nucleic acids of transplantable

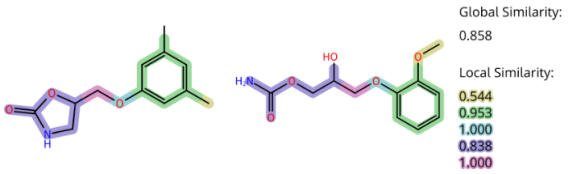
tumors or into other normal growing tissues. The three tissues chosen were rat liver (both of normal and tumor-bearing animals), intestinal mucosa, and the Flexner-Jobling carcinoma(*172*).”

## METAXALONE

1962

Analogue of mephenesin and methocarbamol




## METHYLDOPA

1962

It was first synthesized in a search for chemotherapeutic compounds.

“As part of a program to investigate chemotherapeutic possibilities among amino acid analogs, our attention was turned to derivatives of phenylalanine and particularly of the biologically important 3,4-dihydroxyphenylalanine (DOPA) (*173*)”

From the discoverer(s):

“The blood pressure reducing effects of a-methyl-3,4-dihydroxy-dl-phenylalanine (methyldopa) were discovered by us in human hypertensive subjects in the fall of 1959. To that point in time, the compound had not been considered to have any intrinsic pharmacological activity and its therapeutic potential was not predictable. The compound was administered to patients because of its biochemical properties as a competitive inhibitor of dopa-decarboxylase, and as part of an ongoing clinical research programme on the interrelationships between alterations in vasoactive amine metabolism and blood pressure in patients with hypertension. Administration of doses sufficiently large (g quantities) to produce a biochemical (enzyme-inhibitory) effect in the intact human was an essential ingredient for discovery of the antihypertensive effects(*174*).”

## IOTHALAMATE MEGLUMINE

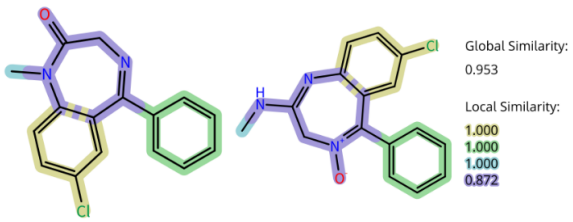
1962

Contrast agent

## DIAZEPAM

1963

Analogue of chlordiazepoxide




## METRONIDAZOLE

1963

It was discovered on the basis of assessing both the safety (LD50 in mice, rats and dogs) and activity (treating the inoculation of T. vaginalis in mice) of different compounds isolated from a strain of Streptomyces. Its antibacterial effect was later discovered accidentally(*175-177*).

“Metronidazole is one of the rare examples of a drug developed against a parasite which has since gained broad use as an antibacterial agent. Briefly, at Rhone-Poulenc labs in France, extracts of *Streptomyces* spp. were screened for activity against *Trichomonas*

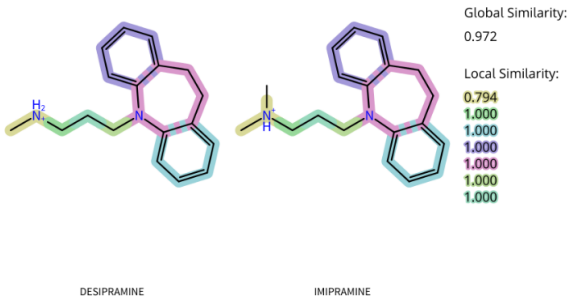
*vaginalis*, a cause of vaginal itching. Azomycin, a nitroimidazole, was identified, and metronidazole, a synthetic derivative, was used to treat chronic trichomonad infections, beginning in 1959(*175*)"

"The antibacterial activity of metronidazole was discovered by accident in 1962 when metronidazole cured a patient of both trichomonad vaginitis and bacterial gingivitis(*175*)"(*176*)

## DESIPRAMINE

1964

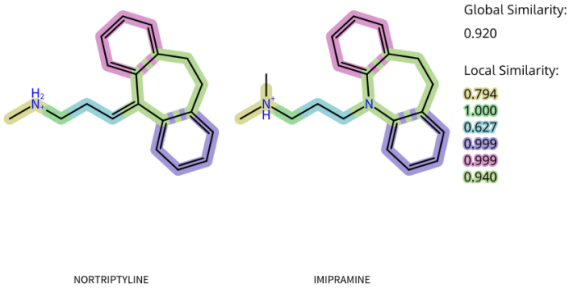
Analogue of imipramine




## NORTRIPTYLINE

1964

Analogue of imipramine




## TRIAMTERENE

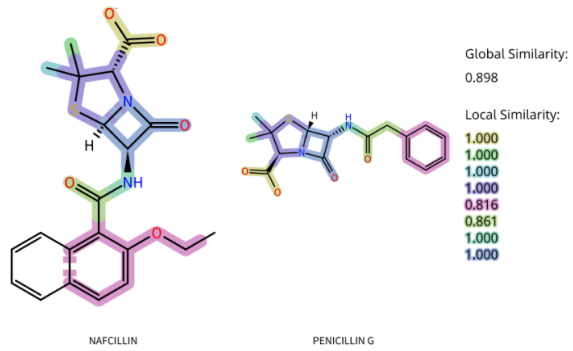
1964

"The triamterene ring system is found in many naturally occurring compounds, such as folic acid and riboflavin. These compounds are important in the regulation of metabolism in humans. The observation that xanthopterin was capable of effecting renal tissue led Wiebelhaus, Weinstock, and associates to test a series of pteridines in a simple rat diuretic screening procedure. One compound, 2,4-diamino-6,7-dimethyl-pteridine showed sufficient diuretic activity to encourage further investigation of the diuretic potential of the pteridines. A number of related 2,4-diaminopteridines were studied, but only 2,4-diamino-6,7-dimethyl-pteridine showed good activity in both the saline-loaded and saline-deficient rat. Changes in the 2,4-diamino part of the molecule resulted in a marked decrease in diuretic activity(*178*)."

## NAFCILLIN

1964

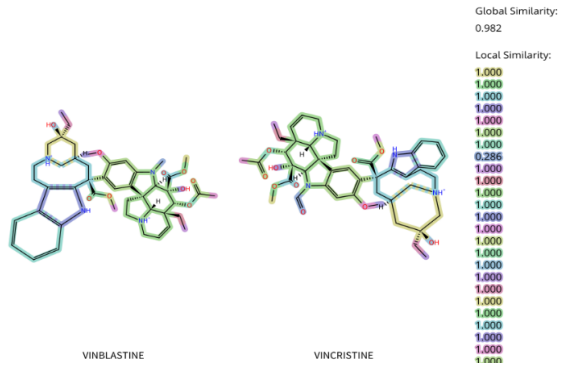
Penicillin analogue(*21*)




## VINCRISTINE

1963

Analogue of vinblastine(*166*)




## LINCOMYCIN

1964

"The term lincomycin is based on Lincoln, Nebrasca, where the antibiotic was first

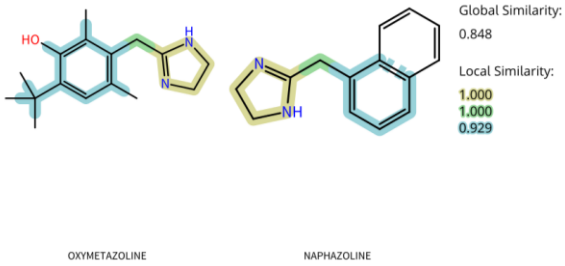
isolated from Streptomyces lincolnensis in a soil sample(*179*)."

I could not find the earliest paper reporting lincomycin(*180*), yet, based on the time of discovery and the trends at that time, and a related paper(*181*), it seems that it was probably discovered based on screening the samples against various bacteria *in vitro* and *in vivo*(*179, 181*).

## OXYMETAZOLINE

1964

Analogue of naphazoline




## MELPHALAN

1964

Analogue of nitrogen mustard


## DACTINOMYCIN

1964

"The group name actinomycin was coined by Waksman, who discovered these antibiotics in cultures of *Actinomyces antibioticus* in 1940. Only 9 years later publications revealed a first glimpse into the structure of actinomycins(*182*)."

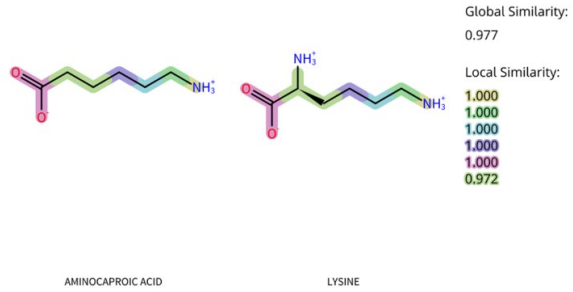
From the discovery paper:

"A comparative study of the inhibitory effect of the active substance against a large number of bacteria, using solid or liquid culture methods, brought out the fact that many of the Gram-positive bacteria were largely or completely inhibited by a concentration of 0.1 mg per liter of medium(*183*)."

## AMINOCAPROIC ACID

1964

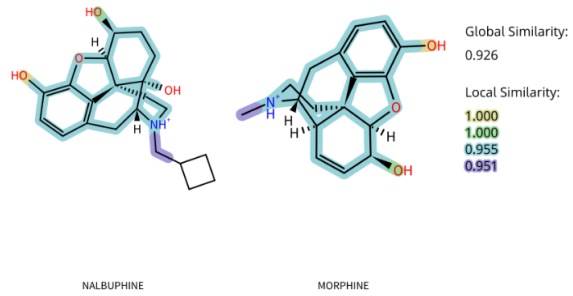
Analogue of the amino acid, lysine




## NALBUPHINE

1964

Analogue of morphine(*21*)




## PRALIDOXIME

1964

Antidote

## DOXAPRAM

1965

"It is known chemically as 1-ethyl-4-(2-morpholinoethyl)-3,3-diphenyl-2-pyrrolidinone. Doxapram was first synthesized in 1962 and found to have a strong, dose-dependent respiratory stimulant action in mammals. A pressor response following doxapram administration was also noted. Both of these effects were perceived to occur via stimulation of the

central nervous system (CNS). In fact, animals 'anesthetized' with phenobarbital were awakened by high dose intravenous doxapram while untreated animals developed convulsions. As such doxapram has been categorized as an analeptic agent (a stimulant of the central nervous system) with greater margin of safety than other CNS stimulants available at that time such as picrotoxin or pentylenetetrazol(*184*)."

I could not find the discovery paper cited in the previous quotation:

Ward JW, Franko BV. A new centrally acting agent (AHR-619) with marked respiratory stimulating, pressor, and "awakening" effects. Fed Proc 1962;21:325.

## INDOMETHACIN

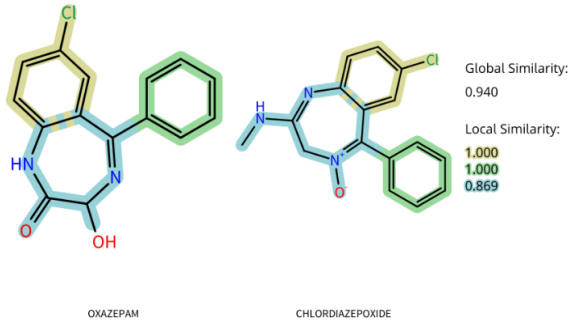
1965

It was discovered by screening 350 compounds in these animal models: carrageenan-induced rat paw model of inflammation, cotton string granuloma test, erythema elicited in the depilated skin of guinea pigs following irradiation with ultraviolet (UV) light:
"Across the Atlantic, Charles Winter, initially at Merck, Sharp, and Dohme and later at Parke-Davis, tried to develop his own model of inflammatory pain. He eventually developed the cotton string granuloma test and used it to identify indomethacin (synthesized by T. Y. Shen) as a potent antiinflammatory drug. Indomethacin was also particularly active in the carrageenan-induced rat paw model of inflammation. This assay turned out to be especially useful for measuring antiinflammatory activity. A similar model hadbeen used earlier by Randall and Selitto for detecting the analgesic activity of new compounds. Through the use of these models, 3 different chemical classes of drugs were discovered. First, Merck, Sharp, and Dohme identified indole antiinflammatory agents. Among 350 indole compounds screened in animals, the most successful were indomethacin (marketed in 1964) and sulindac. Indomethacin is still regarded as the gold standard for a compound that combines both anti-inflammatory and analgesic activity(*185*)."

## OXAZEPAM

1965

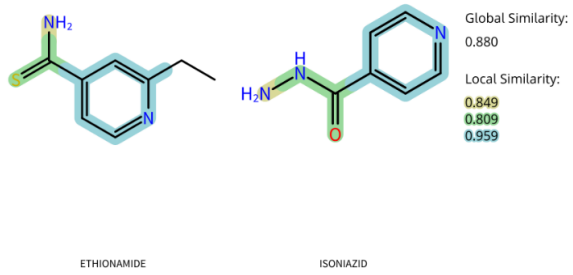
Analogue of chlordiazepoxide(*21*)




## ETHIONAMIDE

1965

Analogue of isoniazid




## TOLNAFTATE

1965

"This compound was developed by Japanese scientists who, over a ten-year period, assayed 3,000 topically applied drugs for toxicity and antifungal activity. In 1960, O-2-naphthyl *m*, N-dimethylthiocarbanilate was synthesized. This compound (tolnaftate) had antifungal activity and a low sensitizing index(*186*)."

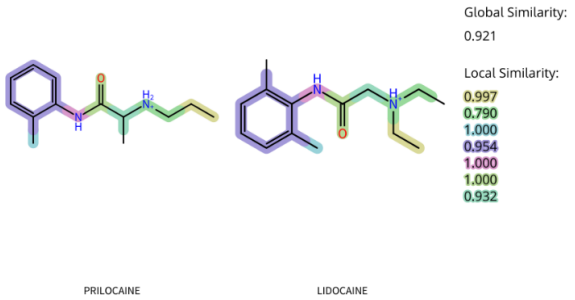
I could not retrieve the discovery report(*187*), but according to the quoted paragraph which is from a related paper, and trends at the time,

it seems that the screening was taken place against fungi cultures or animals infected with fungi.

PRILOCAINE

1965

Analogue of lidocaine




COLLAGENASE CLOSTRIDIUM HISTOLYTICUM

1965

Homologous of an endogenous enzyme, collagenase

AMANTADINE

1966

"l-Adamantanamine (amantadine), a stable, colorless, crystalline amine with an unusual symmetrical structure, reproducibly and selectively inhibits influenza viruses in tissue culture, chick embryos, and mice. The compound studied is the water-soluble salt, amantadine hydrochloride. Most of the tissue culture studies were carried out by plaque-inhibition techniques similar to those described (1), although hemagglutination inhibition and hemadsorption inhibition methods were also used. […]

Antiviral activity was also demonstrated in cultures of monkey kidney cells, canine kidney cells and human amnion cells. The activity of amantadine hydrochloride in mice was similar to that in tissue culture and in chick embryos(*188*)."

From the cited paper regarding the used tissue culture studies:

"A procedure has been developed whereby agar diffusion technics used in bacteriology can be applied to antiviral agents. Chick embryo cell monolayers were grown in Pyrex baking dishes, infected with virus and overlaid with agar. Filter paper discs impregnated with the test materials were deposited on the hardened agar surface. After proper incubation the virus produced plaques in the cell sheet. except in the area around a disc containing an antiviral agent. Since size of the plaque-free zone was proportioned to concentration of the antiviral agent present in the disc. bioassays were simply performed in exactly the same manner as done with antibacterial antibiotics(*189*)."

Regarding the discovery of the therapeutic potential of amantadine for Parkinson's Disease:

"Serendipitous discovery can also occur when a valuable indication for a drug is found even though it was not originally sought. The unexpected benefit scenario played out in the 1960s with the discovery that amantadine had important actions not just for addressing viruses and treating influenza, but also for treating Parkinson disease (PD) symptoms. […]

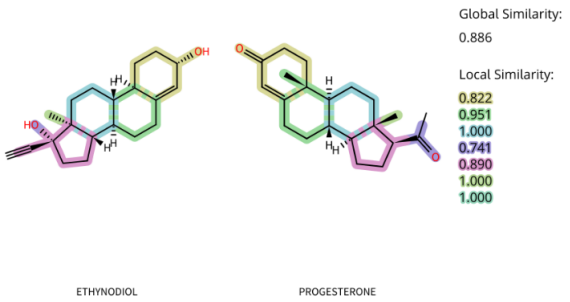
In April 1968, a 58-year-old woman with PD had reported to them an improvement in rigidity, tremor, and akinesia while taking amantadine for flu. She reported that her symptoms worsened upon stopping the medication. Prior to this report, minor CNS stimulation by amantadine was noted in animal studies and these symptoms included psychomotor agitation, tetrabenazine antagonism, anorexia, and convulsions. CNS stimulation and psychosis was also noted in human patients receiving 200 mg daily, and the CNS side effects were included in the package insert. The manufacturer, Smith Kline & French, did not have any similar adverse case reports, and recommended a test on a small population of 10 patients. Seven of these initial 10 patients reported improvement in PD

symptoms without any side effects. These promising findings prompted the first clinical trial of amantadine for PD in June 1968(*190*)"

## ETHYNODIOL

1966

Analogue of progesterone




## FUROSEMIDE

1966

"Muschaweck and Hajdu (1964) commented that, as the sulfonamide (thiazide) diuretics gained broad use in the late 1950s, several important side effects of relatively low incidence became evident, for example, increased $K^+$ excretion, elevated blood glucose, and elevated serum uric acid levels. Because of this, Muschaweck and Hajdu considered that there was room for improvement in the area of sulfonamide diuretics. Synthetic efforts in an aromatic sulfonamide series eventually led to the anthranilic acid derivative furosemide. In the dog, furosemide effected a considerable and equimolar excretion of $Na^+$ and $Cl^-$, accompanied by a greatly enhanced excretion of water, at doses that did not increase $K^+$ loss(*191*)."

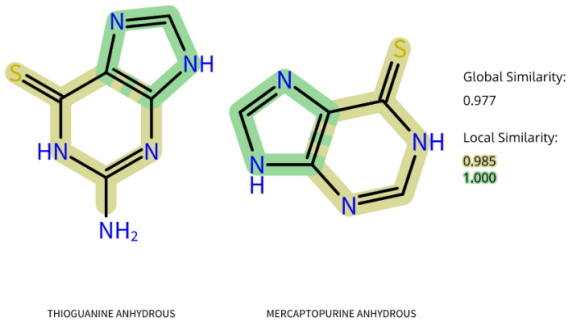
"The discovery of sulfonamides and the elucidation of their mechanism propelled medicinal chemistry forward. In the drug discovery field, the sulfonamide structure proved to be a rich source of molecules with many different, and useful, pharmacological properties. An early spin-off came from the clinical observation that some sulfonamides increased excretion of sodium bicarbonate in the urine by inhibiting carbonic anhydrase, an enzyme with an important role in renal bicarbonate excretion. This prompted researchers to develop improved diuretics. Modification of the sulfonamide structure led eventually to acetazolamide the first commercially available carbonic anhydrase inhibitor, as a diuretic in 1952. Following the diuretic trail led in turn to chlorothiazide (1957), the first of the thiazide diuretics, which is still in widespread use. Though devoid of carbonic anhydrase inhibitory activity, it was much more effective than acetazolamide in increasing sodium excretion. Still, further modifications led first to furosemide (1962)(*192*)"

Also see the acetazolamide entry.

## THIOGUANINE

1966

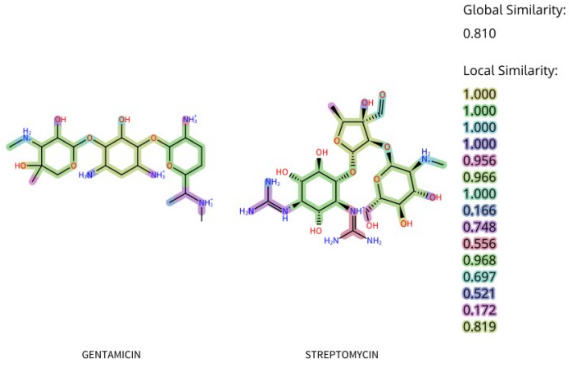
Analogue of mercaptopurine (purine analogue)




## GENTAMICIN

1966

Analogue of streptomycin



## ALLOPURINOL SODIUM

1966

From the discoverer(s):

"Since we knew from metabolic studies that 6-thiouric acid was one of the principal products of 6-MP catabolism, it seemed possible that we could interfere with this oxidation by inhibiting the enzyme responsible for it, xanthine oxidase. In the early days of seeking antimetabolites for the natural purines in our laboratory, xanthine oxidase had been one of the test enzymes. Doris Lorz had identified many substrates as well as inhibitors of this enzyme. These compounds had also been tested on *L. casei* and on animal tumors. To test for xanthine oxidase inhibition in vivo, we chose a compound that had no inhibitory effects on bacteria or tumors, and was nontoxic, but which was a potent inhibitor of xanthine oxidase. This compound was the hypoxanthine analog, 4-hydroxypyrazolo(3,4-d)-pyrimidine (allopurinol). When allopurinol was given to mice together with 6-MP, it did indeed inhibit the oxidation of 6-MP and potentiated the antitumor and immunosuppressive properties of 6-MP three- to fourfold. Moreover, the toxicity of 6-MP to mice appeared to be potentiated only twofold, so that the chemotherapeutic index of 6-MP was increased. With the collaboration of Wayne Rundles, we explored this combination in patients with chronic granulocytic leukemia, in whom the efficacy and metabolism of 6-MP could be investigated. The oxidation of 6-MP to thiouric acid was found to be inhibited in a dose-related manner, and the antileukemic activity of 6-MP was potentiated proportionally. When 300 mg of allopurinol was given together with 110 mg of 6-MP, 6-MP increased fourfold, whereas urinary thiouric acid was four times lower. Later investigations showed that the increased activity of 6-MP was accompanied by a proportional increase in toxicity. Thus, although less 6-MP was required to produce an antileukemic effect, the therapeutic index of 6-MP for leukemia remained essentially unchanged.

Xanthine oxidase is responsible not only for the oxidation of 6-MP, but also for the formation of uric acid from hypoxanthine and xanthine. Consequently, treatment with allopurinol produces a marked decrease in both serum and urinary uric acid. This presented the possibility of a unique approach to the treatment of gout and other forms of hyperuricemia(*113*)."

## ACETYLCHOLINE

1966

"Acetylcholine was first synthesised in 1867, and forty years later it was shown to be an extremely potent physiological depressor 'a hundred times more active in causing a fall of blood-pressure than is adrenaline in causing a rise.' Adrenaline itself was isolated in 1894 by Edward Schäfer and George Oliver […]

It was not until 1913 that naturally occurring acetylcholine was first isolated in the WPRL by Dale and his colleague Arthur Ewins. Their discovery of acetylcholine as a rare contaminant in a batch of ergot was a 'lucky accident' that Dale was fond of claiming in later life. Dale gleefully reported at the time to T.R. Elliott: 'We got that thing out of our silly ergot extract. It is acetyl-choline and a most interesting substance. It is much more active than muscarine, though so easily hydrolysed that its action, when it is injected into the blood-stream, is remarkably evanescent, so that it can be given over & over again with exactly similar effects, like adrenaline. Here is a good candidate for the rôle of a hormone related to the rest of the autonomic nervous system. I am perilously near wild theorising."

The following year Dale published an extensive paper on the pharmacology of an array of choline derivatives, and he noted two principal effects of acetylcholine: one that could

be reproduced by injections of muscarine; and one reproduced by nicotine. […]

He listed several instances of close correspondence between the effects of acetylcholine and the parasympathetic nervous system, but noted:

'The question of a possible physiological significance, in the resemblance between the action of choline esters and the effects of certain divisions of the involuntary nervous system, is one of great interest, but one for the discussion of which little evidence is available. Acetyl-choline is, of all the substances examined, the one whose action is most suggestive in this direction [of mimicking parasympathetic activity]. [...] On the other hand there is no known depot of choline derivatives, corresponding to the adrenine [adrenaline] depot in the adrenal medulla, nor, indeed, any evidence that a substance resembling acetylcholine exists in the body at all.' […]

In 1921 the Austrian pharmacologist Otto Loewi performed what is now regarded as a classic experiment, when he revealed that a denervated beating frog's heart could be made to slow and stop by the passage over it of fluid taken from that surrounding an innervated heart that slowed and stopped in response to stimulation of its vagus. Loewi suggested that a chemical, which he called *vagusstoff*, was released from the vagus of the first heart upon stimulation and transferred to the second, denervated heart.

Further work from Loewi and his colleagues showed that vagusstoff was a choline ester that was rapidly hydrolysed by an esterase, but he did not suggest that it was acetylcholine, which had still not been found to occur naturally in the animal body. Although Dale was one of those intrigued and excited by vagusstoff, and the possibility of its identification as acetylcholine, he remained concerned about acetylcholine's apparent absence from the animal body, as he confided to a colleague at the beginning of 1929:

'We are still struggling with the acetylcholine problem, which I mentioned to you when I saw you in the autumn. I am more and more convinced that the thing is there to be found, if only we can overcome the technical difficulties.'

Ironically, it was only a matter of months later that Dale and his chemist colleague at the NIMR, Harold Dudley did find acetylcholine as a natural constituent of the mammalian body. It was particularly unexpected as they were actually looking for endogenous histamine. In the light of its natural occurrence, Dale and Dudley reviewed the suggestive evidence of an acetylcholine-like substance being involved in a range of physiological activities […]

## The eserinised leech muscle: the key to acetylcholine

Less than a year later, Henry Dale wrote enthusiastically to Otto Loewi:

'I cannot close this letter without saying what a joy it is to have Feldberg back here, however much one deplores the conditions, which have driven him out of his own country. His importation of the leech test, which he based on Fuhner's earlier observations, seems likely to be as stimulating for my own work on chemical transmission, as the expulsion of the Huguenots from France was for the British textile industry.'

The leech test revolutionised the analysis of the role of acetylcholine. The principal problem that continued to bedevil physiological studies on acetylcholine was the extreme transiency of its effects, as it was quickly hydrolysed by circulating acetylcholinesterase. What Feldberg's leech-muscle preparation did was to provide a simple, reliable method to detect that acetylcholine. As he himself acknowledged:

'To make use of a metaphor: perhaps it was that I had brought with me a key that would open the doors. Dale and Gaddum seemed to

know what lay behind them, but I had the key.'

That 'key' was the use of eserine, which inhibited the activity of the enzyme acetylcholinesterase. The technique was based on the discovery by the German pharmacologist Führer, that when eserine was added to an organ bath in which a leech muscle was suspended, the muscle became extremely sensitive to acetylcholine, and he suggested the preparation as an assay system for eserine. Feldberg merely reversed the procedure and used the eserinised muscle as a sensitive and simple assay for acetylcholine(*193*)."

From the 1914 isolation paper cited of Ewins cited in the previous quotation:

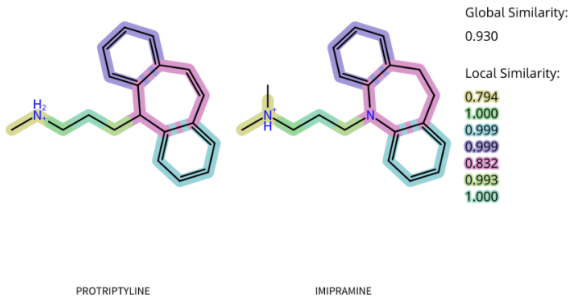
"In addition, however, to those of apparent therapeutic importance, certain other effects are shown in a more or less marked degree by all samples of the drug and by some with marked intensity. These effects have been familiar to the pharmacological workers in these laboratories for some years, but apparently have not been the subject of exact description or investigation. Conspicuous among these is an inhibitor effect on the heart, suggesting an intense though curiously evanescent muscarine action.

Finding that the prominence of this effect in the action of different specimens of ergot ran closely parallel with their stimulant action on intestinal muscle, and that both effects were abolished by atropine, Dr Dale was led to suspect the presence in ergot of a principle producing both these effects. He was also able to devise a convenient method for its physiological estimation by the use of a loop of rabbit's intestine isolated according to Magnus's method. When an opportunity recently occurred of obtaining an adequate supply of a preparation which exhibited this type of action with marked intensity, he suggested to me that an attempt should be made to identify the supposed new principle, and has followed the successive steps of its isolation with the physiological control. This paper deals with the chemical procedure by which the principle in question was isolated and identified. The details of its action will be described elsewhere by Dale(*194*)."

## PROTRIPTYLINE

1967

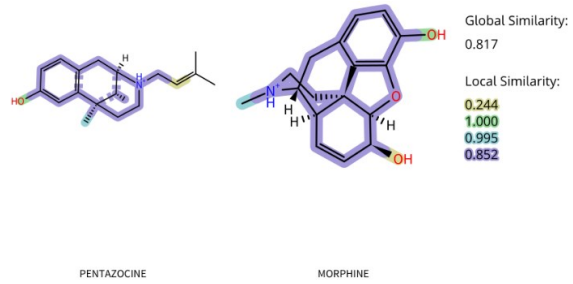
Analogue of imipramine




## PENTAZOCINE

1967

Analogue of morphine(*21*)




## HYDROXYUREA

1967

It was first synthesized in 1869(*195*). It was observed that it inhibits the cell growth of leukocyte(*196*). This inspired the investigations of its antitumor effects(*197*).

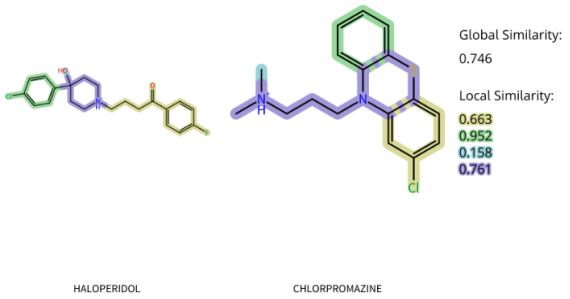
"Hydroxyurea was synthesized by Dresler and Stein. It is a compound soluble in water that spreads equally throughout the body fluids. At first, it was shown that HU inhibits the leukocyte cell growth. However, its use as an antitumor agent began only in the 1960s as it was found that HU blocks DNA synthesis through inhibition of the ribonucleotide

reductase enzyme(*197*).”

## HALOPERIDOL

1967

Analogue of chlorpromazine




Quoting from a paper by Paul Janssen and his colleagues which is relevant to the discovery of haloperidol(*198*):

“All pharmacological results to be described were obtained in adult white mice of both sexes. The substances under investigation were administered in aqueous solution by subcutaneous injection. The 5 screening methods adopted were chosen for the following reasons:

(1) In view of the desirability to obtain quantitative data on a large number of new compounds, preference was given to relatively simple methods,

(2) Experimental evidence showed these 5 methods to be **reproducible** within this laboratory. All results to be described were systematically **duplicated** on a **blind** basis with an interval of about one month and the **more important compounds were retested several times in various seasons over a period of up to 4 years**. Very few statistically significant (P 0.05) differences were found between successively obtained data.

(3) All CNS depressants investigated in this laboratory are active in at least one of the 5 screening tests used. Qualitatively different results, allowing for gross classification of a new compound, are obtained in this series of tests with various types of known CNS depressants such as morphine-like narcotics, hypnotics, neuroleptics, sedatives with atropine-like activity (e.g. benactyzine, scopolamine, promethazine), muscular relaxants, anti-histamines, etc.

(4) The effects of administration were measured at several intervals after dosage in order to obtain data on peak effect and duration of action and to minimize the risk of ‘missing’ significant activity(*198*).”

Pharmacological tests(*198*):

(A) Inhibition of righting reflex in mice.

(B) Potentiation of the hypnotic effect of pentobarbital in mice.

(C) Pentobarbital potentiation ratio (PPR).

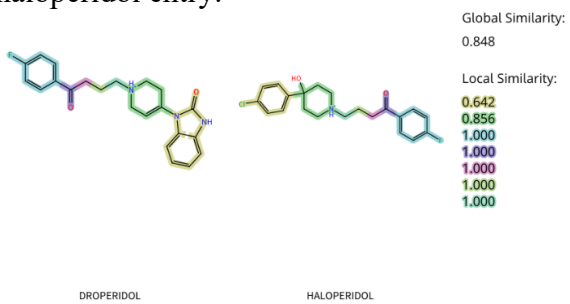
(D) Influence on induced Coordinated activity (rotating rod).

## DROPERIDOL

1967

Analogue of haloperidol

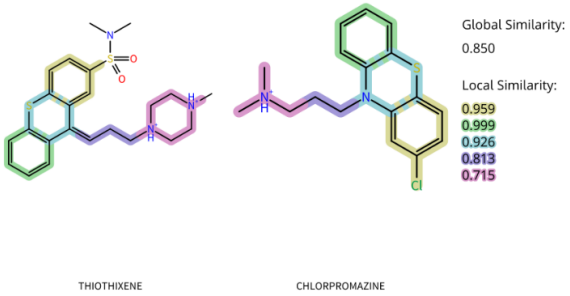
Also discovered by the Janssen team, see the haloperidol entry.




## THIOTHIXENE

1967

Analogue of chlorpromazine



## PROPRANOLOL

1967

Following quotations in this entry are from the discoverer, the legendary James Black:

"This lecture illustrates the early stages in the planning and discovery of propranolol, an adrenaline β-adrenergic receptor antagonist, and cimetidine, a histamine H2-receptor antagonist-the first examples of clinically useful drugs from each of these classes. The significance of selective agonists, partial agonists, and syntopic antagonists and the importance of the bioassay and the use of molar models in the drug discovery process are discussed. For the future, an outline of potential developments in hormone-receptor concepts is offered leading to the conclusion that progress may depend on improvements in bioassays and related molar modeling(*199*)."

Pronethalol, the prototype compound of propranolol was discovered based on the structure of isoprenaline and its analogue, DCI and using physiologically-relevant in vitro assays:

1. "the classical Langendorff preparation, the isolated, spontaneously beating, guinea pig heart(*199*)"
2. "a technique for simultaneously recording blood pressure and heart rate, in analog form, in anesthetized animals(*199*)"
3. "an in vitro assay based on guinea pig cardiac papillary muscles as a way of measuring the contractile effects of isoprenaline independently of rate changes(*199*)."

After the discovery of pronethalol, in order to find a better candidate:

"Pronethalol always seemed to us to be a prototype drug, good enough to answer questions of principle but not good enough to be marketable. So a large chemical group, directed by Crowther, was assembled to try to find a more active, safer replacement for pronethalol. The discovery of ICI 45520, propranolol, a naphthyloxy propanolamine derivative, was the result.

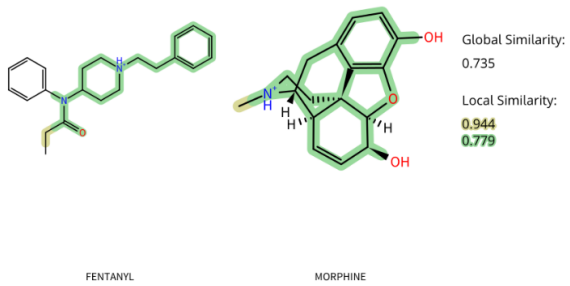
Our bioassays, which had been developed as qualitative screens, had now to be adapted for comparative quantitative bioassay. The isolated, spontaneously beating, guinea pig right atrial preparation proved to be excellent for these assays. The nature of the surmountable antagonism by propranolol was analyzed by relating the rightward displacement of cumulatively derived dose-response curves to the concentration of antagonist. The linearity and slope of the Schild plot relating these variables indicated the likelihood that adrenaline and propranolol were competing for the(*199*)."

## FENTANYL

1967

R 4263 = fentanyl

Analogue of morphine(*21*)




From Paul Janssen, one of the discoverer(s):

"Recent findings in this laboratory revealed the extremely high narcotic potency of certain 4-anilino-piperidines (fig. 15).

In these surprisingly active compounds, the phenyl ring, attached to the piperidine nucleus through a nitrogen atom, is separated by a chain of 4 atoms from the basic nitrogen, whereas in all the other potent narcotics, previously discussed, this chain consists of only three atoms. […]

FIG. 15: Compound R 4263, the extremely potent (up to 5,000 times morphine) prototype of a new series of 4-anilino-piperidines.

Figure 19, summarizing the relevant data discussed in this paper, represents the common stereochemical features found among the compounds that are known to display typical morphine-like properties at low dose levels.

Because these molecules look alike chemically, it appears reasonable to assume that there might be something like a common receptor for morphine-like drugs(*200*).”

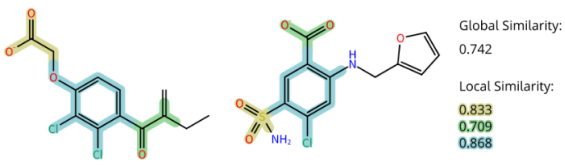
From the disclosing patent:

“Evidence that the analgesic effect of phentanyl is potentiated by dehydrobenzperidol is obtainable by the technique of Branchi and Franceschini [Brit. J. Pharmacol. 9, 280 (1954)]. Briefly, this method comprises placing an arterial clip, the jaws of the clip being covered with thin rubber tubing, on the root of the tail of a mouse for 30 seconds. If, following drug treatment, the animal does not bite the clip within the allotted period, the drug is considered to have induced an analgesic effect. The untreated animals always bite the clip when it is placed on the base of the tail. In our studies we observed that the animal vocalized in addition to biting at the clip of the tail. This second parameter was also taken into account in our experiments. Thus, for an analgesic effect to be present the animal must neither vocalize nor bite the clip. In the data given in Tables I-IV below, the drugs were given in the form of 0.1 molar tartaric acid solutions subcutaneously to white albino mice(*201*).”

## ETHACRYNIC ACID

1967

Analogue of furosemide

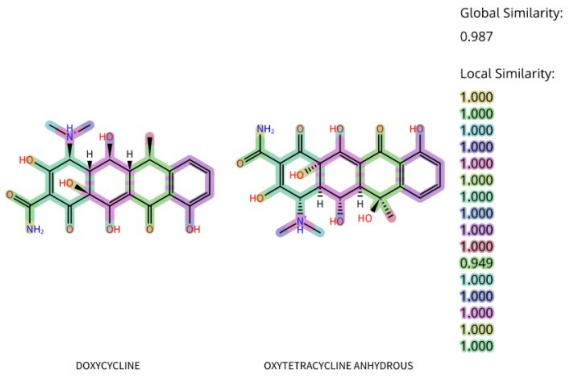



ETHACRYNIC ACID FUROSEMIDE

## DOXYCYCLINE

1967

Analogue of oxytetracycline(*21*)




DOXYCYCLINE OXYTETRACYCLINE ANHYDROUS

## ETHAMBUTOL

1967

From two papers of the discovery team:

“In the course of screening randomly selected synthetic compounds, N, N’ -diisopropylethylene-diamine was found to protect mice from an otherwise lethal infection with *Mycobacterium tuberculosis*, strain H37Rv. Following this lead, numerous related compounds ‘were synthesized without appreciable improvement in activity until hydroxyl functions were introduced. The most promising compound of this series was found to be the dextro isomer of 2,2’-Cethylenediimino)-di-l-butanol dihydrochloride which has an efficacy index (tolerance/potency) similar to that of isoniazid when administered orally and superior to that of streptomycin when given parenterally(*202*).”

“This paper reviews the laboratory chemotherapeutic studies from which ethambutol emerged as a suitable candidate for pharmacological work in animals in preparation for clinical trial in man. Investigation of this series of compounds followed the observation of activity in N, N’-diisopropyl ethylenediamine in the screening of randomly selected compounds. The ethylenediamines described herein are not related to known

antituberculous agents and comprise an entirely new type of antimycobacterial structure.

Extensive exploration of analogs of this active compound was justified when the characteristics of its activity were determined. The activity of N, N'-diisopropyl ethylenediamine was specifically antimycobacterial *in vivo* and i*n vitro*, and its full activity resulted from oral as well as parenteral administration using various dosage schedules. All activities cited are *in vivo* against a uniformly fatal Mycobacterium tuberculosis, var. hominis H37Rv infection in mice characterized by rapidly fulminating disease of the lungs produced by intravenous injection of the bacterial culture(*203*)."

## MEFENAMIC ACID

1967

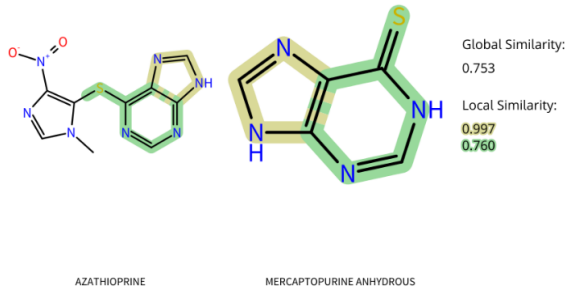
"The Parke Davis Co. (Detroit) introduced the N-phenyl anthranilic acids ('fenamates'), originally identified by Claude Winder as inhibitors of the UV erythema in guinea pigs. Mefanamic acid (Ponstan, 1961), flufenamic acid (Arlef, 1963) and sodium meclofenamate (Meclomen, 1964) were all successively introduced for treating arthritis(*89*)."

"To understand these clinical observations, a pharmacologist at Geigy, Gerhard Wilhelmi, developed novel models of inflammation. Phenylbutazone turned out to be particularly active in reducing the erythema elicited in the depilated skin of guinea pigs following irradiation with ultraviolet (UV) light. This was the first model of inflammation used to define the activity of what we now call nonsteroidal antiinflammatory drugs (NSAIDs). By applying this model, several phenylbutazone analogs and the phenylbutazone metabolite, oxyphenbutazone, as well as the fenamates, another chemical class of antiinflammatory agents, were discovered to be of particular value in inflammation and inflammation-related pain(*185*)."

## AZATHIOPRINE

1968

Analogue and prodrug of mercaptopurine (purine analogue)




## DEFEROXAMINE

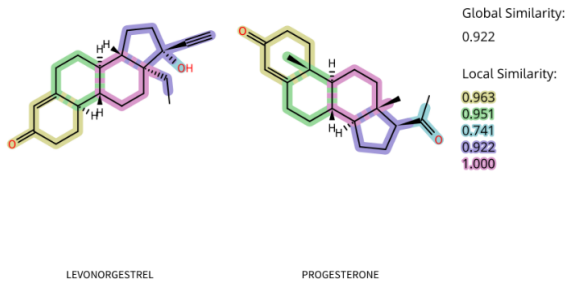
1968

Iron-chelating agent

## LEVONORGESTREL

1968

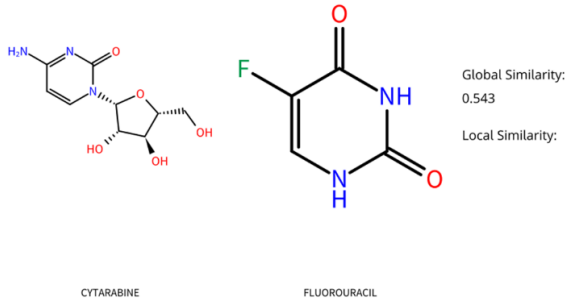
Analogue of progesterone(*21*)




## CYTARABINE

1969

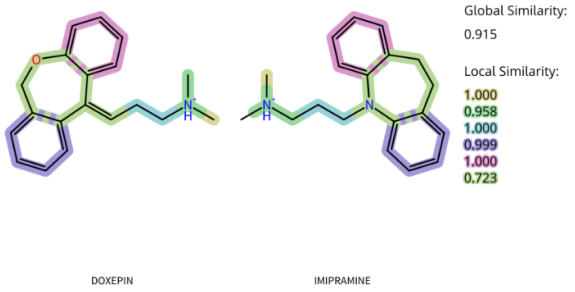
Analogue of fluorouracil (Pyrimidine)(*21*)




## DOXEPIN

1969

Analogue of imipramine




## PROCARBAZINE

1969

From the discovery papers:

"When testing a series of hydrazines for another purpose 1-methyl-2-benzyl-hydrazine was found to have a pronounced tumour inhibitory effect. The systematic variation of its structure showed that efficacious compounds were of general formula *R*-NH-NH-$CH_3$, *R* representing a wide variety of organic radicals, particularly substituted benzyl groups(*204*)."

From the discovery paper cited in the previous quotation:

"1-Methyl-2-benzyt-hydrazine has been found to inhibit the growth of transplantable tumours in mice and rats. As this compound did not show a satisfactory therapeutic index and as it led furthermore to liver damage, a large series of derivatives has been synthesized by ZELLER et al. in order to find substances having better chemotherapeutic properties combined with lower toxicity. Only compounds with the group -NH-NH-$CH_3$ a show marked cytotoxic effects. In this paper the tumour inhibiting properties of 1-methyl-2-*p*-(isopropylcarbamoyl)benzyl-hydrazine hydrochloride and 1-methyl-2-p-allophanoylbenzyl-hydrazine hydrobromide are described. A detailed report on these investigations will be given elsewhere.

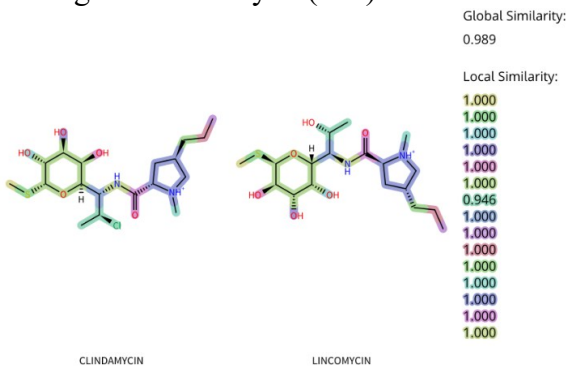
*Methods.* The experiments were done on the following transplantable tumours: Ehrlich carcinoma (solid form), Ehrlich carcinoma (ascitic form), Crocker sarcoma S180, Walker carcinosarcoma 256 and uterus epithelioma (Guérin) T8.

In the case of tumours growing in solid form, small tumour fragments were implanted subcutaneously, where-as of the Ehrlich ascites carcinoma ascites cell suspensions were injected intraperitoneally. Groups of ten animals were used for each dose. Daily administration of the compounds in aqueous solution was started on the day after the implantation, either by intraperitoneal or oral route(*205*)."

## CLINDAMYCIN

1970

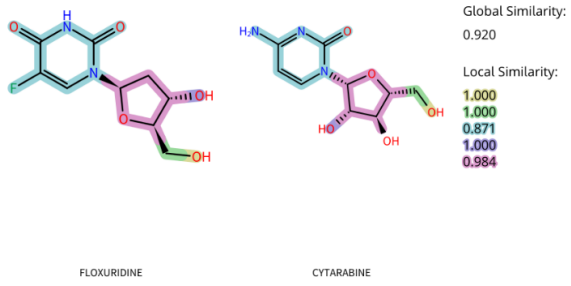
Analogue of lincomycin(*179*)




## FLOXURIDINE

1970

Analogue of cytarabine (Pyrimidine)




## PENICILLAMINE

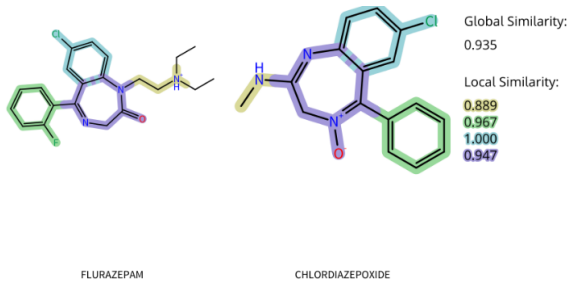
1970

Copper chelating agent

## FLURAZEPAM

1970

Analogue of chlordiazepoxide




## KETAMINE

1970

From the discoverer(s):

"PCP and its derivatives are the result of the initial discovery of a new and unexpected chemical reaction, then unexpected pharmacological activity and potential therapeutic merit, then disappointment and a subsequent systematic search for better chemical derivatives, again for potential therapeutic benefit. […]

The story of PCP starts in 1956, just 24 years ago, when a medicinal chemist, Dr. Victor Maddox of the Product Development Department of Parke Davis and Company in Detroit, Michigan, began to investigate chemical reactions to Grignard reagents with nitriles. What that means is that there are special ways of making new organic chemicals of which the Grignard reagent is a classic one. Dr. Maddox was interested in elaborating some rather new, stable immino or ketone compounds with novel chemical structures which he hoped would have therapeutic merit. What actually occurred in the reaction using the chemicals, called a-aminonitriles, was a very unusual elimination of the nitrile function and substitution by rather large (what we called aryl or alkyl moieties) of the Grignard reagent. The second compound in this series made by Dr. Maddox, using this novel and unique reaction, was PCP itself. Having prepared adequate quantities of the first as well as the second of these compounds, Dr. Maddox submitted them to a pharmacologist by the name of Dr. Graham Chen at Parke Davis for general pharmacological testing. This testing was known as the GP (for general pharmacological) series and PCP was assigned number GP 121 as its code name. Shortly thereafter, about a week after Dr. Maddox submitted the material, Dr. Chen called Dr. Maddox and excitedly told him that GP 121 was the most unique compound that he, Dr. Chen, had ever examined. He called it a 'cataleptoid anesthetic' and because of it, the so-called CL-1 series of chemicals was born. In fact, Dr. Chen developed the pigeon-righting reflex as the basis of studying this series of 'cataleptoid anesthetics.' PCP had properties similar to a cataleptoid agent called bulbocapnine, a very old compound coming from a flower called Dutchman's Breeches. Dr. Chen asked Dr. Maddox to come over to the pharmacology laboratory to observe some cats which received low doses of PCP. The cats were in a state of catalepsy. One of them was sitting in this state for 24 hours. The only movement besides breathing that was observable was that of the cat's eyes moving back and forth in this sitting position. Another most unusual demonstration of the effects of PCP was in the rhesus monkey in which it was possible to give an essentially wild Indian monkey a small dose of PCP and produce serenity, tranquility and peace. Hence, the name Sernyl® and subsequently Sernylan® came about. […]

As patients were anesthetized with PCP, it became obvious that the drug, when properly administered by an anesthesiologist, was indeed very safe, far safer than most anesthetics that were then available. There was a peculiar problem that about 30 percent of the patients (unpredictably) had emergence delirium. There was the sensation of feeling no arms or legs and being in outer space. […]

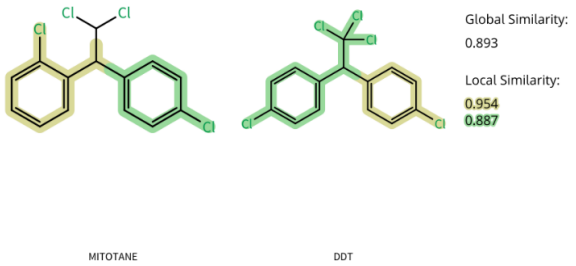
In 1962 Cal Stevens, then head of Organic

Chemistry at Wayne State University and a consultant to Parke Davis, made some novel ketone analogs of PCP which were tested by Dr. Duncan McCarthy at Parke Davis in monkeys. In 1963 Cl 581, ketamine, was found to be the best as an anesthetic(*206*)."

## MITOTANE

1970

Analogue of the insecticide dichlorodiphenyl trichloroethane (DDT). DDD, an insecticide analogue of DDT, was shown to produce adrenal atrophy in dogs(*207, 208*).




## LEVODOPA

1970

Also see the dopamine entry.

"L-Dopa, the naturally occurring isomer of the amino acid 3,4-dihydroxyphenylalanine, was first isolated in 1913 from legumes (seedlings of *Vicia faba*) by Marcus Guggenheim (1913). Already two years earlier, Casimir Funk (1911) had synthesized D,L-dopa in the laboratory. Both he and Guggenheim considered the amino acid as a possible parent compound of adrenaline. […]

Guggenheim, in addition to isolating L-dopa, was also the first to perform, with the isolated material, some simple pharmacology. In a self-experiment, Guggenheim ingested 2.5 g of L-dopa and noticed its emetic action which, however, he interpreted as an unspecific irritation of the gastric mucosa […] In Guggenheim's hands, L-dopa was essentially ineffective, be it on the rabbit blood pressure, on the isolated rabbit uterus and intestine, or on the conscious rabbit's general behaviour.

The view that L-dopa was essentially devoid of biological activity seems to have prevailed for many years. However, in 1927, nearly fifteen years after Guggenheim's negative observations, Hirai and Gondo (1927) found that D,L-dopa caused a strong hyperglycemia in the rabbit. In 1930 Hasama demonstrated that in the rabbit D,L-dopa, in contrast to the vasopressor effect of adrenaline, produced a clear fall in arterial blood pressure […]

In view of these early 'DA' and L-dopa studies, including the study by Van Arman (1951) in rats with adrenals depleted by insulin, it was not surprizing that in reserpine-treated animals (rabbits), Carlsson, in 1958, found that D,L-dopa injections restored depleted brain DA. At about the same time, L-dopa was found to cause central, behavioural as well as EEG activation and to antagonize reserpine's 'tranquilizing' effects […]

Probably the most decisive observation in the history of L-dopa was the discovery of the DA deficit in the striatum specifically in patients with PD […]

Together with the relationship previously demonstrated in laboratory animals, between reserpine-induced tranquilizing action and L-dopa and brain DA, the striatal DA deficit, limited specifically to the brain of patients with PD, immediately suggested the step 'from brain homogenate to treatment', that is the rational use of L-dopa in order to replenish the missing striatal DA in the brain of patients suffering of PD. In view of the fact that there existed since the early 1940s ample experience with the use of intravenously injected L-dopa in humans (and the accompanying side-effects, including the recent study by Degkwitz et al., 1960), in 1961 Hornykiewicz together with the neurologist Birkmayer performed a trial with i.v. L-dopa in a group of 20 patients. They for the first time reported on a dramatic improvement of all motor deficits related to the symptom of akinesia, lasting for several hours. At the same time, and

independently, Theodore Sourkes and Gerald Murphy induced the neurologist Andre Barbeau to give L-dopa orally to PD patients, and observed a beneficial effect on the Parkinsonian symptom of rigidity(*209*)."

## FLAVOXATE

1970

From the discovery paper:

"The basic esters of carboxylic acids form a large group of substances with various pharmacological properties, e.g. local anaesthetic, spasmolytic, nicotinolytic and tranquilizing. As the type of biological action seems to be determined very often by the esterifying acid, a study was undertaken to examine the pharmacological properties of basic esters of new types of acids.

Previously some chromone and flavone carboxylic acids had been tested; the investigation has now been extended to 3-methylflavone-8-carboxylic acid, which forms the subject of this paper.

The pharmacological screening showed that one of the derivatives of the series, i.e. the piperidinoethyl ester (Rec 7-0040) [Flavoxate], possesses a very marked papaverine-like muscle-relaxing activity. The detailed pharmacological properties will be described elsewhere. Particularly interesting is the observation that the product does not seem to affect normal tone or movements of intestine but it inhibits specifically spasms provoked by various agents. Rec 7-0040 also has analgesic and local anaesthetic activity which could perhaps be of therapeutidal importance in cases where the spastic condition is sustained by pain stimuli(*210*)."

From the related discovery paper mentioned in the previous quotation:

"The pharmacological properties of piperidinoethyl-3-methyiflavone-8-carboxylate hydrochloride (Rec 7-0040), a new papaverine-like smooth-muscle relaxant, are described. The new drug has a lower acute toxicity than papaverine and, on many preparations, a higher antispastic activity, whereas the movements of the intestine seem less affected by Rec 7-0040 than by papaverine. The smooth-muscle-relaxing activity of the new drug can be demonstrated also *in vivo* on the intestinal and bronchial musculature. The dilator activity on the peripheral vascular bed is about 10 to 20 times lower than that of papaverine. In contradistinction to papaverine, Rec 7-0040 shows also a marked analgesic and local anesthetic action. The new compound does not seem to interfere with the autonomic nervous system(*211*)."

## COSYNTROPIN

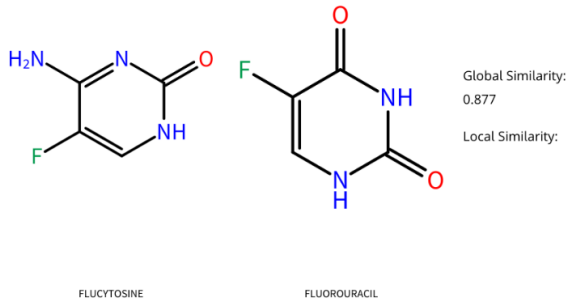
1970

Diagnostic

## FLUCYTOSINE

1971

Analogue of fluorouracil (Pyrimidine Analogue)




## PYRANTEL

1971

The screening program leading to the discovery of pyrantel comprised these models: mice infected with *Nematospiroides dubius* (*Heligmosomoides polygyrus bakeri*), rats infected with *Nippostrongylus muris*, mice infected with three parasites that covered three intestinal niches within the host (the duodenum, ileum, and cecum) (two nematode suborders (Strongylata, Ascaridata) and one cestode order (Cyclophyllidea)), mice with

natural infections of *Syphacia obvelata* and *Aspicularis tetraptera*, inoculated with 40 larvae of *N. dubius*, and 5000 ova of *Hymenolepis nana*, infected sheep, infected dogs(*212-215*)

## CEFALEXIN

1971

From the discoverer(s):

"In 1945, when the remarkable therapeutic properties of penicillin were becoming widely known in Europe, he looked for antibiotic-producing organisms near a sewage outlet by the seashore, thinking that antibiosis might be involved in self-purification of the effluent. […]

Brotzu quickly isolated from a sample of seawater a fungus that he identified as *Cephalosporium acremonium* and that produced antibiotic material with activity against gram-positive and gram-negative bacteria. Later work in Oxford was to show that this organism was able to produce at least three antibiotics, all new and all with some chemotherapeutic properties. The chance that such an organism would be discovered in such a small-scale screening program must have been very small.

Brotzu appears to have dispensed with toxicity experiments in animals. He injected culture filtrates of the organism directly into staphylococcal and streptococcal lesions, particularly boils and abscesses. He also made a crude extract containing active material and boldly injected it intramuscularly and intravenously into patients with brucellosis, paratyphoid infections, and typhoid fever; although his patients showed febrile reactions, he thought that the results were promising, especially in the case of typhoid(*216*)."

## CYSTEINE

1971

Endogenous amino acid(*217*)

## CAPREOMYCIN

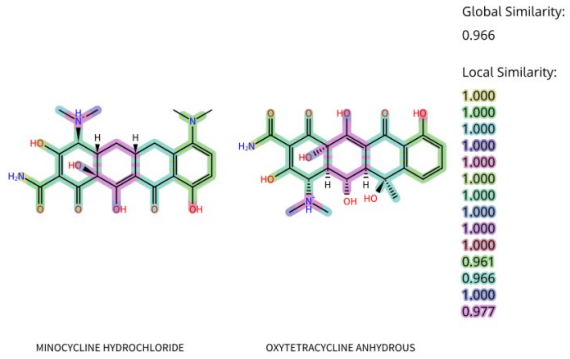
1971

"In 1960 HERR et al. isolated an antibiotic from the fermentation liquid of *Streptomyces capreolus* that chiefly inhibited the growth of mycobacteria. This was capreomycin(*218*)."

## MINOCYCLINE HYDROCHLORIDE

1971

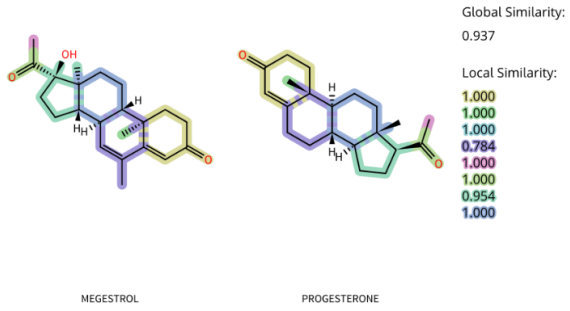
Analogue of oxytetracycline(*21*)




## MEGESTROL

1971

Analogue of progesterone




## HALOPROGIN

1971

"Haloprogin was shown to have a broad in vitro spectrum for dermatophytes, *Candida albicans* and related yeasts and certain gram positive bacteria(*219*)."

I could not find the full-text of the 1963 discovery paper cited in the previous quotation: PMID: 14274963

## RIFAMPIN

1971

From the discoverer(s):

“Rifampin was developed in the Dow-Lepetit Research Laboratories (Milan, Italy) as part of an extensive program of chemical modification of the rifamycins, the natural metabolites of *Nocardia mediterranei*. One peculiar fact was that all of the studies leading to highly active derivatives were performed on a molecule (rifamycin B) that was itself practically inactive. The first chemical modifications led to the discovery of rifamycin SV […]

An intensive strategy for chemical modification of the basic rifamycin structure was planned, with the aim of obtaining a compound with the following improvements over rifamycin SV in chemotherapeutic properties […]

Some of these derivatives showed good in vivo activity when administered orally. […]

Many of these derivatives were extremely active, both in vitro and in vivo, against M. tuberculosis and other gram-positive bacteria and were moderately active against gram-negative bacteria. The in vivo activity of some of these derivatives in infected animals was of the same order whether the products were administered orally or parenterally; this observation suggested good absorption from the gastrointestinal tract. In various experimental infections, the hydrazone of 3-formylrifamycin SV with N-amino-N’-methylpiperazine, designated rifampicin or rifampin, was the most active after oral administration and was also the least toxic. Rifampin was therefore selected for clinical studies(*220*)”

## FLUOCINONIDE

1971

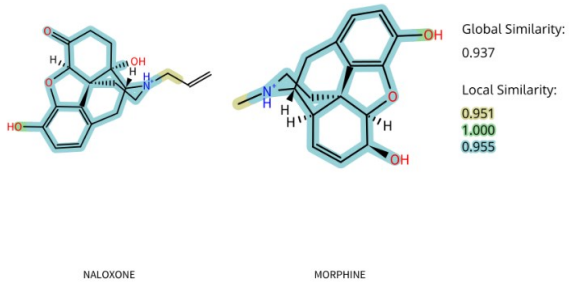
Analogue of cortisone(*21*)

Error in similarity calculation by FTrees

## NALOXONE

1971

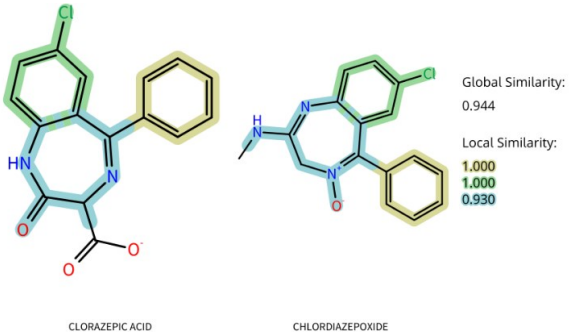
Analogue of morphine(*21*)




## CLORAZEPIC ACID

1972

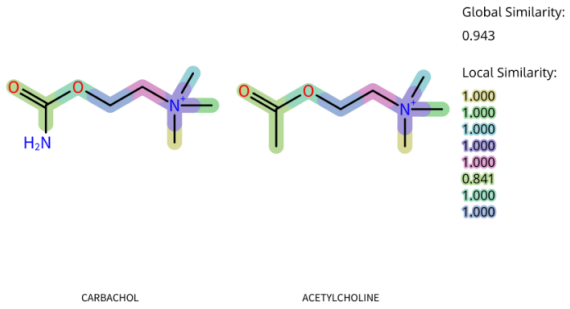
Analogue of chlordiazepoxide(*17*)




## CARBACHOL

1972

Analogue of acetylcholine




## PANCURONIUM

1972

Malouetine was extracted in 1960 from *Malouetia bequaertiana* and it was shown in animal experiments that it had similar

neuromuscular blocking activity to d-tubocurarine but was only one-third as toxic.

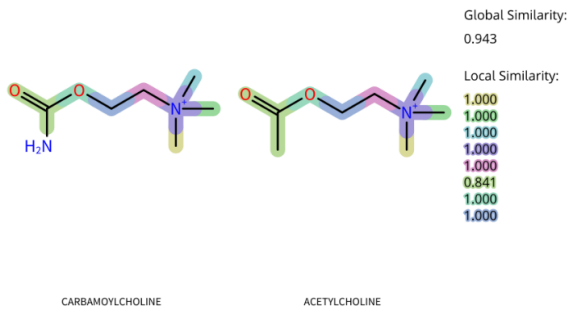
“Aware of the early reports on malouetine, a pharmacist, Mohammed Alauddin, had the idea of using the steroid nucleus as a supporting moiety upon which to append two quaternary ammonium groups in different spatial arrangements(*221*).”

The experiments of Alauddin, Martin-Smith, Lewis Caddy, and Sugrue tested the synthesized series in these models: Cat gastrocnemius muscle/sciatic nerve, Hen gastrocnemius muscle/sciatic nerve, Frog rectus abdominis muscle, Rat phrenic nerve/diaphragm. These experiments for the first time challenged the ‘two-point’ attacment theory for binding to acetylcholine receptors, and later led to the discovery of an analogous compound, pancuronium. They also had direct role in the discovery of pancuronium via the consultation of two of its researchers (Martin-Smith and Lewis) to members of the discovering team (Colin L. Hewett, W. Roger Buckett, David S. Savage)(*222*).

## CARBAMOYLCHOLINE

1972

Analogue of acetylcholine




## CROMOLYN

1972

Dr. Roger Altounyan noted that prior inhalation of one compound partially protected antigen-challenged guinea pigs, even though it had no bronchodilator properties.

“Roger knew that human asthma and bronchospasm induced in guinea pigs had different features (eg, antihistamines did not help his asthma) and was convinced that the experimental compounds needed to be tested in human asthma. He therefore persuaded the chemists to give him some to try on asthma that he would induce in himself.

At the start of each clinic, he would induce an asthmatic attack in himself either by inhaling histamine or methacholine or an aerosol of an extract of guinea pig hair, to which he was sensitive, measuring its progress and severity on the basis of $FEV_1$. He then tested the ability of new compounds to prevent or reverse these attacks by inhaling them either before or after the challenge. Most new compounds had little effect, but prior inhalation of one intensely bitter, short-acting compound with no bronchodilator properties did significantly reduce his asthmatic reaction. Incidentally, it was ineffective in protecting guinea pigs.

Between July 1957 and eventual success 8 years later, he must have induced about a thousand asthmatic attacks in himself. Some were frighteningly severe: he often allowed the $FEV_1$ to fall to less than 0.5 L before aborting the attack with isoproterenol. Several of the new compounds provided limited protection against antigen challenge, but none were sufficiently potent, acceptable, or both to be therapeutically useful. But as the work continued, he began to see a structure-activity relationship to guide the development of new compounds.

Although a new compound clearly protected against inhaled antigen, he was wondering if it would work in natural clinical asthma. This was tested in a volunteer patient with severe allergic asthma. These studies on himself and uncontrolled studies on volunteer patients gave birth to cromolyn(*223*).”

## FLUORESCEIN

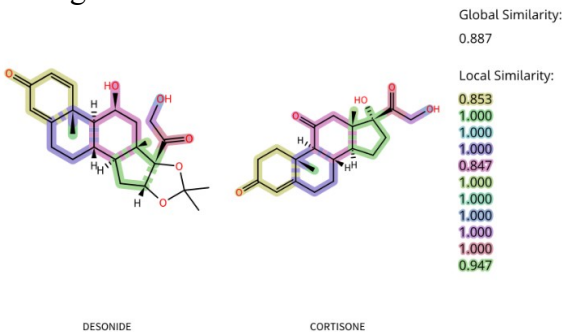
1972

Diagnostic

DESONIDE

1972

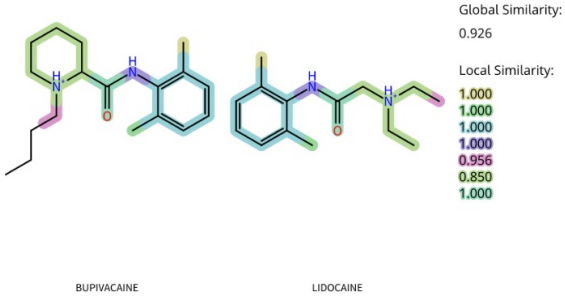
Analogue of cortisone




BUPIVACAINE

1972

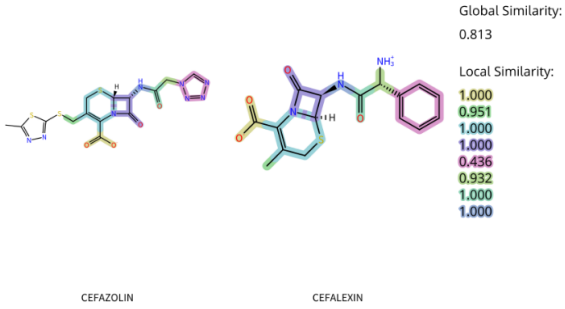
Analogue of lidocaine




CEFAZOLIN

1973

Analogue of cefalexin(*21*)



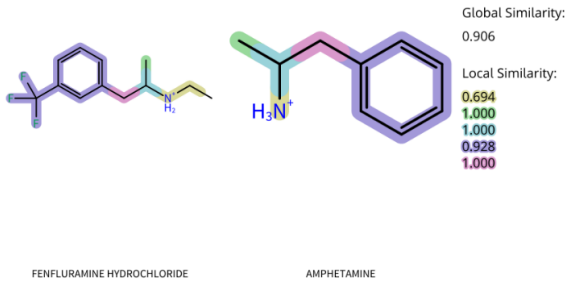

TECHNETIUM TC-99M

1973

FENFLURAMINE HYDROCHLORIDE

1973

Analogue of amphetamine




DIAZOXIDE

1973

After the discovery of the antibacterical sulfonamides, it was observed that they had some side effects on glucose metabolism, some of them had hyperglycemic effects, some others hypoglycemic effects and others without any obvious effect on blood sugar. After the birth of diuretics out of sulphonamides, it was observed that chlorothiazide had also some hyperglycemic and antihypertensive effects. Some postulated that its antihypertensive effect is not entirely dependent on its diuretic effect. To test this, a sulfamyl-less analogue of chlorothiazide, diazoxide, was synthesized. During further animal and human tests, its potential for the treatment of hyperinsulinemic states was discovered.

"This historical narrative on the antihypertensive hyperglycemic sulfonamide, diazoxide, really begins in the 1930's with studies of the antibacterial sulfonamides. […]

The toxicity of the sulfonamides was studied by a number of investigators in the late 1930's. Even earlier (1930), Ruiz and colleagues in a little-read Argentinian journal, reported several sulfonamide compounds as having a hypoglycemic effect. […]

Loubatieres, in studies from 1942 to 1946, also at Montpellier, suggested the use of hypoglyc emic sulfonamides in diabetes and described their mechanism of hypoglycemic action. He also found that some sulfonamides were hypoglycemic some were

hyperglycemic and that others had little or no effect on 'blood sugar' levels.

Logically, those studies of the sulphonamides causing hypoglycemia were the first to be exploited, resulting eventually during 1954-1957 in highly useful agents in the treatment of diabetes after earlier agents had been found too toxic. Tolbutamide and chlorpropamide are representatives of this class. […]

Early in the use of chlorothiazide, Wilkins, Finnerty, and Goldner and coworkers reported that this sulfonamide elevated blood glucose in certain susceptible individuals. […]

Rubin, then in M. M. Winbury's Department at Schering Corporation, had already decided to test the hypothesis that benzothiadiazines that are not diuretic might reduce blood pressure. He used both the normal anesthetized dog and arterial strips to determine whether certain benzothiadiazines, which had been tested and set aside by Dick Taylor during the development of trichlormethiazide because they were nondiuretic, would, nevertheless, lower blood pressure. One of the early compounds he tested that satisfied the criteria of a nondiuretic hypotensive was diazoxide. The structure of diazoxide shows that there is a striking similarity to chlorothiazide, with the sulfamyl group being absent. […]

The toxicology studies in the dog, with 200 mg/kg of diazoxide and 8 mg/kg of trichlormethiazide, by Eggert and his associates at Schering Corporation, had unexpectedly revealed remarkable adverse synergism. Hyperglycemia, ketoacidosis, and death occurred as early as eight weeks after the start of daily administration in some dogs. […]

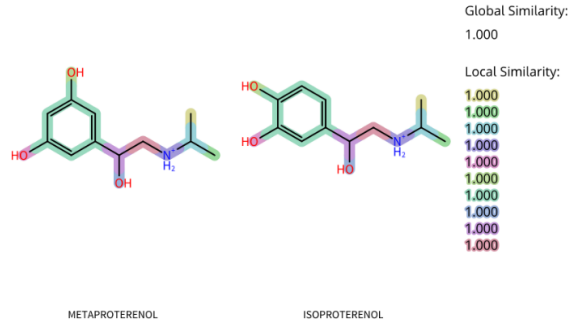
This extraordinary adverse synergistic effect of the combination of these drugs on blood glucose was duplicated in controlled clinical trials […]

Dollery reported in 1962 that hyperglycemia had occurred in two patients being treated for hypertension with diazoxide plus hydrochlorothiazide. He demonstrated suppression of insulin secretion, and proposed this as the mode of hyperglycemic action(*129*)."

## METAPROTERENOL

1973

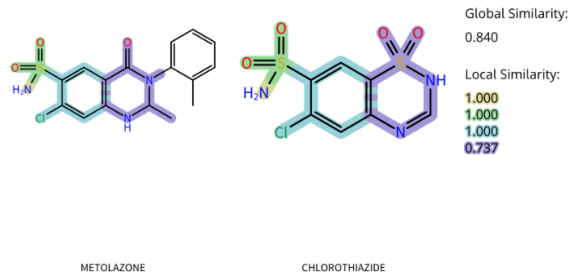
Analogue of isoproterenol




## METOLAZONE

1973

Analogue of chlorothiazide




## TRIMETHOPRIM

1973

It was discovered during the search of Hitchings, Elion and their colleagues for antimetabolites. In these studies, screening and structure-activity comparison of the compounds were based on inhibiting the growth of *Lactobacillus casei*.

From George Hitchings, one of the discoverers:

"But as testing was extended, it was found that structural modification that might enhance the activity against one microorganism might diminish it against another, while the reverse might be true for another structural

modification(*224*)."

## MITOMYCIN

1973

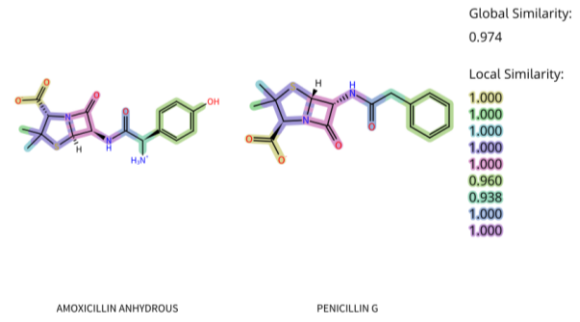
"A research for new anti-tumor substances produced by soil actinomycetes, has been carried in our laboratory for the past several years. As a result, several aspects of cazinophilin were found and are reported in the preceding papers. Recently, the fermentation broth of a strain, isolation #V621, having growth-inhibitory activity against gram positive and gram negative bacteria, was found to exert destructive effect upon the cells of EHRLICH carcinoma and YOSHIDA sarcoma which resulted in the prolongation of the survival period of the host animals. The broth also showed virucidal activity *in vitro* against Newcastle disease virus and influenza virus and parasitocidal activity against ascaris.

Then, isolation of active principles from the fermentation broth was tried and at least several substances were obtained. A group of these active substances which were found to be previously undescribed compounds was named Mitomycin(*225*)."

## AMOXICILLIN ANHYDROUS

1973

Penicillin analogue(*21*)




## DOPAMINE

1974

Also see the levodopa entry.

From one of the discoverers:

"Synthesized in 1910 by Barger and Ewins (1910) and by Mannich and Jacobsohn (1910), dopamine (3-hydroxytyramine, β-3,4-dihydroxy-phenylethylamine) was classified - in the same year - by Barger and Dale (1910) as a weak sympathomimetic (vasopressor) drug. It is remarkable that in the time span of 30 years which followed Barger and Dale's classical paper, only 4 other original pharmacological papers on dopamine can be found in the literature.

This crucial discovery permitted Blaschko to postulate, in 1939, the now established biosynthetic pathway for catecholamines, thus giving dopamine its first physiological role in the body, namely that of an intermediate in the formation of noradrenaline and adrenaline. […]

The first observations on the occurrence of dopamine in tissues of mammalian peripheral organs and in body fluids, including urine, adrenal medulla, heart and sympathetic nerves and ganglia, were made in the late forties and early fifties. […]

In 1942 Holtz and Credner made the puzzling observation that - unlike the vasopressor noradrenline - dopamine lowered the arterial blood pressure in the guinea pig and, to a lesser extent, the rabbit. Although Holtz and Credner gave their observation a completely negative interpretation, suggesting that it was due to a non-specific action of the corresponding aldehyde (3,4-dihydroxy-phenylacetaldehyde) formed from dopamine by the action of monoamine oxidase, the observation as such proved of great importance. When, in 1956, Blaschko raised the question about dopamine's physiological role in the body, he asked Hornykiewicz, who at that time was his postdoctoral fellow, to re-examine the observations made by Holtz and Credner, and, in doing so, to use, in addition to dopamine and L-dopa, epinine and iproniazid, the first potent, a few years earlier developed, in vivo monoamine oxidase inhibitor.

Equipped with these pharmacological tools, Hornykiewicz soon demonstrated that the vasodepressor action of dopamine in the guinea pig was a specific effect of dopamine itself and not due to the aldehyde metabolite formed from dopamine by monoamine oxidase(*226*)."

From the discovery paper of Dale cited in the previous quotation:

"The elucidation of the structure of the active principle of the supra-renal medulla by the work of Abel, v. Fürth, Takamine, Aldrich, Pauly, and Jowett, and its synthesis by Stolz and by Dakin, almost simultaneously, led to the physiological investigation of substances nearly related to it in chemical structure. […]

All the active bases examined by these and other observers have been catechol derivatives. Dakin, indeed, concluded that the catechol nucleus was the essentially active group in the adrenine molecule, basing this view on the observation that catechol itself-causes a rise of blood-pressure when injected intravenously, while the base methyl-amino-ethanol, $CH_2(OH)CH_2$ . $NHCH_3$, which may be regarded as the detached side-chain of the adrenine molecule, has no such action. The same conception has been adopted by Schultz. Recently, however, we found that certain amines produced by putrefaction, none of them possessing a catechol nucleus, have an action very similar to that of adrenine. On the other hand we shall give evidence that the rise of blood-pressure produced by catechol is due to an action of an entirely different type. It became clear, therefore, that the conception put forward by Dakin, and adopted by others, was inadequate, and it became of interest to trace the variations in the intensity of the specific action through a series of compounds intermediate between the putrefactive animes-in particular *p.* hydroxyphenylethylamine-and adrenine itself. This was the main object of our investigation, but incidentally the changes of physiological activity accompanying other changes of structure have been studied. […]

*Experimental Methods.* The action with which we are concerned is the immediate peripheral effect on involuntary muscle and gland cells produced by intravenous injection(*227*)."

From the discovery paper of Hornykiewicz cited in the first quotation in this entry:

"The depressor action of dopamine upon the arterial blood pressure of the guinea-pig has been studied. […]

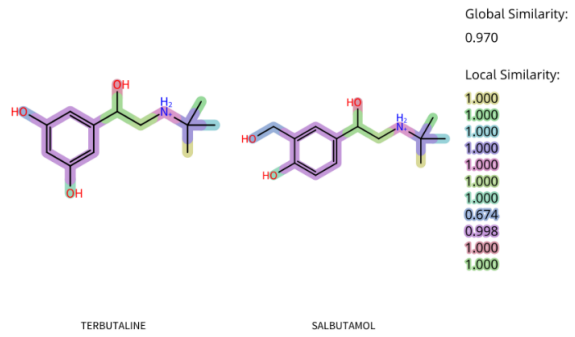
The experiments to be described were undertaken in order to find out, firstly, if the response of the arterial blood pressure of the guinea-pig to dopamine could serve as the basis for a method of assay and, secondly, whether support for the role of amine oxidase in the depressor response to dopamine in the guinea-pig could be obtained. […]

Male guinea-pigs of 400 to 650g. were anaesthetized with ethyl urethane. A polythene tube was introduced into the right jugular vein and heparin, 10 mg./kg., was administered. The left carotid artery was cannulated and the blood pressure was recorded, using the mercury manometer described by Condon. All substances were administered intravenously(*228*)"

## TERBUTALINE

1974

Analogue of salbutamol(*21*)




## XENON XE-133

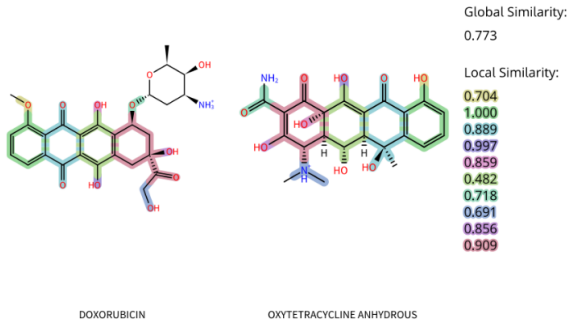
1974

Radiopharmaceutical

DOXORUBICIN

1974

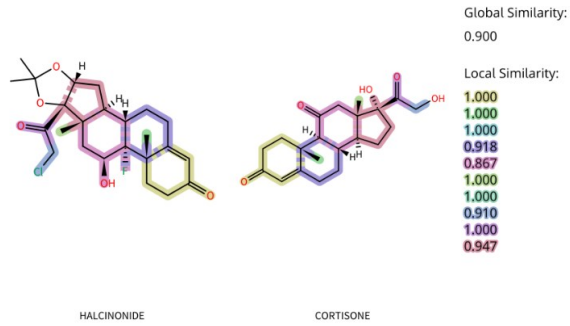
Analogue of oxytetracycline(*21*)




HALCINONIDE

1974

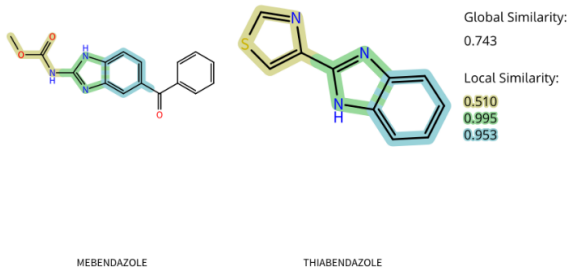
Analogue of cortisone




MEBENDAZOLE

1974

Analogue of thiabendazole(*229*)




Discovery of thiabendazole:

"We wish to report the discovery of a new class of anthelmintic agents possessing a broad spectrum of activity for gastrointestinal parasites of domestic animals. Some of the compounds are among the most potent chemotherapeutic agents known, complete larvacidal activity being manifest *in vitro* at 10-5 y/ml. This potency coupled with the absence of activity toward other microorganisms and negligible mammalian toxicity suggests a unique interference with a metabolic pathway essential to a variety of helminths. […]

2-(4'-Thiazolyl)-benzimidazole (I, generic name: thiabendazole) was outstanding in anthelmintic activity among several hundred analogs studied in some detail. […]

Thiabendazole has significant anthelmintic activity for gastrointestinal parasites in sheep, goats, cattle, horses, swine, dogs and poultry(*230*)."

MICONAZOLE

1974

The antifungal activity of the pharmacophore was first observed in 1943(*231*).

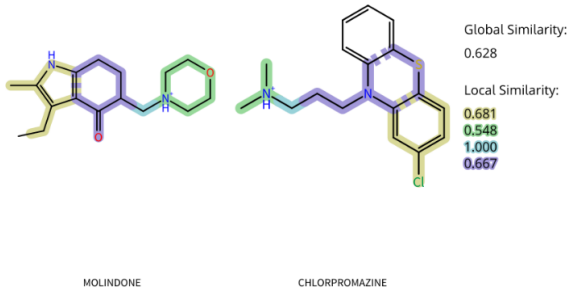
"An abstract of a paper appeared which described the pharmacological properties of benzimidazole. The structural similarity of this compound to the biotin analogue in which we were interested was apparent. Furthermore, the similarity of the symptoms observed in animals receiving benzimidazole to those seen in biotin deficiency suggested that the action of benzimidazole might be related to its structural similarity to biotin. In order to determine whether benzimidazole owed its biological potency to competition with biotin, the production of biotin deficiency was attempted in several microorganisms by addition of benzimidazole(*232*)."

This was ignored in that time, because there was not much need for it. In 1951, various derivatives of this pharmacophore were screened for their antifungal activity using cultures of *Trichophytongranulosirni* and *Milcrosporori eipserim*(*231, 233*).

## MOLINDONE

1974

Analogue of chlorpromazine(*234*)




## CLONIDINE

1974

From the discoverer(s):

"At the beginning of the 1960s Boehringer Ingelheim planned to synthesize a peripherally active adrenergic compound for nasal decongestion as simple nose drops. Imidazoline-derivatives with decongestive properties are substituted amidines in which the amidine function is incorporated into an imidazoline structure. However, at that time a replacement of the -$CH_2$- bridge by an -NH- group had not been achieved chemically in compounds substituted at both the 2- and 6-positions of the phenyl ring. The problem was solved by introducing chlorine atoms as substituents. Although the resulting drug indeed had a remarkably high vasoconstructive and decongestive effect at low concentrations, it turned out that other effect were more significant. After administration of the drug to a secretary she fell asleep for 24 h, developed low blood pressure, marked bradycardia, and dryness of the mouth. Clonidine was subsequently developed for its blood-lowering effect and introduced into the clinical routine in 1966(*235*)."

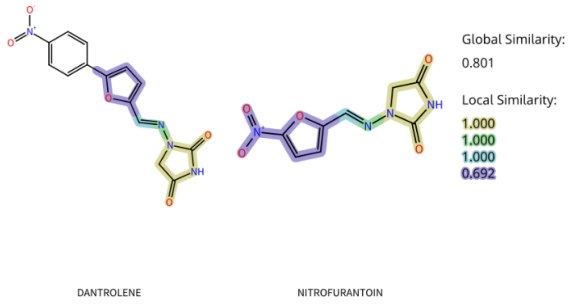
"The decongestive effective was determined by Dr Hoefke according to the method described by Binet and Araudinet. In anaesthetized dogs, the connection between nose and pharynx was blocked by paraffin-soaked cotton wool. Additionally, the nostrils were closed by a special balloon catheter. By these means, the changes in volume within the nose could be plethysmographically determined using a Marey capsule. The change in volume within the nasal cavity could be recorded on a smoked drum(*235*)."

## DANTROLENE

1974

Analogue of nitrofurantoin

Its structure is a close analogue of nitrofurantoin. After synthesis, it was administered to rats and mice.




## IBUPROFEN

1974

"Ibuprofen= 2-(4-isobutylphenyl) propionic acid, was first recognised by its effect in reducing the erythema (reddening) caused by exposing the shaved skin of guinea pigs to UV radiation(*89*)."

"They were noticed to be paralyzed the following morning, although breathing, pupillary reflexes, and blood pressure were normal. When left for several days in this state, their abdomens developed a waffling effect caused by the grill of the cage. It was realized a new type of muscle relaxant had been found(*236*)."

## IOTHALAMATE SODIUM I-125

1974

Contrast agent

## NITROPRUSSIDE

1974

Nitroprusside and its effects were discovered as early as the last decades of the nineteenth century(*237*).

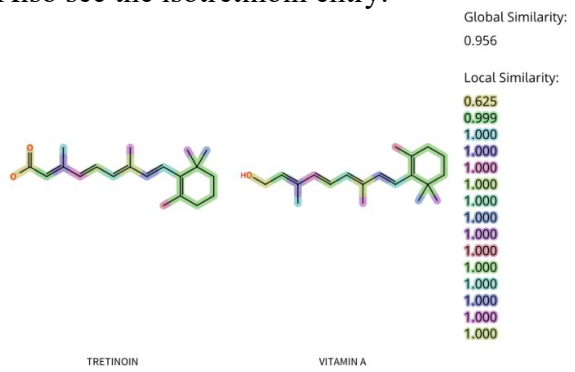
Also see the nitroglycerin entry.

## TRETINOIN

1974

Analogue of Vitamin A

Also see the isotretinoin entry.




"The importance of retinol (vitamin A) was discovered during World War I and subsequent research showed that its deficiency gives rise to xerosis and follicular hyperkeratosis. The retinoid drug project was launched in 1968 to synthesize compounds similar to vitamin A by chemical manipulation of its molecule to improve clinical efficacy and safety. The use of these substances in therapy dates back some 3000 years to ancient Egypt, where liver was used to treat endemic night blindness. The modern history of retinoids, however, began in 1909 when an essential factor in the viability of an embryo in the fatty extract of the egg yolk, called vitamin A, was discovered. Retinoids finally were introduced into the treatment of dermatoses including photoaging more than two decades ago(*238*)."

## BENZYLPENICILLOYL POLYLYSINE

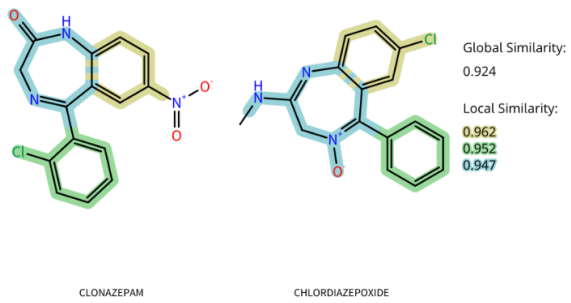
1974

Diagnostic

## CLONAZEPAM

1975

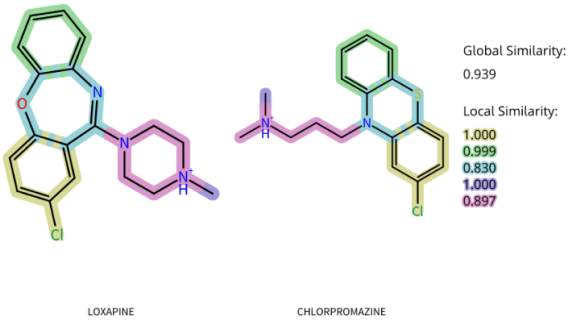
Analogue of chlordiazepoxide




## LOXAPINE

1975

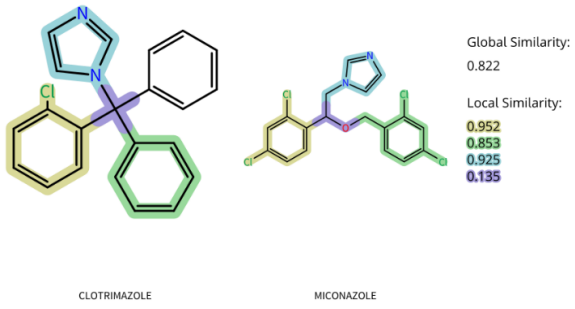
Analogue of chlorpromazine(*234*)




## CLOTRIMAZOLE

1975

Analogue of miconazole(*231*)




## GLUCONIC ACID

1975

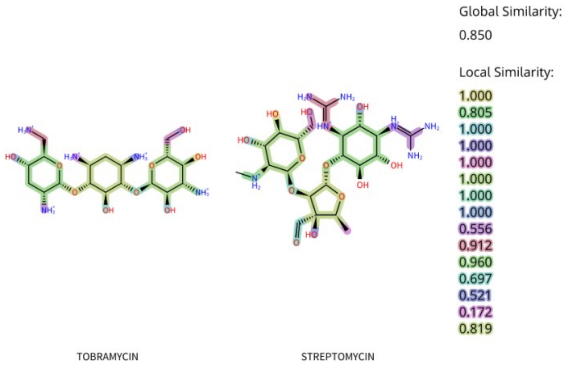
natural compound produced by simple dehydrogenation of glucose. It is used as excipient

in formulations of pharmaceuticals, foods, and other products.

## TOBRAMYCIN

1975

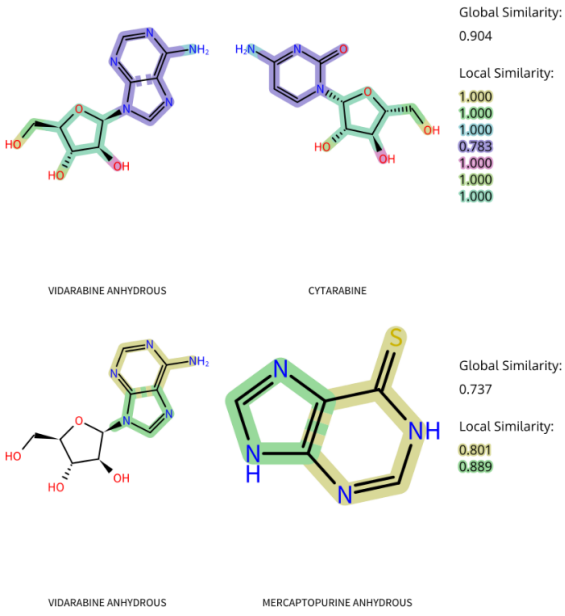
Analogue of streptomycin




## VIDARABINE

1976

Analogue of mercaptopurine and cytarabine




## CALCITONIN SALMON

1975

Homologue of the endogenous calcitonin

## CARBIDOPA

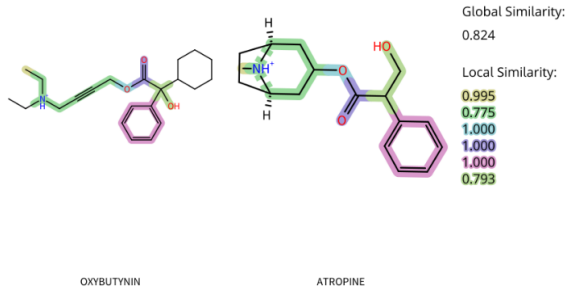
1975

Secondary

## OXYBUTYNIN

1975

Analogue of atropine




## DACARBAZINE

1975

"Several 5(or 4)-(3-alkyl-3-methyl-1-triazeno)imidazole-4(or 5)-carboxamides (111-X) were prepared and are recorded in this report. Relevant to the structure-activity question, however, is the fact that the bis(2-chloroethy1)triazeno derivative prepared subsequently to these compounds, is the most active of the triazenoirnidazoles versus mouse lymphoid leukemia L1210(*239*)."

"Several 5(or4)-(3-alkyl-3-methyl-l-triazeno)imidazole-4 (or 5)-carboxamides (111-X) were prepared from 5-diazoimidazole-4-carboxamide and the appropriate N-alkyl methylamine. Most of these derivatives significantly increased the life span of leukemic (L1210) mice. Inhibition of the growth of sarcoma 180, adenocarcinoma 755, and Walker carcinosarcoma 256 was observed, but inhibition of solid tumors was generally accompanied by large, adverse, host-weight changes(*239*)."

"Compound I has now been found to display good antileukcmic activity against the leukemia L1210 system in the primary screen of the Cancer Chemotherapy National Service Center. The antileukemic activity of I and its imidazole analog II are comparable, but the toxicity of I is much less than that of II(*240*)."

## SINCALIDE

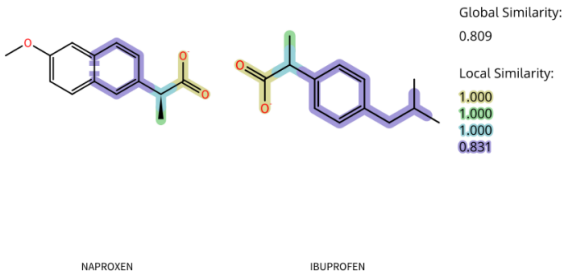
1976

Diagnostic

NAPROXEN

1976

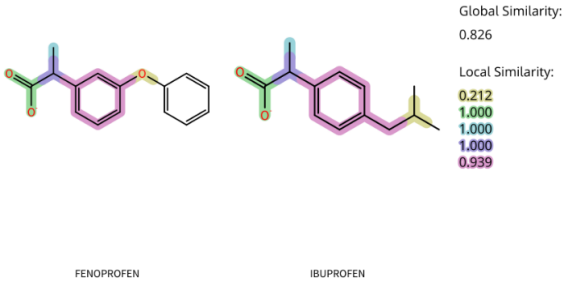
Analogue of ibuprofen(*21*)




FENOPROFEN

1976

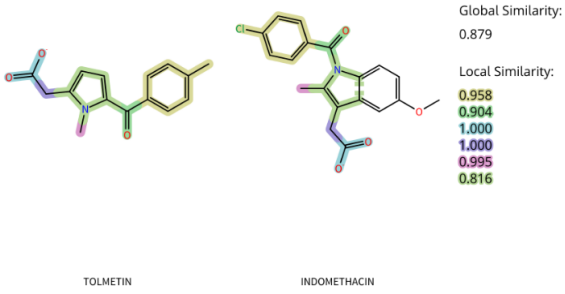
Analogue of ibuprofen




TOLMETIN

1976

Analogue of indomethacin




METOCLOPRAMIDE

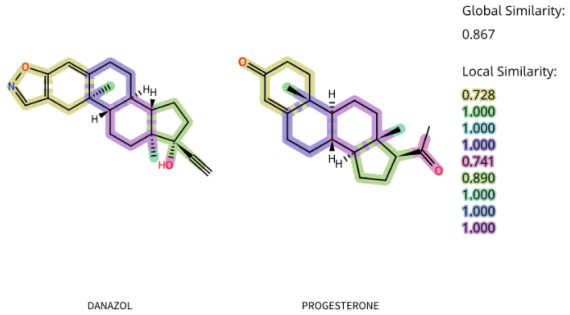
1976

"This drug was identified by Laboratoires Delagrange in France in the mid-1950s, during a programme aimed at improving the properties of procainamide, a cardiac anti-arrhythmic and local anesthetic drug derived from procaine. Although some anti-emetic activity was known to exist within this class of molecule, chlorination of the benzene ring of procainamide (2-chloroprocainamide) significantly increased anti-emetic activity in dogs. However, more interesting was the absence of the sedative activity of the phenothiazine structures prompting an evaluation of related structures. In particular, methoxy-2-chloro-5-procainamide or metoclopramide, had negligible local anesthetic or cardiac anti-arrhythmic activity but an ability to inhibit emesis in dogs evoked by apomorphine and hydergine, in addition to copper sulfate. Soon after, metoclopramide was found to stimulate gastric emptying, speed the rate of transit through the small intestine and reduce symptoms associated with various upper digestive tract disorders(*241*)."

DANAZOL

1976

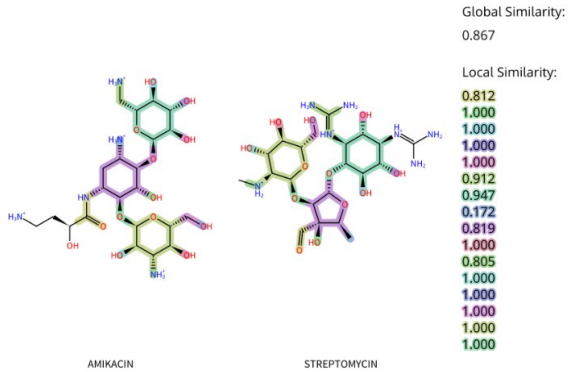
Analogue of progesterone




AMIKACIN

1976

Analogue of streptomycin(*21*)



## LOMUSTINE (Nitrosoureas)

1976

"In the 1950s, after the alkylating agents had become established as useful chemotherapeutic agents, the National Cancer Institute organized a comprehensive screening program to discover new compounds with antitumor activity. Several animal tumors were investigated for use in the screening assay, and the L1210 murine leukemia line was chosen for much of the testing; literally thousands of synthetic and naturally occurring compounds were tested for activity against this tumor. In 1960, Greene and Greenberg reported that the synthetic compound, N-methyl-N '-nitro-N-nitrosoguanidine (MNNG), resulted in a moderate increase in the lifespan of mice carrying intraperitoneal L1210 cell(*242*)."

"Since MNNG represented a new class of compounds, the National Cancer Institute decided to investigate its activity further and to synthesize analogs of MNNG in an attempt to find more active derivatives. A synthetic program was started at the Southern Research Institute in Birmingham, AL, and new compounds were tested for activity against L1210 cells(*242*)."

## PRAZOSIN

1976

"DISCOVERY OF PRAZOSIN: Prazosin was the most interesting of several hundred compounds that were synthesized and evaluated in our Medical Research Laboratories at Groton, Connecticut. […]

Several prototype structures were synthesized that could be regarded as hybrids since they incorporated structural features of the natural substrates cyclic-AMP and cyclic-GMP and the known inhibitors of phosphodiesterase. papaverine and theophylline, both of which cause direct relaxation of vascular smooth muscle.

Pharmacological experiments showed that prazosin acted on vascular smooth muscle to reduce total peripheral resistance, and distribution studies with radioactive prazosin-2-$^{14}$C in dogs support this, in that high concentrations of radioactivity are found in the blood vessels (Hess, 1974)(*243*)."

I could not find the manuscript that was cited as describing the initial structure-activity studies; "(Hess, 1974)"

## LOPERAMIDE

1976

Meperidine (pethidine) was at first introduced as an anticholinergic synthesized based on atropine and scopolamine. In clinic, it had shown opium-like analgesic and antidiarrheal effects. In order to separate these activities, Paul Janssen used Straub mouse tail test for opiate activity and the electrically driven guinea pig ileum *in vitro* for antispasmodic activity. He succeeded in invention of loperamide, diphenoxylate, and fentanyl(*149*).

## GALLIUM CATION GA-67

1976

Inorganic

## HUMAN SERUM ALBUMIN I-131

1976

Radiopharmaceutical

## CARMUSTINE

1977

Analogue of mechlorethamine

DINOPROSTONE

1977

Trans isomer of the endogenous prostaglandin $E_2$(*217*)

"The history of the eicosanoids dates back to 1930 when Kurzrok and Lieb, studying artificial insemination, found that human seminal fluid could relax or contract uterine strips taken from patients who were fertile or infertile, respectively. This observation did not stimulate a search for a new biologically active factor […]

In 1933 and 1935, Goldblatt observed the effects

of human seminal plasma on isolated organs, or following injection into animals. He noted that the principle could be distinguished from other known active compounds. Von Euler made similar, independent observations in 1934, using sheep vesicular gland extracts and human seminal plasma(*244*)."

From the 1930 discovery paper of Kurzrok and Lieb:

"In the treatment of human sterility, one of us (R. K.) has made many attempts to secure pregnancy by means of artificial insemination. Of the dozens of attempts. only 2 were probably successful. In a number of cases it was observed that when 0.5 cc. of semen was injected into the uterine cavity, the semen was promptly expelled, even though the patient was kept in an extreme Trendelenburg position. A similar quantity of Ringer's solution similarly injected was invariably retained. The patient always gave the same reaction, apparently independent o i the phase of the menstrual cycle. These observations led to the following questions : What is the action of human semen upon the human uterus? Do 2 human uteri ever react differently to the same semen? Does one uterus react differently to the semens of 2 different individuals? The answers to these questions can be found in the following observations. […]

Immediately after the removal of the uterus from the patient, adjacent strips were cut from it, and dropped into iced Ringer's solution, and placed in the refrigerator until required for an experiment. The strips were cut parallel to the fibers of the external muscular layer. […]

The experiments were done as soon as possible after the collection of the semen; usually within 3 hours. The uterine strips were suspended in 100 cc. of warm, oxygenated Ringer's solution, and 1 cc. of the warm semen was added. In all cases, contraction of the uterus caused ascent of the lever(*245*)."

From the 1935 discovery paper of Goldblatt cited in the previous quotation:

"Both seminal fluid and extract were tested for their effects on the blood-pressure of cats and rabbits under either with and without preliminary treatment with atropine; on the isolated small intestine of the rabbit with and without atropine; on the isolated uterus of the virgin guinea-pig; on the isolated seminal vesicle of the guinea-pig and on the eserinized rectus abdominis of the frog(*246*)."

From the discovery paper of Euler cited in the first quotation in this entry:

"Bei der Prüfung verschiedener Organe auf das Vorkommen eines von Euler und Gaddum in Darmmuskulatur und Gehirn gefundenen aktiven Prinzips mit atropinfesten, blutdrucksenkenden und darmerregenden Wirkungen an Kaninchen konnten in gewissen Sekreten und Extrakten aus accessorischen männlichen Genitaldrüsen ähnliche Wirkungen nachgewiesen werden, zum Teil in auffallend hohem Ausmaß(*247*)."

Translation from Google Translate:

"When examining various organs for the presence of an active principle found by Euler and Gaddum in the intestinal muscles and

brain with atropine-resistant, antihypertensive and intestinal effects in rabbits, similar effects could be demonstrated in certain secretions and extracts from accessory male genital glands, in some cases to a remarkably high extent(*247*).”

## CIMETIDINE

1977

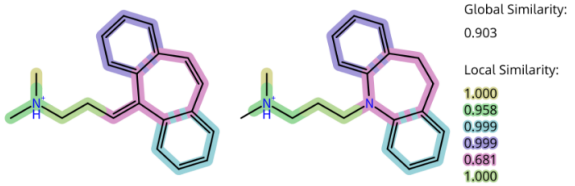
From the discoverer, Sir James Black:

“The bioassay systems were easily selected. For in vitro assays, guinea pig ileal muscle was the classical system for studying antihistamines such as mepyramine. Guinea pig atrial tissue looked like a good assay for mepyramine-refractory histamine responses. For the assay of acid secretion, no in vitro assays were available. We chose the Ghosh and Schild method of lumen perfusion of the stomach of anesthetized rats, but the method worked reliably only after it had been substantially modified by Parsons, my new colleague. The chemical program, from the start, concentrated on making analogs and derivatives of histamine(*199*).”

## CYCLOBENZAPRINE

1977

Analogue of imipramine



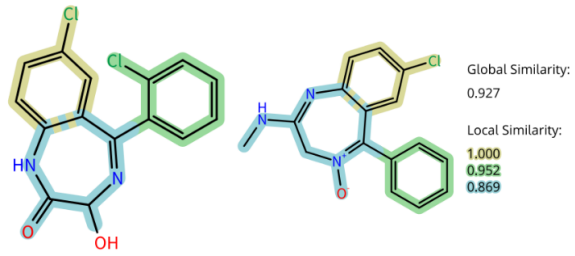

CYCLOBENZAPRINE IMIPRAMINE

“Early studies of cyclobenzaprine use assessed this drug for potential mood-altering properties, such as depression, and this was initially of promise, given that cyclobenzaprine differs from amitriptyline by only one double bond. Eventually, most subsequent studies focused on the drug’s muscle relaxant properties(*248*).”

## LORAZEPAM

1977

Analogue of chlordiazepoxide

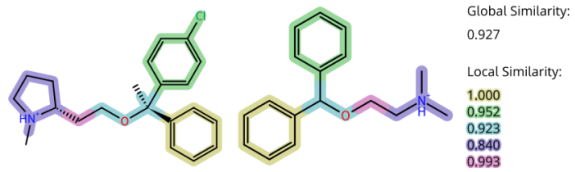



LORAZEPAM CHLORDIAZEPOXIDE

## CLEMASTINE

1977

Analogue of diphenhydramine(*21*)

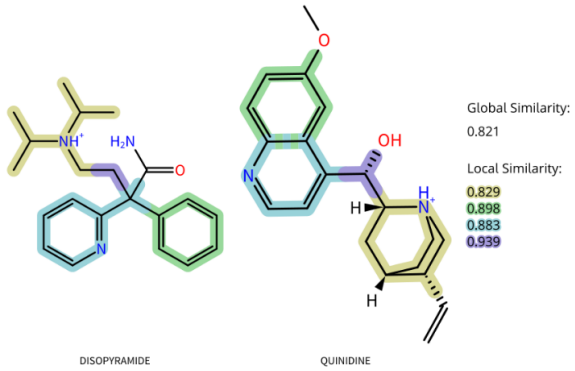



CLEMASTINE DIPHENHYDRAMINE

## DISOPYRAMIDE

1977

Analogue of quinidine




DISOPYRAMIDE QUINIDINE

## COLESTIPOL HYDROCHLORIDE

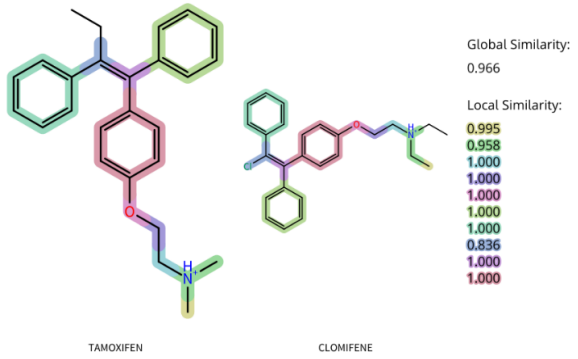
1977

Chelating agent

TAMOXIFEN

1977

Analogue of clomifene.




"Today, tamoxifen is one of the world's best-selling hormonal breast cancer drugs. However, it was not always so. Compound ICI 46,474 (as it was first known) was synthesized in 1962 within a project to develop a contraceptive pill in the pharmaceutical laboratories of ICI (now part of AstraZeneca). Although designed to act as an anti-estrogen, the compound stimulated, rather than suppressed ovulation in women(*249*)."

"ICI Pharmaceuticals (now known as AstraZeneca) had an interest in the pharmacology of synthetic derivatives of triphenylethylene in the 1940s and 1950s, and ICI chemists had synthesized several non-steroidal oestrogens that were used at high doses to treat breast cancer. However, the market for the treatment of advanced breast cancer was extremely modest, with at most a few thousand patients who might respond for about a year.

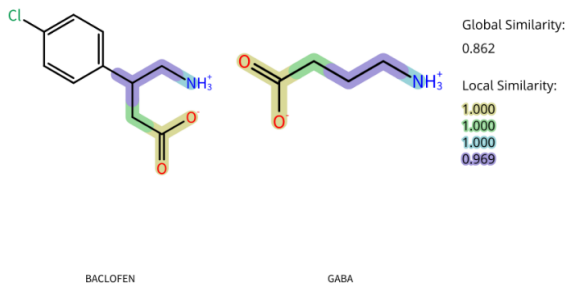
As the programme was tasked to find anti-fertility agents, the group used models of reproduction in rats to identify suitable contraceptive agents. These studies culminated in the identification of ICI46,474, the trans isomer of a triphenylethylene — subsequently named tamoxifen—as a potentially safer medicine for clinical applications.

The fact that tamoxifen had paradoxical full oestrogen-like actions in mice, but not in rats, created some uncertainty in the late 1960s about the action of tamoxifen in humans. Fortunately, Walpole had a specific interest in cancer therapy and included coverage of the 'control of hormone-dependent tumours' in the patent on tamoxifen, which primarily focused on 'the management of the sexual cycle'(*250*)"

BACLOFEN

1977

Structure of baclofen is an analogue of the endogenous neurotransmitter, GABA, yet it was designed to be more lipophile to increase penetration to CNS. It failed in its original purpose as an antiepileptic(*251*).




From the original patent:

"Die neuen Verbindungen besitzen wertvolle pharmakologische, insbesondere zentralhemmende Eigenschaften. So hemmen sie beispielsweise bei Versuchen an Mäusen, Katzen, Kaninchen und Hunden die Aktivität von Neuren, die an der Steuerung der Motorik beteiligt sind(*252*)."

Translation from Google Translate:

"The new compounds have valuable pharmacological properties, in particular central inhibiting properties. For example, in experiments on mice, cats, rabbits and dogs, they inhibit the activity of neurs involved in motor control(*252*)."

TECHNETIUM TC-99M MEDRONATE

1977

Diagnostic

DIFLORASONE

1977

Analogue of cortisone

Error in similarity calculation by FTrees

CLOCORTOLONE

1977

Analogue of cortisone

Error in similarity calculation by FTrees

DESOXIMETASONE

1977

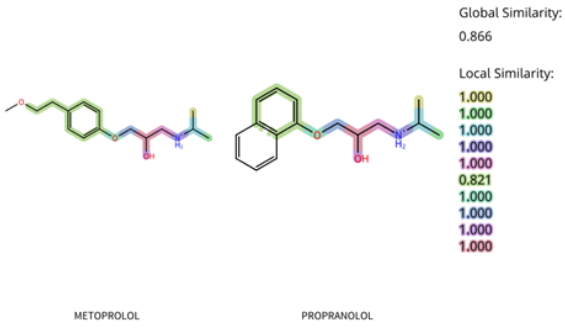
Analogue of cortisone

Error in similarity calculation by FTrees

METOPROLOL

1978

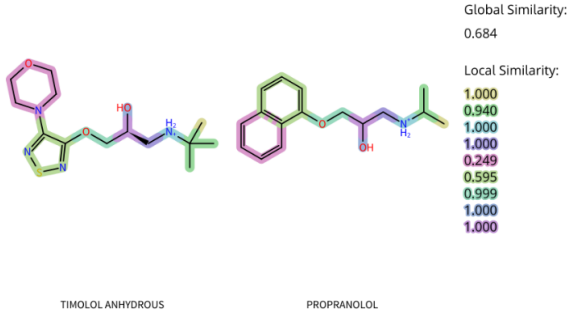
Analogue of propranolol(*253*)




TIMOLOL

1978

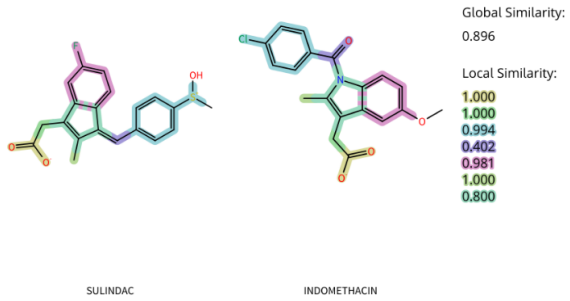
Analogue of propranolol(*253*)




SULINDAC

1978

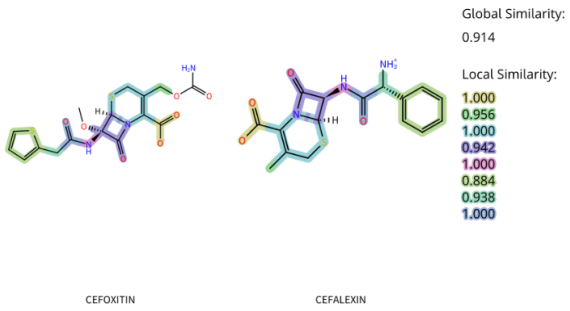
Analogue of indomethacin(*21*)




CEFOXITIN

1978

Analogue of cefalexin




BRETYLIUM

1978

"Serendipidy was a major factor in the discovery of the forerunner of bretylium. Starting in the early 1950's, Dr Hey of Leeds University had been examining the relationship between structure and nicotine-like action in a series of substituted phenylcholine ethers. As an extension of this work choline 2:6 xylyl ether bromide was made and examined This compound became known as TM1O and later as xylocholine. It produced a brief rise in blood pressure in cats, characteristic of the series, but tachyphylaxis to this response was unusually rapid in onset and falsely attributed to a long lasting local anaesthetic action. Later the important observation was made that TM10 abolished, for long periods, contractions of the nictitating membrane caused

by stimulation of the postganglionic cervical sympathetic nerve, without impairing, except briefly, the contractile responses of the membranes to injected adrenaline(*254*)."

## NATAMYCIN

1978

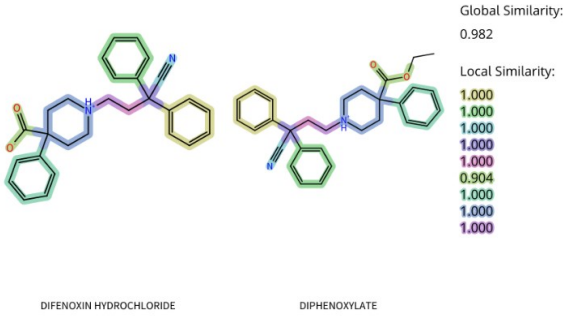
I could not retrieve the full-text of the report.

"Physical properties, activity, toxicity, and the effect on the circulatory system and faecal flora of pimaricin, a new crystalline antibiotic, prxcoduced by *Streptomyces natalensis* (a new sp. to be described elsewhere) are discussed. This substance, belonging to the polyene group of antibiotics, is highly active against a large variety of yeasts and fungi (including *Candida albicans, Histoplasma capsulatum*, and dermatophytes at 3-50 µg./ml.) but shows no activity against bacteria(*255*)."

## DIFENOXIN HYDROCHLORIDE

1978

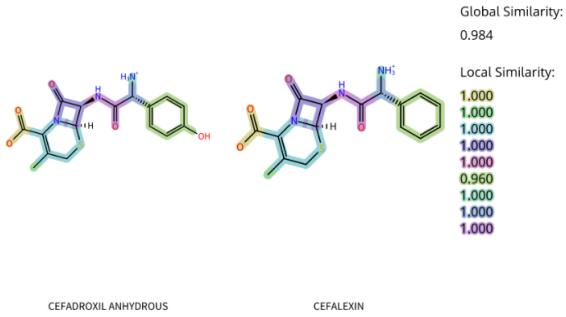
Analogue of diphenoxylate




## CEFADROXIL

1978

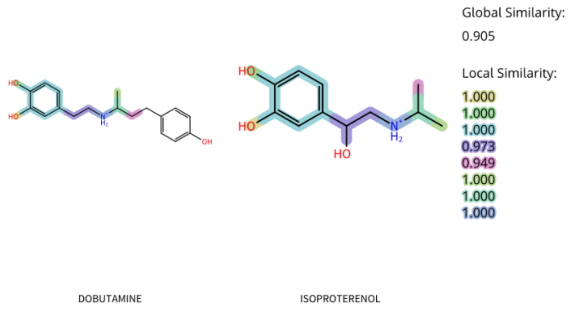
Analogue of cefalexin(*21*)




## DOBUTAMINE

1978

Analogue of isoprenaline




"Tuttle, a pharmacologist, and Mills, a medicinal chemist, systematically modified the structure of isoproterenol/isoprenaline with the goal of generating new drugs to improve cardiac function. […]

The first pass screen involved testing compounds, including dobutamine, in feline papillary muscle preparations since this was a preferred model for measuring contractility. It was in this setting that it was observed that removing the hydroxyl group resulted in similar positive inotropic effects to isoproterenol without the same effect on heart rate. Contractile potency was compared among the different agents, and in vivo testing was carried out in mongrel dogs(*256*)."

## BROMOCRIPTINE

1978

"Ergot has been studied for many years as a source of various alkaloids and has long been known as a uterotonic (a drug that regulates the function of the uterus). As far back as 1869, two doctoral dissertations were defended in Russia that described experiments on dogs and lactating women (with low social responsibility) whose children were sent to an orphanage. Ergot's ability to stop lactation was discovered(*257*)."

"In 1954, Shelesnyak published the first paper showing that the ergot extract known as ergotoxine, a mixture of ergocornine,

ergocryptine and ergocristine, inhibited the formation of deciduomata in pseudopregnant rats and also interfered with early gestation in the rat by preventing progresterone production by the corpus luteum it prevented implantation of the fertilized ovum and thus had an anti-fertility effect. […]

Flückiger realized that ergocornine could not be used in humans due to its oxytocic and vascular effects. He therefore set out to modify its structure and bring out the prolactin-lowering action without the oxytocic or vascular effects. Bromocriptine was the compound which he made and which became the first dopamine agonist to be approved for treatment of patients. […]

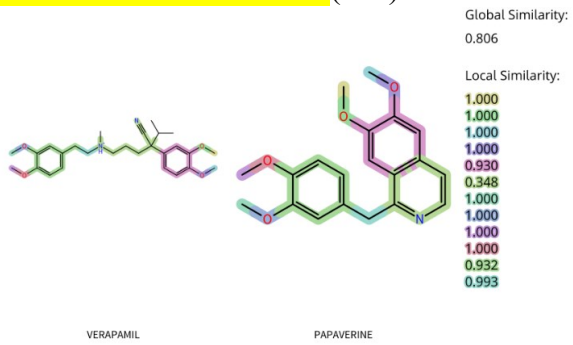
No immunoassays were available at that time for measurement of either GH or prolactin. Thus, Prof. Flückiger had to rely on in vivo bioassays when studying the prolactin activities in his rats – suppression of lactation, inhibition of implantation of the fertilized ovum or blocking pseudopregnancy. We now know that prolactin has different roles in humans than in the rat. It is not luteotrophic and suppression of prolactin restores fertility in patients with hyperprolactinemia. The next twist in the story was that bromocriptine was developed as an inhibitor of prolactin secretion in the human. Dopamine receptors had not yet been identified and it was unknown how ergocryptine or bromocriptine suppressed prolactin secretion(*258*)."

The bioassay used in the first publication describing bromocriptine was evaluating the pregnancy of rats(*259*).

## VERAPAMIL

1978

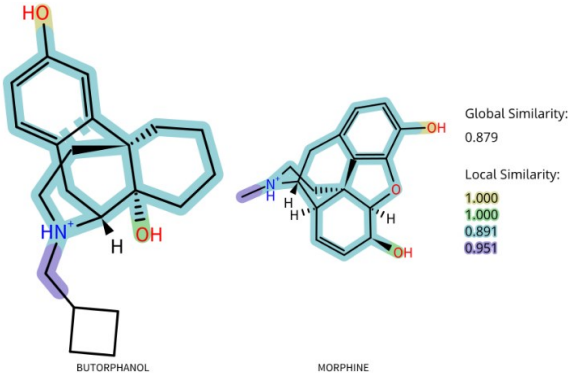
"Papaverine, unlike the other two alkaloids, is not an analgesic or narcotic. It acts by relaxing smooth muscle, and in animals it depresses conduction in cardiac muscle and prevents chloroform induced ventricular fibrillation. In the 1930s it was tried without success in angina, hypertension, and arrhythmias. However, it was popular for the relief of intestinal colic and this led in 1957 to the German pharmaceutical firm Knoll producing a very active synthetic analogue D365. D for their chemist, Ferdinand Dengel. This became known as verapamil and in 1963 Albrecht Fleckenstein made a seminal discovery of calcium antagonism as its mode of action. In 1972 Schamroth, Krikler, and Garrett were the first to link the arrhythmia terminating action of verapamil with the concept of calcium channel blockade(*260*)."




## BUTORPHANOL

1978

Analogue of morphine(*21*)




## ASPARAGINASE

1978

"The advances that led to the use of L-asparaginase in cancer therapy were (1) the discovery that guinea pig serum inhibits certain transplanted leukemias of the mouse (KIDD, 1953), (2) the finding that the cells of some tumors die *in vitro* unless supplied with L-

asparagine, (3) the demonstration that the enzyme L-asparaginase is the antileukemic factor in guinea pig serum, (4) the demonstration that the inhibitory effect of asparaginase is not restricted to mouse leukemias with a long history of transplantation (5) the finding that asparaginase with antileukemic activity can be isolated from *E. coli*, a potentially inexhaustible source, and (6) the successful use of *E. coli* L-asparaginase in the treatment of primary lymphosarcoma of the dog(*261*)."

From the discovery paper cited in the previous quotation:

"In experiments undertaken for other purposes the observation has recently been made that subcutaneous lymphomas of two kinds promptly regress following the injection of normal guinea pig serum intraperitoneally into mice carrying them, the animals meanwhile remaining lively and fleshy and devoid of signs of illness, while the growths of untreated control animals, and those of mice given serum from rabbits or horses, enlarge progressively and kill their hosts. Furthermore, in control experiments two transplanted mammary carcinomas and a transplanted fibrosarcoma of mice did not regress but grew unimpeded following the injection of guinea pig serum into mice bearing them. The findings provide an example, unique thus far, of a naturally occurring substance that brings about regression of a single type of cancer cells in riving animals without doing obvious harm to the latter(*262*)."

## CISPLATIN

1978

"Cisplatin was serendipitously discovered by Rosenberg and his coworkers in 1965 who, while investigating the effect of electric current on bacteria, observed growth inhibition accompanied by a filamentous clustering of the cells around the Pt electrode. The phenomenon was found to be due to the interaction of the growth medium and the Pt electrode, which led to the formation of a Pt complex, cis-diamminedichloroplatinum(II). Fortunately, the investigators concluded that this Pt compound might exert also antitumor activity. Their hypothesis was confirmed in tumor cell cultures and transplantable murine tumor models(*263*)."

From the discovery paper cited in the previous quotation:

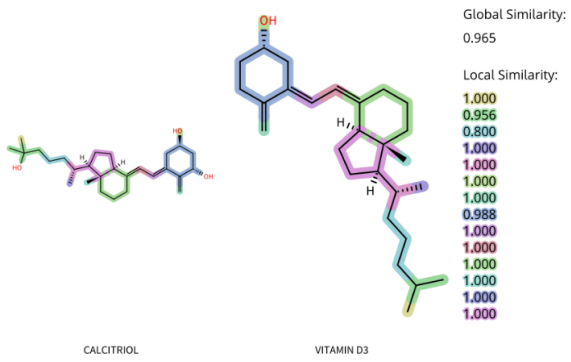
"IN an investigation of the possible effects of an electric field on growth processes in bacteria, we have discovered a new and interesting effect. In *E. coli*, the presence of certain group VIIIb transition metal compounds in concentrations of about 1-10 parts per million of the metal in the culture medium causes an inhibition of the cell division process. The bacteria form long filaments, up to 300 times the normal length, which implies that the growth process is not markedly affected.

We have now tested a number of platinum and other group VIIIb compounds to determine the most effective anions and cations for this effect. The chemicals were inoculated so as to maintain a concentration of 8 p.p.m. of the metal in the nutrient medium of the cell for a period of 2 h. The effects fall into three categories: the bacteria were killed; there was no apparent change; a minimum of 20 per cent of the bacteria were forced into a filament form(*264*)."

## CALCITRIOL

1978

Active form of vitamin D(*21*)



## DESMOPRESSIN

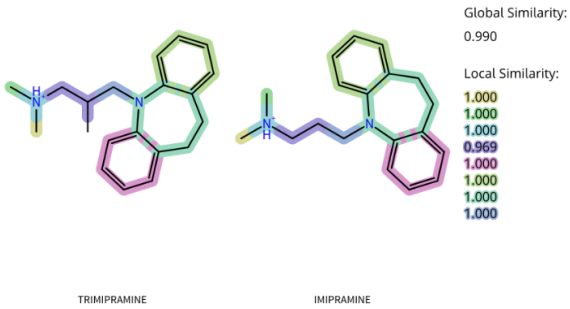
1978

Analogue of the endogenous vasopressin(*1*)

## TRIMIPRAMINE

1979

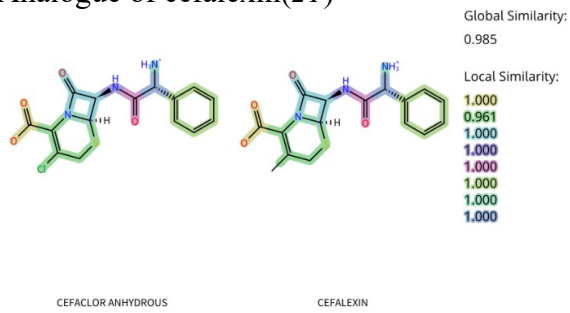
Analogue of imipramine




## CEFACLOR

1979

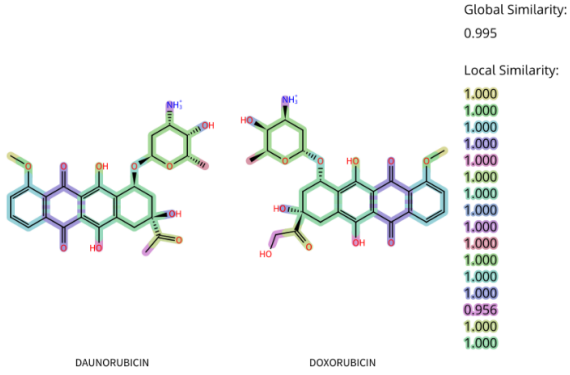
Analogue of cefalexin(*21*)




## DAUNORUBICIN

1979

Analogue of doxorubicin




First observations of the antitumor activity of daunorubicin was in mice and rats with tumours. Its structure was suggested because of the antitumor of another similar structure, cinerubine, whose antitumor activity was shown in animals and cell cultures(*265-267*).

## MINOXIDIL

1979

From the discoverer(s):

"The compound originally focused upon was N,N-diallylmelamine (DAM; U-7720). Interestingly enough, this agent had not been synthesized by Upjohn chemists but rather had been ordered out of an American Cyanamid chemical catalog. In the course of empirical screening, Upjohn scientists found that orally administered DAM reduced gastric acidity in pyloris-ligated rats and immediately wondered if this was accomplished by an anticholinergic mechanism. The absence of water solubility described for DAM at that time, which eventually proved to be misleading, was nevertheless fortuitous since it resulted in the conduct of an in vivo study in conscious dogs instead of the more customary in vitro assessment of reversal of acetylcholine actions on intestinal smooth muscle. […]

clinical interest in DAM subsided when a trial later that year in humans disclosed no reversal of hypertension after as much as a 2-g oral dose of DAM(*268*)."

By identifying the structure of its different metabolites via investigating their effects in rat and dogs, it was recognized that the reason of the inefficacy of the drug in humans was its little transformation to the active metabolite.

"Indeed, dogs and rats produced 14 to 17 times as much DAMN-O as did humans. Finally, the dose-response relationships of DAM and DAMN-O were compared in rats(*268*)."

The active metabolite, DAMN-O, was tested in another clinical trial. But because of the incidence of congestive heart failure and also

showing some toxicities in canines, its assessment was discontinued. Because of the unique direct peripheral vasodilator effect of DAMN-O, more analogues were synthesized and tested for reducing blood pressure and salt retention.

"We also studied the metabolic fate of minoxidil in other animals and added the rhesus monkey to the growing list of species in which this family of agents failed to induce cardiac lesions(*268*)."

Minoxidil was selected for clinical trials. Minoxidil got the FDA's approval of an emergency-use protocol in late 1970.

"It was at this stage of development that minoxidil's potential as a hair growth stimulant emerged. Chidsey made the first observation of hypertrichosis in several refractory hypertensive patients whose treatment continued beyond 2 weeks. Two dermatologists who were consulted about this phenomenon were intrigued and innovatively tested the drug topically for localized action. Interestingly, topical minoxidil evoked hair growth that was localized to the site of application on the upper arm(*268*)."

## ISOFLURANE

1979

"The anesthetic properties of several fluorinated hydrocarbons were reported by Robbins in 1946. In the period 1946–1959, three fluorinated compounds, two ethers, and one hydrocarbon were introduced into clinical practice: fluoroxene by Ohio Medical Products in 1951, halothane by Ayerst Laboratories and Imperial Chemical Industries, PLC in 1955, and methoxyflurane by Abbott Laboratories in 1959. […]

[T]he goal of which was to synthesize a new volatile anesthetic at least equal to, but hopefully better than, halothane, the market leader at the time. […]

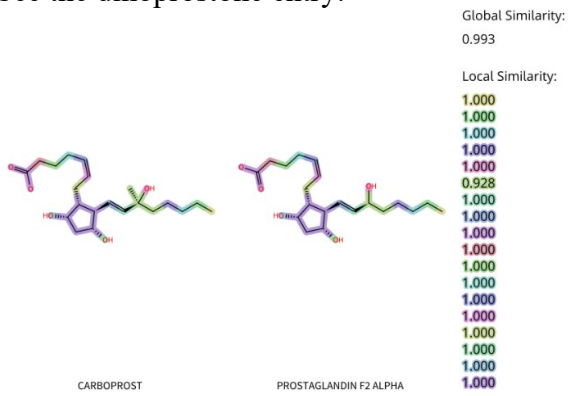
[I]t was possible to synthesize several hundred fluorinated compounds for testing as anesthetic agents. Most of the compounds failed when tested in mice, but three did not—enflurane, isoflurane, and desflurane. These three were all patented as anesthetics and are currently approved and marketed(*269*)."

## CARBOPROST

1979

Analogue of the naturally occurring prostaglandin $F_2$alpha(*1*)

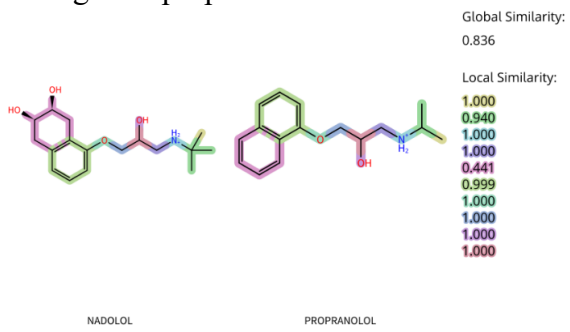
See the dinoprostone entry.




## NADOLOL

1979

Analogue of propranolol




## AMCINONIDE

1979

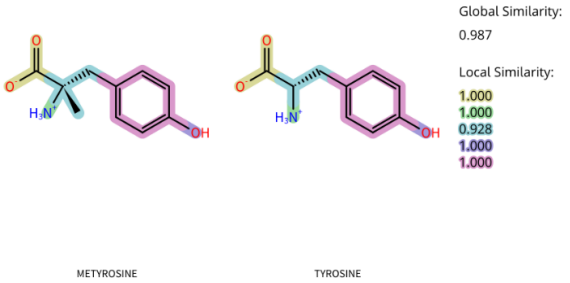
Analogue of cortisone

Error in similarity calculation by FTrees

## METYROSINE

1979

Analogue of the natural amino acid, tyrosine




ALTERATION of sympathetic function, both centrally and peripherally, underlies the usefulness of a number of clinical procedures and therapeutic agents. Prominent among these are various types of surgical sympathectomy and chemical agents which enhance, mimic, displace, or interfere with the actions of the sympathetic transmitter, noradrenaline. An approach to sympathetic regulation in man which has not been done previously is the inhibition of synthesis of the catecholamine hormone. This report presents preliminary data on the successful inhibition of catecholamine synthesis with a chemical agent in man. Alpha-methyl-tyrosine (α-M.P.T.), one of the analogues of tyrosine which we have shown to inhibit the hydroxylation of tyrosine to dopa in animal tissues in vitro (Nagatsu, Levitt, and Udenfriend 1964) and in vivo (Spector, Sjoerdsma, and Udenfriend 1965) was administered to patients and found to lower urinary excretion of noradrenaline, adrenaline, and their major metabolites.

Patients with phaeochromocytoma generally showed decreases in blood-pressure, fewer hypertensive paroxysms, and decreased requirement for phenoxybenzamine while receiving α-M.P.T. at doses in the range of 1000-3500 mg. per 24 hours. Blood-pressure changes, however, were absent or equivocal in patients with essential hypertension(*270*).”

From the 1964 discovery paper cited in the previous quotation:

“After demonstration of the decarboxylation of 3,4-dihydroxy-phenylalanine (dopa) to dopamine, the pathway for bio- synthesis of norepinephrine shown in Fig. 1 was proposed. […] Reports of the enzymatic conversion of tyrosine to catecholamines by tissue slices and minces have generally been unconvincing owing to large and variable blanks with boiled preparations. It has now been possible to demonstrate that brain, adrenal medulla, and sympathetically innervated tissues contain a specific hydroxylase that catalyzes the conversion of L-tyrosine to dopa. […] The present communication describes the isolation, purification, and characterization of a soluble tyrosine hydroxylase from beef adrenal medulla. The soluble tyrosine hydroxylase requires for activity tetrahydropteridine derivatives comparable to those previously observed for phenylalanine hydroxylase. […]

*Conversion of Tyrosine to Dopa in Tissues Slices, Minces, and Crude Tissue Extracts*- More than 10 years ago, studies in this laboratory showed that tyrosine could be converted to catechol derivatives by slices and minces of adrenal medulla and other tissues. However, it was found that heated tissues were almost as active. Recent studies by Iyer, McGeer, and McGeer illustrate this point. Because of the activity in heated preparations it was even considered that nonenzymatic reactions could conceivably explain aromatic hydroxylation in the adrenal gland. In recent studies it has been found that slices of tissues having sympathetic innervation convert only L-tyrosine to dopa; L-tyrosine is not active. When such tissue slices are heated, the activity may increase or decrease to some extent, but now both D- and L-tyrosine yield dopa. An example of such studies with adrenal and spleen slices is shown in Table I. It became apparent from these initial studies that intact tissues contain a stereospecific tyrosine-hydroxylating system.

A number of aromatic compounds related to tyrosine and dopa were tested as inhibitors

with the use of brain particles and purified adrenal enzyme. It is of interest that a large number of aromatic amino acids were effective inhibitors. In these cases only the L-amino acids were active. The inhibition with n-amino acids is probably of a competitive nature. This was definitely established for α-methyltyrosine. The finding that catechol compounds can inhibit may be a manifestation of product inhibition since dopa, norepinephrine, and related compounds inhibit. The compound α-propyl-3,4-dihydroxyphenylacetamide, which was suggested to be an inhibitor of dopa formation from studies *in vivo*, appears to be a somewhat better inhibitor than dopa or the other naturally occurring catechol derivatives. The mechanism of the catechol inhibition has not been investigated(*271*)."

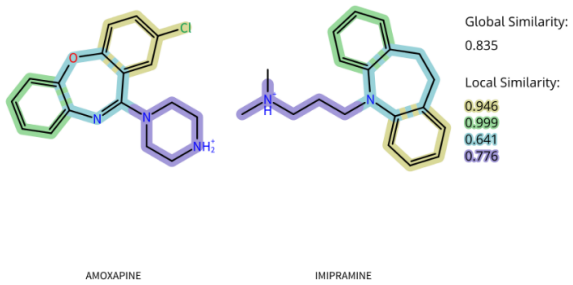
From the 1965 discovery paper cited in the first quotation in this entry:

"Repeated administration of the tyrosine hydroxylase inhibitor, α-methyl-tyrosine to guinea pigs decreased catecholamine levels in brain stem, caudate nucleus, heart and spleen to undetectable levels. Serotonin was unaffected. That the catecholamine decrease was a consequence of inhibition of tyrosine hydroxylase was shown by the following: tissue concentrations of norepinephrine failed to rise following monoamine oxidase inhibition and decarboxylase inhibitors failed to block the α-methyl-tyrosine effect; the conversion of tyrosine-$C^{14}$ to norepinephrine was inhibited whereas that from dopa-$H^3$ was not; and there was a normal uptake of exogenous norepinephrine by heart and spleen in animals pretreated with α-methyl-tyrosine. Preliminary studies of the pharmacologic consequences of blockade of norepinephrine synthesis indicate impairment of motor activity and mild sedation in cats and guinea pigs and a reduction of the tyramine and norepinephrine pressor responses in guinea pigs and rats(*272*)."

## AMOXAPINE

1980

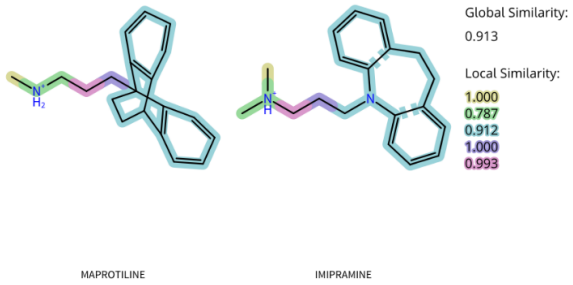
Analogue of imipramine




## MAPROTILINE

1980

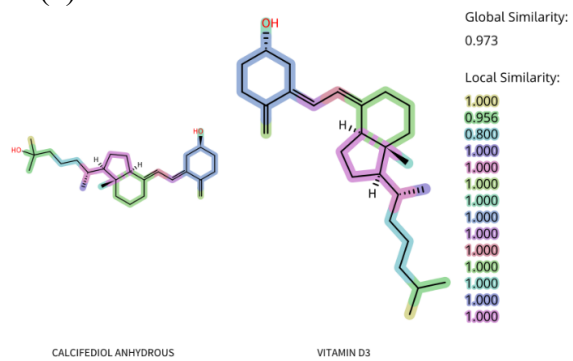
Analogue of imipramine




## CALCIFEDIOL

1980

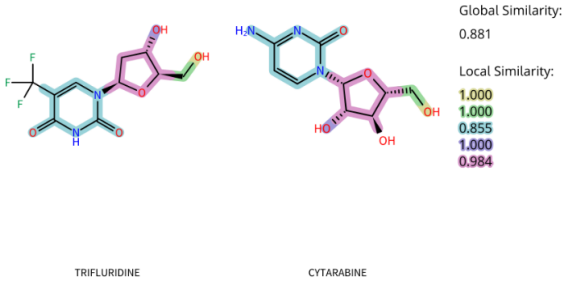
A biologically active vitamin D3 metabolite(*1*)




## TRIFLURIDINE

1980

Analogue of cytarabine

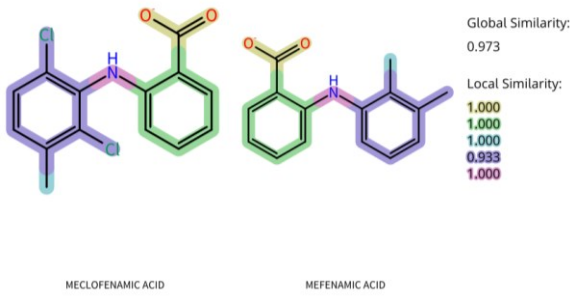



"It is a nucleoside analogue, a modified form of deoxyuridine, similar enough to be incorporated into viral DNA replication(*1*)."

MECLOFENAMIC ACID

1980

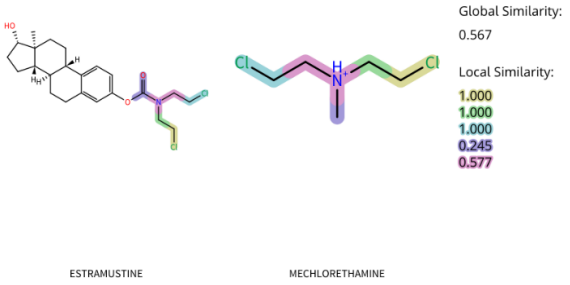
Analogue of mefenamic acid




ESTRAMUSTINE

1981

Analogue of nitrogen mustard




"Estramustine is a combination of estradiol with nitrogen mustard. In vivo, the nitrogen-mustard moiety becomes active and participates in alkylation of DNA or other cellular components(*1*)."

SUCRALFATE

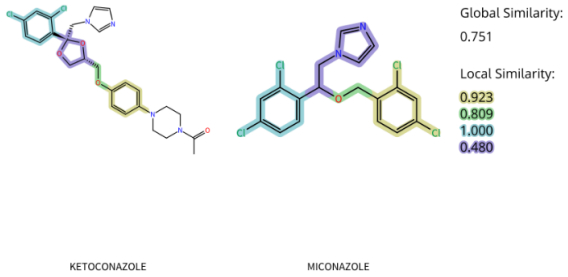
1981

Acts as a physical barrier.

KETOCONAZOLE

1981

Analogue of miconazole(*21*)




TRAZODONE HYDROCHLORIDE

1981

"Although trazodone is inactive in standard laboratory tests for antidepressant agents, interest that it might have antidepressant activity arose from studies in normal volunteers as well as from efficiacy studies in other psychiatric disorders(*273*)."

From the discoverer(s):

"The mental pain hypothesis of depression provided the rationale for developing an entirely new generation of antidepressants. Their prototype was trazodone, followed by various derivatives … These antidepressants are devoid of the aminergic properties of monoamine oxidase inhibitors and tricyclics that in the 1960s were considered the distinctive characteristics of antidepressants; therefore, they could never be detected by the old animals models of depression that relied on amine depletion(*274*)."

From the discoverer(s):

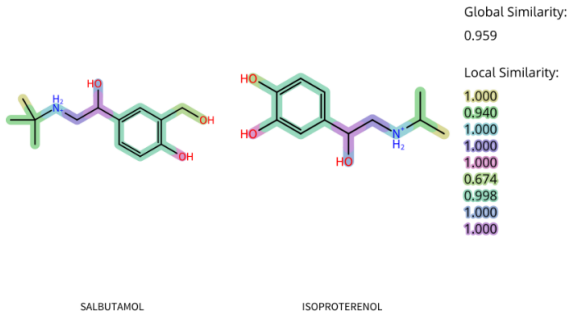
"This observation led to a working hypothesis proposing that substances capable of inhibiting the response to noxious stimuli in animals could possess antidepressant effects in humans. Accordingly, a pharmacological study of trazodone was performed with a battery of animal models entirely different from that used for first-generation antidepressants. This approach led to foreseeing the potential

usefulness of trazodone and other compounds in depression despite a pharmacological profile different from that of the tricyclics(*275*).”

## SALBUTAMOL

1981

Analogue of isoproterenol




From the discoverer(s):

“Sympathomimetic amines are widely used for the treatment of reversible airways obstruction. Isoprenaline has been extensively used, following demonstration of its bronchodilator activity in animals and man. Isoprenaline is, however, effective only when given by aerosol or sublingual routes because it is rapidly inactivated by catechol-O-methyl transferase. It can also cause marked side effects due to stimulation of β-adrenoceptive receptors (β-receptors) in the cardiovascular system. More recently, orciprenaline, the resorcinol analogue of isoprenaline, was shown to be an effective bronchodilator when given by aerosol or by mouth, with some selectivity for bronchial smooth muscle […]

It seemed possible that other chemical groupings might subserve for the catechol function in isoprenaline-like compounds to yield β-receptor stimulant drugs, which were not substrates for catechol-O-methyl transferase and had very high selectivity for bronchial smooth muscle. […] Of many compounds made and tested in these laboratories, 2-*t*-butylamino-l-(4-hydroxy-3-hydroxymethyl) phenylethanol (Salbutamol, AH 3365) was chosen for detailed study because it seems to have a very selective action on bronchial muscle. Some of the pharmacological results are given in this paper(*276*).”

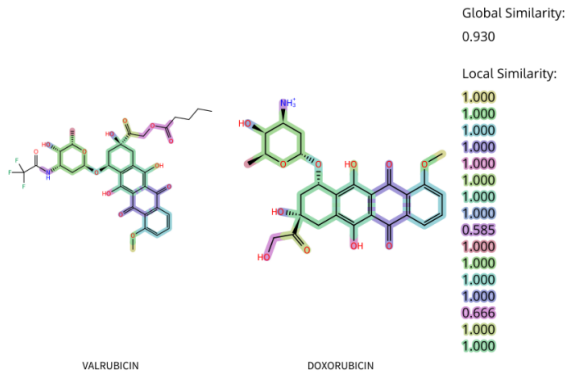
The reported assays(*276*):

- ✓ Comparison of the effects of salbutamol, isoprenaline and orciprenaline in anaesthetized animals
  - Antagonism of acetylcholine-induced bronchospasm in the guinea-pig
  - Actions on blood pressure, heart rate and respiration of dogs
  - Antagonism of bronchoconstriction caused by vagal stimulation in open chest cats and dogs
  - Effects on peripheral blood flow in the skinned hind limb of the dog
- ✓ Comparison of the effects of salbutamol, isoprenaline and orciprenaline on Acetylcholine-induced bronchospasm, and heart rate in conscious guinea-pigs
- ✓ Comparison of the effects of salbutamol, isoprenaline and orciprenaline on acetylcholine-induced bronchospasm, and heart rate in conscious guinea-pigs
- ✓ Effects of salbutamol and isoprenaline on isolated tissues
  - Tracheal chain of the guinea-pig.
  - Atria of the guinea-pig.

## VALRUBICIN

1981

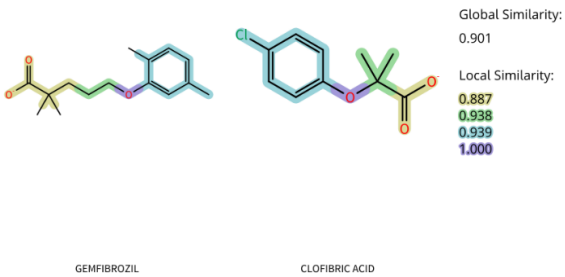
Analogue of doxorubicin(*277*)



## GEMFIBROZIL

1981

Analogue of clofibrate(*21*)



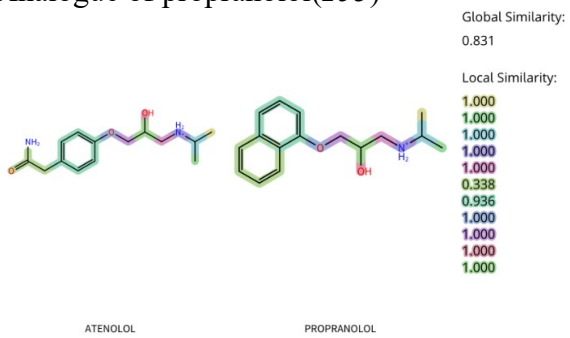

Discovery of clofibrate:

"Cottet reported that farm workers exposed to an insecticide which was sprayed from the air over fields in the region of Clermont-Ferrand in France became ill and were found to have remarkably low plasma cholesterol. This insecticide (phenyl ethyl acetic acid) had been developed by the agricultural division of Imperial Chemical Industries (ICI). A chemist in ICI, Jeff Thorp, recognized the potential of this substance and synthesized an analogue, chlorophenoxyisobutyrate (later called Atromid-S or clofibrate). Because of our published interest in cholesterol metabolism and plasma lipoproteins, Thorp telephoned me one day in 1957 asking whether Boyd and I might be willing to study the cholesterol-lowering effects of this analogue. For 3 years, we explored its effects, mostly in rats, finding it to be particularly effective in adrenalectomized rats. In those days, there were no requirements to present a clinical programme to any scientific or ethics committee, since there were no such committees! Therefore, slowly, I began to use it in healthy men starting with a dose of 250 mg daily. After a further 2 years, we identified that a daily dose of 1.5 g or more reduced plasma cholesterol concentrations consistently and significantly but wrongly labelled it as an orally active androsterone. Our subsequent research showed that its action was not related to androsterone activity, though we did not understand the mechanisms through which it lowered plasma cholesterol and more impressively plasma triglycerides(*278*)."

## ATENOLOL

1981

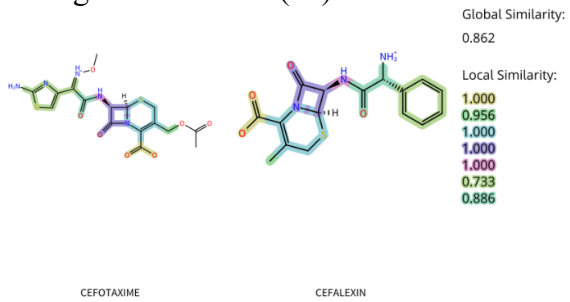
Analogue of propranolol(*253*)




## CEFOTAXIME

1981

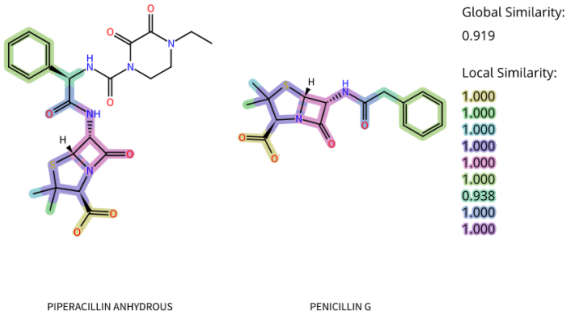
Analogue of cefalexin(*21*)




## PIPERACILLIN

1981

Analogue of penicillin(*21*)




## CAPTOPRIL

1981

"**From viper's venom to drug design: treating hypertension** […]

The concept of inhibiting ACE, which plays an integral role in blood pressure control by converting angiotensin I into the powerful hypertensive peptide angiotensin II, originated from an unusual source. The toxic effects of venom from a Brazilian viper (*Bothrops jararaca*) were found to be due to a sudden, massive drop in blood pressure. This piqued the interest of Nobel prize winning scientist, Sir John Vane, under whose auspices it was revealed that the snake venom was a potent inhibitor of ACE. Vane took this discovery to the pharmaceutical company Squibb, where two scientists, David Cushman and Miguel Ondetti, began working on creating a synthetic ACE inhibitor for use in treating hypertension(*279*)."

From the discoverer(s):

"In 1968, Dr. Y.S. Bakhle demonstrated that dog lung ACE was inhibited by a mixture of peptides from the venom of the Brazilian viper *Bothrops jararaca*, a mixture first described in 1965 by Sergio Ferreira as bradykinin-potentiating factor (BPF) […] We isolated, characterized, and synthesized six longer ACE-inhibitory peptides […]

The most potent of the larger peptides that we had sequenced, a nonapeptide, was very stable; its name, teprotide, reflects the four proline residues that help to confer this stability. Teprotide and a large number of analogues were thoroughly characterized in vitro and in vivo. […]

This exercise was not completely in vain; it showed how rare, indeed, were specific inhibitors of ACE, it also demonstrated that these, whether designed or stumbled upon, could be readily identified using a simple guinea pig ileum test system developed by Dr. Rubin and his colleagues. Success in this simple in vitro test was also highly predictive of activity in vivo, including antihypertensive activity. […]

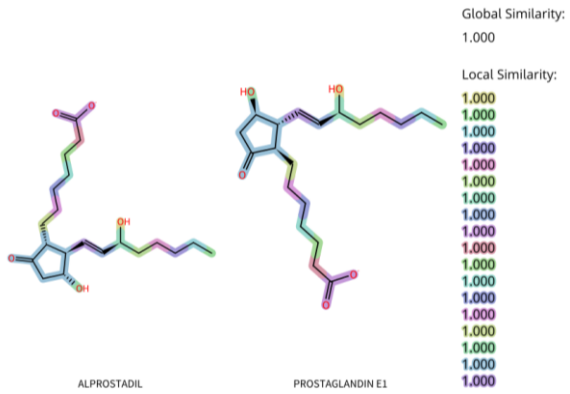
Since we needed an analogue of a dipeptide that would bind effectively to ACE, Ala-Pro was the obvious choice from our studies with the *B. jararaca* peptides. The compound suggested from such deliberations was D-2-methylsuccinyl-L-proline, although we decided to first make the much simpler molecule succinyl-L-proline, an analogue of the dipeptide Gly-Pro. From this moment of conception on March 13, 1974, only a year and a half passed before the first synthesis of captopril. Our thought processes, however, had been conditioned by results obtained during the preceding 6 years. Succinyl-L-proline had disappointing potency as an ACE inhibitor, since it had about 30,000 times less activity than our eventual goal, captopril. The key result with this prototype compound, however, came in Dr. Rubin's guinea pig ileum test. Unlike the 2,000 or so random compounds that we had previously tested, succinyl-L-proline had the properties of a specific ACE inhibitor: it inhibited contractile actions of angiotensin I and potentiated those of bradykinin, without having any effects on contractile actions of angiotensin II or those of several other smooth muscle agonists(*280*)."

"The structure of captopril had originated in peptides. Squibb scientists had taken a peptide obtained from snake venom and designed analogues of it that led, in 1975, to the discovery of the nonpeptide captopril(*281*)."

## ALPROSTADIL

1981

Same as the endogenous prostaglandin $E_1$(*217*). See the dinoprostone entry.



## AMILORIDE

1981

"Amiloride was discovered in the late 1960s during an extensive screening process at the Merck Sharp and Dohme Research Laboratories. Starting with N-amidino-3-amino-6-bromopyrazinecarboxamide, over 300 compounds were tested for their ability to reverse the effects of mineralocorticoids in rats. Of these amiloride was among the most potent in producing natriuresis without a concomitant kaliuresis(*282*)."

From the discovery paper cited in the previous quotation:

"More than 300 compounds were prepared pharmacologically to define the structure activity relationships in this class and to find an agent with an optimally attractive electrolyte excretion pattern. […]

**Pharmacology.-**Members of the series of N-amidino-3-aminopyrazinecarboxamides, when administered orally to rats, produced a diuresis accompanied by a marked increase of $Na^+$ excretion and little or no increase, or even a decrease, in $K^+$ excretion. Such a pattern of electrolyte excretion is the reverse of that produced by the mineralocorticoids, aldosterone and deoxycorticosterone, which cause sodium retention and increased potassium excretion by the kidney. Thus, it appeared that the compounds might act, at least in part, by blocking the renal effects of the mineralocorticoids. Accordingly, the compounds were tested for deoxycorticosterone inhibitory activity by a method based on that of Marcus, *et a1*. Saline-loaded, adrenalectomized Holtzmann rats weighing 130 ± 3 g. were injected subcutaneously with 12 γ of deoxycorticosterone acetate (DOCA), an amount sufficient to produce a maximal decrease in the urinary ratio of Na/K. The animals were then injected subcutaneously with the test compound and placed in metabolism cages, and 7-hr. samples of urine were collected. Analyses of the samples for $Na^+$ and $K^+$ concentrations gave values from which the urinary Na/K ratios could be calculated. The evidence of inhibition of the electrolyte effects of DOCA is a rise in Na/K ratio over that obtained with DOCA alone. The dose of each compound which will produce a 50% reversal of the DOCA effect is listed in Tables I, II, and III in the following codified form.

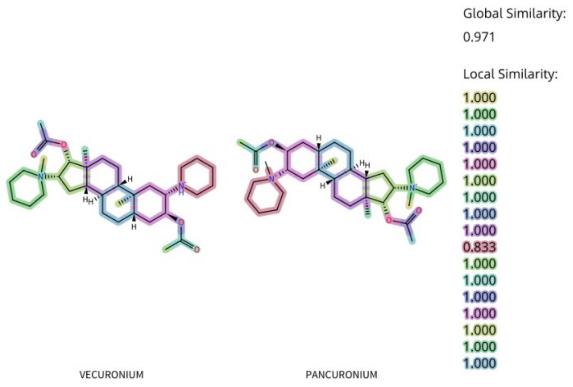
N-Amidino-3-amino-6-chloropyrazinecarboxamide is the most potent DOCA inhibitor of this series, producing a 50% reversal of the DOCA effect at 36 γ/rat. Substitution on the guanidine moiety generally lowered activity, the lowering being, very roughly, proportional to the bulk of the substituents. Only **3** with two methyl substituents, **11** with a benzyl, arid **13** with a hydroxyethyl substituent were approximately equipotent with **1**. Replacement of the chlorine atom by bromine or iodine reduced activity. The acylation products of **1**, **29**, and **30** were weakly active (score ±). […]

The diuretic and natriuretic activities in intact rats and dogs closely parallel the DOCA inhibitory activities; compound **1** is most highly active in both species. At comparable doses, the compounds are generally more effective in the rat than in the dog(*283*)."

## VECURONIUM

1981

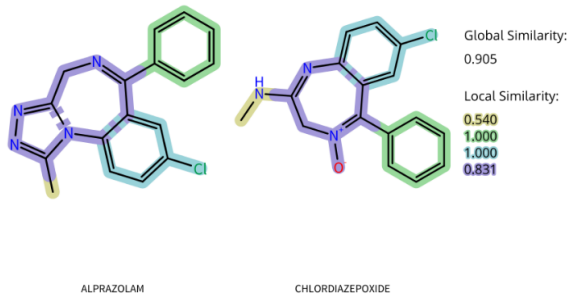
Analogue of pancuronium



## ALPRAZOLAM

1981

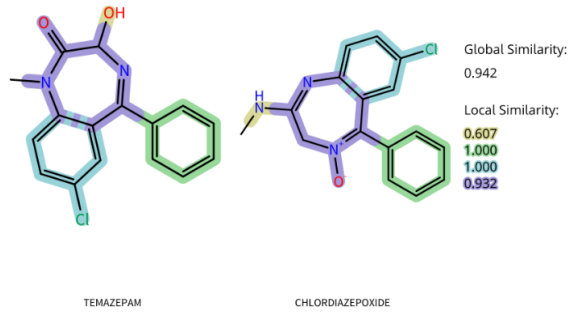
Analogue of chlordiazepoxide




## TEMAZEPAM

1981

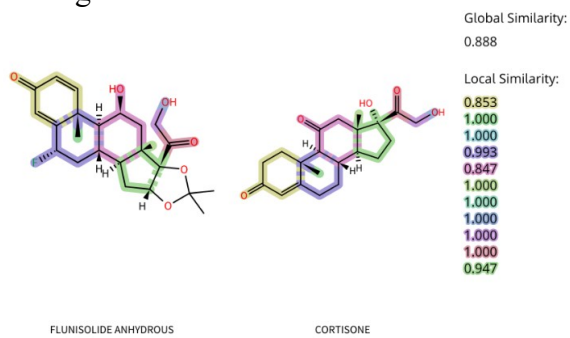
Analogue of chlordiazepoxide(*21*)




## FLUNISOLIDE

1981

Analogue of cortisone




## NIFEDIPINE

1981

"The vision of the pharmacologist Vater was to supply the diseased heart with more oxygen using drugs to dilate the coronary arteries. With this in mind, Vater introduced techniques of measuring the oxygen content in the coronary sinus blood into animal experiments, which indirectly permitted the estimation of any possible coronary dilating effect of compounds. […]

Bossert's starting point was the natural product khellin, a chromone from the Mediterranean plant *Ammi visagna*, which was in 1947 anecdotically reported to have some positive effects on the coronary vessels and heart function, but this was never confirmed. Bossert synthesized a number of chromone, thiochromones, and coumarin derivatives, however, most of them were ineffective in Vater's experiments. Some increased the oxygen content in coronary sinus blood, but only after intravenous not after oral administration, which was the aim of this research. In attempts to improve resistance to enteral enzymes, Bossert performed a stepwise modification of the quinolone basic structure and ended at esterified pyridines. A logical step in structured research, but these compounds were totally inactive in the coronary test performed by Vater. Evidently, the reduction of the molecule size had gone too far. The dihydropyridines appeared most suitable for increasing the molecule size […]

On December 9, 1964, the first compounds of this type, Bs 1861 (Bs = Bossert) was given to a dog. By modern standards it was a high dose, but at that time it was a standard dose for work with the thousands of weak or even ineffective compounds. After an initial increase in oxygen saturation in the coronary sinus, the blood pressure rapidly decreased to such a level that the animal did not survive. During the experiments carried out over the next days, much lower doses were administered; the increase in oxygen saturation in the coronary sinus was still present and of a longer duration. These first steps indicated that the primary goal had been achieved. However, such an event is usually not a copingstone, but rather the start of a new path, which in turn is paved with moments of

success and doubts before one can be certain that the final peak has been surmounted. Hundreds of derivatives were synthesized and tested in an attempt to find the right compound. One and half years later, in June 1966, a powder in a small bottle designated 'Bay a 1040' reached Vater's pharmacological laboratory(*284*)."

## OXIGLUTATIONE DISODIUM

1981

"Oxiglutathione is the oxidized disulfide form of glutathione (GSH) with potential protective activity. Glutathione disulfide (GSSG) is reduced by glutathione reductase to GSH. GSSG and GSH together play important roles in numerous redox reactions, such as those involved in the detoxification of harmful substances and free radicals, and in reactions preventing oxidative damage in erythrocytes. Upon ocular administration in irrigation solution, glutathione disulfide may exert a beneficial effect on the intracellular redox state of glutathione, thereby protecting the integrity and barrier function of the corneal endothelial cells(*1*)."

From the discovery paper:

"FOR some time it has been known that fibroblasts and epithelial cells proliferate indefinitely in vitro in a medium composed of equal parts of plasma and embryo juice. If the factors responsible for the unlimited growth of tissues in such a medium could be known, it seems probable that much could be done to accelerate the normal processes of repair. […] As a means to these ends it seemed desirable to synthesize, if possible, a medium of known chemical composition in which the indefinite proliferation of connective and epithelial tissues would take place. The first step in this direction was made with the discovery that fibroblasts and epithelial cells cultivated in proteoses from certain proteins multiplied extensively, although for a limited period. It was shown later that peptones and the lower fragments of the protein molecule also contribute to the nutrition of fibroblasts. Recently a pure strain of sarcomatous fibroblasts was found to proliferate slowly for a period of fourteen to twenty days in an artificial medium composed of Tyrode solution, nucleic acid, glycocoll and the peptic digestion products of either casein or crystalline egg albumin. Normal fibroblasts in pure culture also multiply for a limited time in this medium. The rate of growth, however, decreases with time, and death of the cells follows. One could attribute the deficiency of this medium in part, at least, to the absence of substances required for the functioning of the respiratory mechanism of the cell. It was also reasonable to suppose that a given oxidation-reduction potential might be as important for cell multiplication as a definite osmotic pressure or hydrogen-ion concentration. Therefore, a study was made of the effect on the nutritive value of this medium of adding to it, (1) ash of liver, (2) glutathione and (3) hemoglobin. […]

The mixture of these three substances with casein digest, glycocoll and nucleic acid was found to have an astonishing effect on the multiplication of sarcomatous fibroblasts. The growth of new tissue was approximately 100 per cent. greater in the first passage than that in the original medium of casein digest, glycocoll and nucleic acid, and was as great as that produced by embryo juice(*285*)."

From the earliest paper (1913) cited in the previous quotation regarding the indefinite proliferation of cells *in vitro*:

"If the rate of the reparation of tissues were activated ten times only, a cutaneous wound would heal in less than twenty-four hours, and a fracture of the leg would be cured in four or five days. […] Jacques Loeb, in his fundamental experiments on artificial parthogenesis, has demonstrated that cell division can be induced by slight changes in the composition of the sea water in which the sea

urchin's eggs are placed. It might even be supposed that certain modifications of the *milieu intérieur* of the tissues of mammals would bring about the multiplication of their cells. In 1907 and 1908 I began, therefore, to study the processes of reparation of small cutaneous wounds and the action of a great many substances on the rate of their cicatrization. It was found that the proliferation of epithelium and of connective tissues was activated under certain conditions by dressings made with the pulp of tissues and organs. For instance, thyroid gland pulp deposited on cutaneous wounds of the dog brought about the formation of exuberant granulations. Applied to bones, it produced a marked thickening of the periosteum. The external coat of an artery preserved in cold storage in a mixture of thyroid gland and Locke's solution, and transplanted afterwards into a dog's carotid, underwent an enormous hypertrophy. However, it was difficult to study with precision the influence of these substances on the tissues of living dogs. It became evident that the changes brought about by them could be more precisely observed if the tissues were isolated from the organism and made to live in a medium of known composition. Therefore, I undertook to adapt to the cultivation of mammalian tissues […]. In some experiments that I made in 1911 with the collaboration of Dr. Burrows, it appeared that the growth of chicken tissues were activated when extracts of the Rous chicken sarcoma and of chick embryo were added to the culture medium.

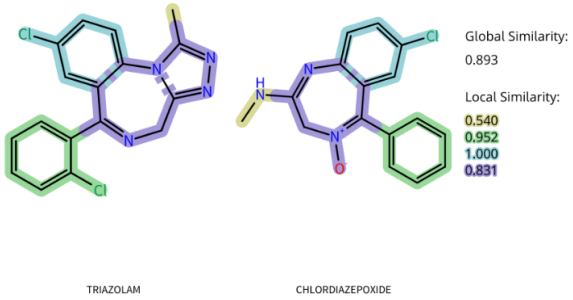
In 1912, by using a more precise technique, I was able to study quantitatively the influence of tissue juices on the growth *in vitro* of connective tissue and some of the characteristics of their activating power. […]

In every experiment the fragments of heart, skin, and periosteum, cultivated in plasma containing an extract, grew more rapidly than their controls. It is certain, then, that tissue juices have the power to activate *in vitro* the growth of connective tissue(*286*)."

## TRIAZOLAM

1982

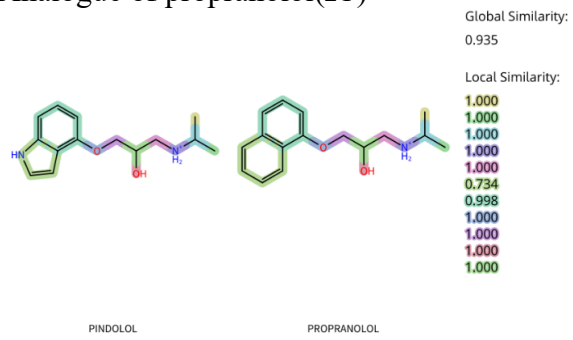
Analogue of chlordiazepoxide(*21*)




## PINDOLOL

1982

Analogue of propranolol(*21*)




## PRAZIQUANTEL

1982

"The compounds were passed on to Bayer for veterinary screening. Using a step-by-step procedure, the most effective substance, praziquantel, was chosen from a total of approximately 400 compounds. This substance was found to be an effective anthelminthic against a broad spectrum of parasitic trematodes and cestodes. The drug was first developed for veterinary use and later tested for the treatment of helminthic infections in humans. The therapeutic potential of praziquantel for the treatment of *S. mansoni* infections was first explored by Andrews and Gönnert in 1977 at the Research Centre Wuppertal using the schistosoma/mouse model(*287*)."

## ACYCLOVIR

1982

From the discoverer(s):

“The first purine nucleoside found to have useful antiviral activity, in the mid 1960s, was adenine arabinoside. This compound could be used not only topically but also intravenously, although the therapeutic index was not very large. In the late 1960s we synthesized and tested other purine arabinosides as antiviral agents and found, to our delight, that 2,6-diaminopurine arabinoside and guanine arabinoside were as active as adenine arabinoside in mice infected with HSV-1 or vaccinia virus. This changed our perspective with regard to which purine bases could be used for making antiviral nucleosides, and led eventually to acyclovir(*288*).”

## ISOTRETINOIN

1982

Analogue of tretinoin and Vitamin A(*21*)

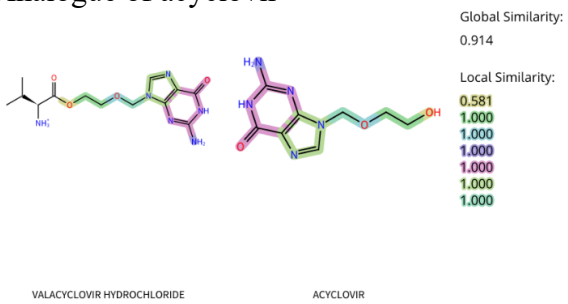
Naturally-occurring endogenous retinoid(*1*)

“While searching for retinoids with less severe side effects than tretinoin, Bollag (Hoffmann-La Roche, Switzerland) discovered and then synthesized isotretinoin (13-cis-retinoic acid) in 1971. As early as 1973 the drug was tried in psoriasis, but the results were not encouraging. However, by 1976 isotretinoin was found to be highly effective in the treatment of disorders of keratinization, particularly Darier’s disease, lamellar ichthyosis, and pityriasis rubra pilaris. It happened that one patient who also had severe acne responded dramatically. Thus serendipity led to the discovery of a drug which is incomparable effective in acne conglobate(*289*).”


## VALACYCLOVIR HYDROCHLORIDE

1982

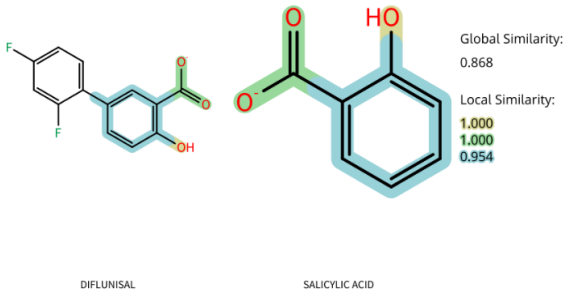
Analogue of acyclovir




## DIFLUNISAL

1982

Analogue of salicylic acid




## DILTIAZEM

1982

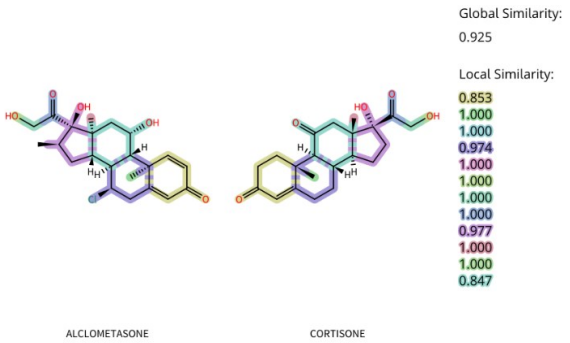
Full-text of the earliest reporting paper published in 1971 could not be found (PMID: 5171789), a 1973 related that reports further studies on its derivatives, summarises the effects reported by that paper while citing it:

“It is a new benzothiazepine derivative with notable coronary vasodilating activity in anaesthetized dogs and in the isolated guinea-pig heart. CRD-401 also exhibits a weak depressive effect, in large doses, on the beating rate and contractile force of the dog heart(*290*).”

## ALCLOMETASONE

1982

Analogue of corticosteroid




## MALATHION

1982

"As an OP [organophosphate] insecticide, malathion was first registered for use in the United States in 1956 by the United States Department of Agriculture (USDA). […]

OP introduced in the 1930s, are manufactured chemical substances that are produced by the reaction of alcohols and phosphoric acid. Their primary effect as insecticide was discovered during military operations when initially used as nerve gases. Malathion, an OP compound, is also known as carbophos, maldison, and mercaptothion. Being a non-systemic, wide-spectrum insecticide, malathion is one of the most frequently used OP pesticides. It has been used for various eradication programs and for public health purposes throughout the United States and other countries. Some of the common areas of usage include agricultural, industrial, and use by the general public.

Malathion was developed during World War II, in the 1950s(*291*)."

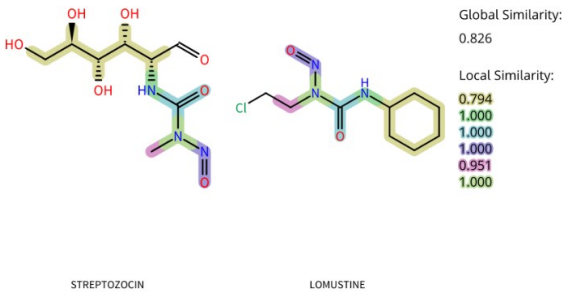
Discovery of organophosphates:

"Their development goes back to 1932 when Willy Lange at the University of Berlin synthesized some compounds containing the P-F linkage. During the synthesis of dimethyl and diethyl phosphofluoridate, he and his graduate student G. von Kreuger, noticed the toxic effects of the vapors on themselves. They wrote '…The vapours of these compounds have a pleasant and strongly aromatic odour. But a few minutes after inhaling, a marked pressure develops in the larynx combined with breathlessness. Then, mild disturbances of consciousness set in and also a feeling of being dazzled and painful hypersensitivity of the eyes to light. The symptoms decrease only after several hours. … Very small quantities produce the effects…' Lange seemed to be fully aware of the potentialities of organophosphorus compound as insecticides, but he soon left Germany and did not continue to work in this field. The father of modern organophosphorus insecticides is therefore considered Gerhard Schrader, a chemist at the I. G. Farbenindustrie (now Bayer A. G.). In the mid thirties in Germany all available resources were used by the State in building defense programs, and the importation of goods which were not considered essential was considerably reduced. The latter included nicotine and rotenone, which were the main products available for crop protection. While working in the synthesis of organic fluorine and sulfur compounds, one day in December 1936, Schrader noticed '…that, on my way home my visual acuity was somewhat reduced. By the following day vision had practically returned to normal and I resumed my work. When other visual disturbances occurred, it became quite obvious that they were caused by a new synthetic substance.' This substance was isolated, but it was too toxic to warm-blooded animals to be used in agriculture. In the early forties, Schrader and his colleagues found a new simple method to synthetize a particular ester of pyrophosphoric acid (tetraethylpyrophosphate; TEPP) which was brought into the market in 1944 under the trade name Bladan. Interestingly, the same compound had been synthetized in 1854 by the French chemist de Clermont who also survived to report on the compound's taste(*292*)."

## STREPTOZOCIN

1982

Analogue of lomustine




It was originally identified as an antibiotic isolated from *Streptomyces achromogenes*

"Streptozotocin, an antibiotic produced by *Streptomyces achromogenes*, is a broad spectrum antibacterial agent and also has antitumor activity in both *in vitro* and *in vivo* systems(*293*)."

"Streptozotocin is an antibiotic extracted from *Streptomyces acromogenes* and prepared in highly purified form. Its molecular weight is 265 with the empirical formula $C_8H_{15}N_3O_7$ containing a N-nitrosomethylamide function. The substance has also been shown to exert antitumoral activity in leukemia L 5178 Y, Ehrlich carcinoma and Walker 256 carcinosarcoma. In 1963, Rakieten et al further reported that streptozotocin is diabetogenic, since its intravenous administration led to frank diabetes in dogs and rats. On the basis of their histologic studies, they attributed this diabetes to damage to the pancreatic B-cells(*294*)."

## CICLOPIROX

1982

Topical antifungal. Based on the abstract, as the full-text could not be found, the discovery of the lead compound seems to have been achieved by using *in vitro* whole-cell fungal assays and then experimental guinea pig dermatophytosis(*295*).

## INDIUM CHLORIDE IN-111

1982

Radiopharmaceutical

## PIROXICAM

1982

During the previous studies aimed at finding antiinflammatory compounds, some beta-diketones such as phenylbutazone had shown antiinflammatory activity(*89*).

From the discovery paper:

"The 1,2-benzothiazin-4-(3H)-one 1,1-dioxide heterocyclic system has received little attention and, in view of the activity found for the aforementioned β-diketonic acids, appeared attractive as a potential source of acidic, and possibly biologically active, compounds. This present paper reports the discovery of potent antiinflammatory activity for certain acidic β-keto carboxamides derived from this class of compounds(*296*)."

After synthesizing various analogues, from the discovery paper:

"Antiinflammatory activity was assessed as inhibition of edema formation in the hind paw of the rat in response to a subplantar injection of carrageenin(*296*)."

## ETOMIDATE HYDROCHLORIDE

1982

"It emerged from their antifungal agent development program, which involved the synthesis of novel imidazole-containing compounds designed to suppress the biosynthesis of the fungal steroid ergosterol by inhibiting the cytochrome P450 enzyme 14α-demethylase. When tested in rats, etomidate exhibited both potent anesthetic activity and a very high therapeutic index(*297*)."

From the discoverer(s):

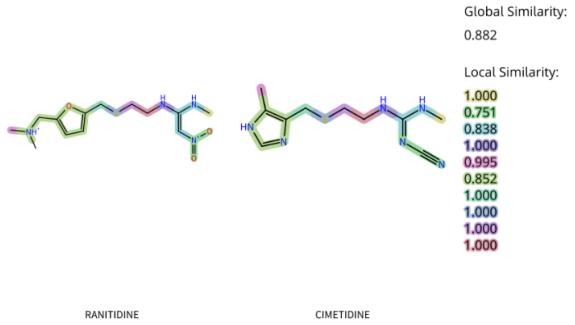
"In these laboratories for a number of years we have been interested in imidazole derivatives as chemotherapeutic agents. During the course of this work we have had occasion to

prepare a number of 1-aralkyl-imidazole-5-carboxylic acid esters. The observation that one of these, upon parenteral or oral administration to rats, induced a profound hypnotic state prompted us to prepare additional analogs of I, specifically type IIIb, in a effort to further delineate the structure-activity correlations governing this class of compounds(*298*)."

## RANITIDINE

1983

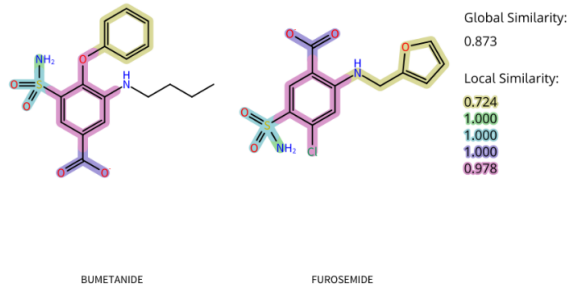
Analogue of cimetidine(*21*)




## BUMETANIDE

1983

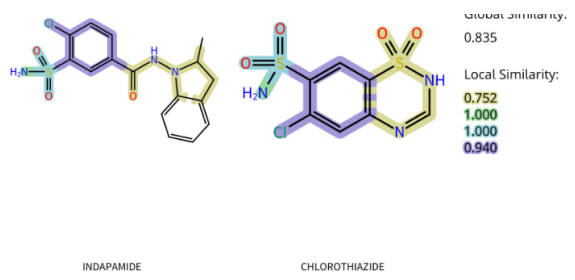
Analogue of furosemide(*21*)




## INDAPAMIDE

1983

Analogue of chlorthalidone




## URSODIOL

1983

Ursodiol (Ursodeoxycholic acid), a naturally occurring hydrophilic bile acid derived from cholesterol, is present as a minor fraction of the total human bile acid pool(*1*).

"Naunyn, in 1892, stated that human gallstones placed in the gallbladder of the dog disappeared after a few months. This has been repeatedly corroborated, and it seems clear that the stone disappears because of the solubility of the cholesterol of the stone in dog bile.

Large and Lutton have demonstrated that not only the dog but also the pig, sheep, and goat will dissolve hum an stones placed in the gallbladder. Ox bile, as well as the bile of the dog, has been shown to have a solvent action on hum an gallstones in vitro.

The solution of human gallstones by animal bile is a slow process in vivo or in vitro and requires long, continuous bathing of the stone in the bile and frequent replenishing of the bile as it becomes relatively saturated with dissolved cholesterol.

Most animal bile is not so different in constitution from human bile, and it seems reasonable to assume that with slight changes in the com position of human bile it might dissolve human stones, or that substances excreted into the bile may be administered which will readily dissolve cholesterol(*299*)."

## HEMIN

1983

"Acute intermittent porphyria is characterized biochemically by the increased urinary excretion of the porphyrin precursors δ-aminolevulinic acid (ALA) and porphobilinogen (PBG). This is believed due to a marked, genetically mediated increase of hepatic ALA synthetase, which is normally the first and rate-controlling enzyme of heme biosynthesis. A decreased activity in the hepatic

conversion of PBG to porphyrins in a patient with acute intermittent porphyria has recently been noted. This suggests a partial block in heme biosynthesis in this case that may relate to the observed induction of hepatic ALA synthetase, the end-product heme having been shown to repress the synthetase production both *in vitro* and *in vivo*. These considerations induced us to study the effect of hematin on the induction of the synthetase in a patient experiencing a devastating attack of acute intermittent porphyria, after numerous other modes of therapy had failed(*300*)."

From the previous relevant literature regarding the clinical, *in vitro,* and *in vivo* findings cited in the previous quotation:

"The enzymes 6-aminolaevulic acid synthetase and 6-aminolaevulic acid dehydrase are concerned in the early stages of tetrapyrrole formation; factors controlling their synthesis have been studied in cultures of *Rhodopseudomonas spheroides* growing exponentially. […]

Low concentrations of iron protoporphyrin (added as haemin) inhibited the synthesis of both ALA synthetase and dehydrase but similar concentrations of protoporphyrin were ineffective(*301*)."

"A method is described for the primary growth of chick embryo liver cells on cover slips in culture, and the factors of the culture medium are considered that affect the induction of porphyrin formation with certain chemicals.

A method is described for following & aminolevulinic acid synthetase (ALA synthetase) activity by the determination of porphyrin fluorescence developed in the cells on cover slips after induction with chemicals or drugs. […]

The chemicals and drugs which induce a porphyria in the chick embryo liver cells in culture may be separated into four classes: the barbiturates which contain three chemical groups that can individually induce; the collidines which contain two chemical groups; the sex steroids; and a miscellaneous class.

Evidence is presented that the control of ALA synthetase in the liver is by feedback repression in which heme may be the corepressor(*302*)."

"**Inhibition by heme occurs at the translational level:** Studies with labeled leucine and orotic acid showed that hemin, at 5 μM, did not affect total protein or total RNA synthesis in chick embryo liver cells. These findings were reconfirmed with radioactive leucine and uridine. In addition, it was found that hemin did not affect radioactive thymidine incorporation, which suggested that DNA synthesis was not affected. Our finding that hemin did not stimulate ribonuclease activity also supported the idea that hemin had no effect on non-specific RNA degradation.

The addition of hemin to isolated mitochondria from induced cells does not directly affect the activity of ALA-synthetase except at concentrations that are, physiologically, abnormally high.

When hemin was added to the liver cells in culture, together with acetoxy-cycloheximide, the rate of decay of ALA-synthetase was 3 hr, i.e., the same as the control rate without hemin, which indicated that hemin did not affect the rate of decay of the enzyme.

An inhibitory effect of hemin on the synthesis of ALA-synthetase was reported in chick embryo liver cells ($K_i$ 3 μM) and confirmed in whole animal studies by Hayashi et al. and by Marver. In the present experiments it was possible to demonstrate that the inhibitory effect is at the translational level. The cells in culture were first pretreated with AIA for 14 hr to increase the level of ALA-synthetase. The medium was then changed twice to remove AIA and replaced with fresh medium to which actinomycin D and hemin were added. It was determined that the average

apparent half-life of ALA-synthetase had decreased to 3.6 hr, as compared with 5.2 hr with actinomycin D alone.

These results suggested that hemin inhibited the synthesis of ALA-synthetase at the translational, rather than at the transcriptional level as had been previously hypothesized. Hemin might inhibit by competing with an inducing chemical for a special site, or act at some other site. On the other hand, hemin might cause a decrease in the lifetime of mRNA for ALA-synthetase. The latter idea is disfavored because, as noted above, hemin did not stimulate an increase in ribonuclease activity(*303*)."

"In the genetic disease acute intermittent porphyria a marked increase in the level of hepatic ALA synthetase has been demonstrated as the explanation for the increased porphyrin precursor excretion seen in this disease.

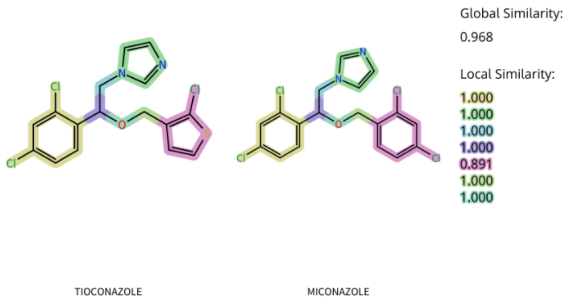
In microorganisms (R. spheroides) data have been presented which suggest control of ALA synthetase by means of both end product (heme) inhibition and repression (Lascelles, 1960). However, it is doubtful that heme is a physiologically significant inhibitor the enzyme in vivo in liver. Granick found no inhibition of ALA synthetase by heme added to liver mitochondria at concentrations of 2.5 x $10^{-5}$ M (Granick, 1966) and Marver et al., found no inhibition of the solubilized enzyme from rat liver until the heme concentration reached 5 x $10^{-4}$ M (Marver et al., unpublished). That heme is involved in the repression of hepatic ALA synthetase, however, is evidenced by its inhibition of induction of the enzyme in cultured chick embryo liver cells at concentrations of about 2.5 x $10^{-6}$ M (Granick, 1966). Further in vivo evidence of the role of heme in repression of hepatic ALA synthetase is the fact that administration of tryptophane to rats is followed by induction of hepatic ALA synthetase. […]

The present studies demonstrate directly in vivo a role of heme in the repression of hepatic ALA synthetase as well as a series of oscillations of the hepatic enzyme which follow a single intravenous injection of heme(*304*)."

TIOCONAZOLE

1983

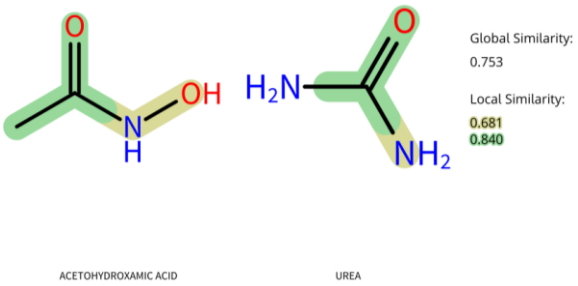
Analogue of miconazole




ACETOHYDROXAMIC ACID

1983

Analogue of the endogenous compound, urea



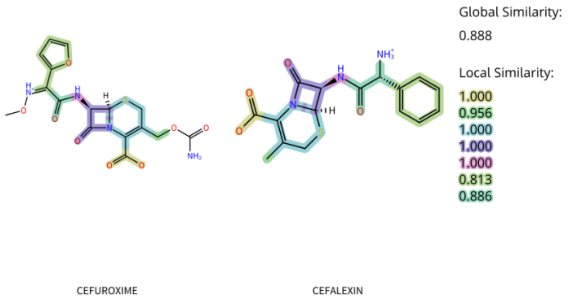

"Acetohydroxamic acid (also known as AHA or by the trade name Lithostat) is a synthetic drug derived from hydroxylamine and ethyl acetate, is similar in structure to urea. In the urine, it acts as an antagonist of the bacterial enzyme urease. Acetohydroxamic acid is used to lower the level of ammonia in the urine, which may help with some types of urinary infections. Acetohydroxamic Acid has no direct antimicrobial action and does not acidify urine directly. It is used, in addition to antibiotics or medical procedures, to treat chronic urea-splitting urinary infections. In 1983 the US Food and Drug Administration approved acetohydroxamic acid (AHA) as an orphan drug for 'prevention of so-called

struvite stones' under the newly enacted Orphan Drug Act of 1983(*1*)."

## CEFUROXIME

1983

Analogue of cefalexin(*21*)




## CYCLOSPORINE

1983

Cyclosporin is the main metabolite of the fungus *Tolypocladium inflatum*.

From the discoverer(s):

"Since the beginning of the antibiotic screening program in 1958, it was usual for Sandoz employees on business trips or vacation to take with them small plastic bags for collecting soil samples. […]

In Z.L. Kis's laboratory, the metabolites were first purified from the original crude extracts on a micropreparative scale. Initially, we were able to isolate and characterize 80 mg of a mixture of cyclosporins as neutral, lipophilic peptides that were presumably cyclic, since no amino or carboxyl endgroups were detectable. The two components in the mixture had a molecular weight greater than 700 Daltons (the limit of mass spectroscopy in those days) and nuclear magnetic resonance suggested that the peptides contained several N-methylated amino acids. They possessed antifungal activity *in vitro*. The computer evaluation of these data showed that we were dealing with a mixture of a novel family of metabolites. Novel and active compounds merit further *in vivo* investigation. […]

A few weeks later, the Viennese Group reported the fungistatic activity of 24-556 in animals as restricted to a relatively narrow range of fungal strains. Our colleague there also commented on the low level of toxicity. […]

Though the antifungal activity did not seem adequate to warrant development at the time, this immediate disappointment was nothing new to us. But the mixture's unusually low toxicity, and the knowledge that microbial metabolites often possess interesting pharmacologic activities other than the antibiotic effects for which they were originally selected, caused us to press on with further pharmacological screening. For many years it had been our practice at Sandoz to screen fungal products as broadly as possible, not only for antimicrobial but also for cytostatic, antiviral, and immunosuppressive activity. The screening tests included a cell culture assay for inhibition of cell proliferation (cytostatic effects) and an *in vitro* model to detect agents able to neutralize cytotoxic T-cell activity (immunosuppression). In addition, a combined *in vivo* test in mice was used to assess both the immunosuppressive and the anticancer activity. This early chemotherapy screening program was eventually enlarged and integrated in 1970 into a general screening program in which some 50 pharmacological parameters were evaluated. Thus, the metabolite mixture 24-556 entered this general screening program in December 1971 and was found to possess potent immunosuppressive properties. By the first half of 1973, a variety of experimental studies showed that 24-556 suppressed both antibody- and cell-mediated immunity. These interesting findings justified the separation of the single components of the mixture 24-556(*305*)."

## ETOPOSIDE

1983

The antitumor potential of the *Podophyllum* extract had long been known(*306*) (refer to

the podophyllotoxin entry), From the discoverer(s):

"Careful fractionation of SP-G lots by systematic and extensive chromatographic procedures - guided by biological testing - first yielded the anomer of podophyllotoxin benzylidene glucoside(*307*)"

"In late 1964, after two years of endeavors to trace down the component responsible for the activity of SP-G in leukemia L-121O, another compound could be isolated (named benzylidene lignan P) which turned out to not only greatly inhibit cell proliferation in vitro but also to produce a remarkable increase of survival time in leukemic mice at low doses. […]

With synthetic lignan P at our disposal it was possible to prepare numerous derivatives; first of all a large series of condensation products with carbonyl compounds. Most of the obtained cyclic acetals and ketals were active in mouse leukemia L-1210(*307*)."

## CLAVULANIC ACID

1984

From the discovery paper(*308, 309*):

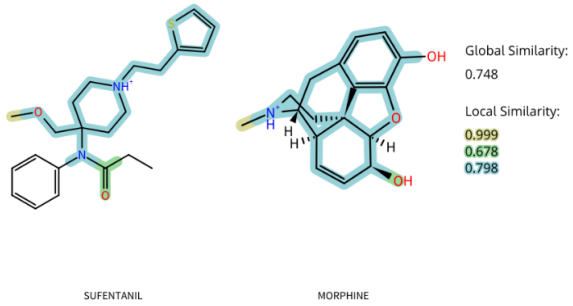
"We now wish to report the isolation of certain naturally-occurring substances which are potent β-lactamase inhibitors and which also possess antibacterial activity. These substances, [...] are produced by certain cultures of *Streptomyces* and were detected in fermentation broths using the following test. Agar plates were prepared containing benzylpenicillin at a concentration of 10 ug/ml and seeded with a strain of *Klebsiella aerogenes* NCTC 418 (ATCC 15380) which owes its penicillin resistance to the production of β-lactamase. Broth samples for test were placed in holes cut in the agar and the plates incubated overnight. Samples containing a diffusible beta-lactamase inhibitor gave rise to zones of inhibition resulting from the protection of the penicillin present in the agar. In the absence of any β-lactamase inhibitor, bacterial growth occurred as a result of the inactivation of the penicillin by the β-lactamase produced by the organism. MM 14151 is produced by *Streptomyces clavuligerus* ATCC 27064 and has been given the trivial name clavulanic acid(*310*)."

## SUFENTANIL

1984

Analogue of morphine and fentanyl

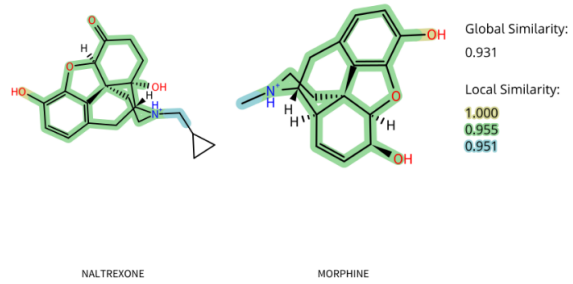
Also see the fentanyl entry and refer to Paul Janssen's article cited there.




## NALTREXONE

1984

Analogue of morphine(*21*)

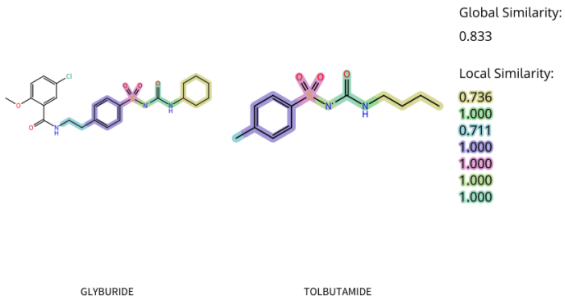



## GLYBURIDE

1984

Analogue of Carbutamide(*21*)

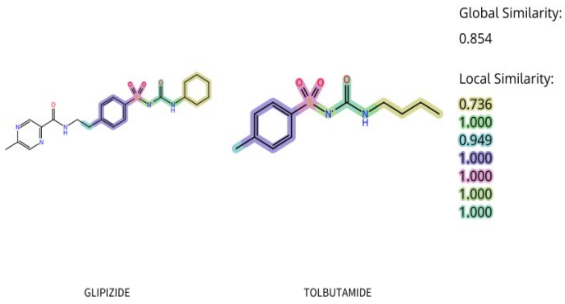
Carbutamide, like tolbutamide, is an analogue of the sulfonamide antibacterials whose glycemic effects where observed numerously after the initiation of their prevalent use(*129*). See the tolbutamide entry.




GLIPIZIDE

1984

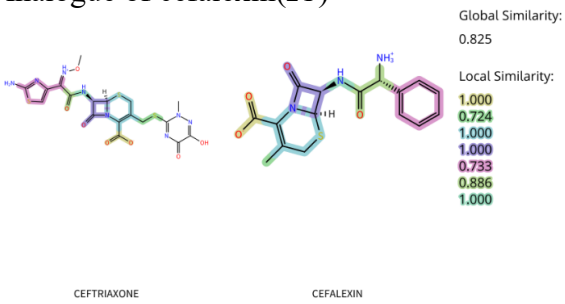
Analogue of glyburide(*21*)




CEFTRIAXONE

1984

Analogue of cefalexin(*21*)




INAMRINONE

1984

"The positive inotropic activity of amrinone was first demonstrated in isolated heart tissues of several animal species including humans. In the isolated cat atria and papillary muscle, amrinone at concentrations of 3-100 p,g/ml caused dose-dependent increases in papillary muscle-developed tension and its rate of development without significantly changing the total duration of the contractile cycle or the time to peak tension. Amrinone caused dose-dependent increases in right atrial-developed tension with minimal increases in right atrial rate(*311*)."

From two earliest reports of the discovering team(*311*):

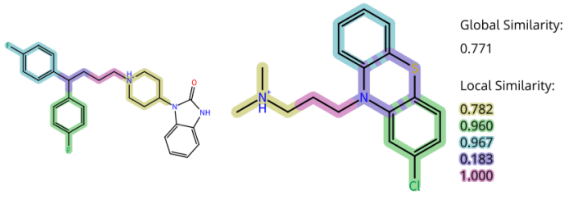
"The cardiotonic activity of a new, noncatechol, nonglycoside agent, amrinone, was investigated in vitro and in anesthestized and unanesthetized dogs(*312*)."

"Amrinone, a 5-amino [3,4'-bipyridin-6(1H)-one, is a non-glycoside and non-catechol inotropic agent. Its activity has been demonstrated in experimental animals both orally and intravenously. This paper describes the in vitro efficacy of Amrinone on human atrial strips as compared with that of isolated cat left and right atria and papillary muscle. Human atria1 strips, obtained during heart surgery, and cat atria and papillary muscle were incubated with increasing doses of A and its effect on contractile force and rate determined. Amrinone caused dose-related increases in contractile force and rate determined(*313*)."

PIMOZIDE

1984

Analogue of chlorpromazine




PENTAMIDINE

1984

In 1929 it was shown for the first time that pathogenic trypanosomes use enormous amounts of sugar for their metabolism; within 24 h they consume about twice their

own mass of sugar. In 1935, this knowledge prompted the American bacteriologist Hildrus Poindexter to treat animals infected with *Trypanosoma equiperdum*, a trypanosome that causes Dourine or covering disease in horses, with insulin to reduce their blood glucose levels. He discovered that trypanosome-infected animals subjected to insulin treatment survived longer and with fewer parasites in the blood compared to controls. In the same year, von Jancsó and von Jancsó and Schern and Artagaveytia-Allende independently found that the hypoglycaemic drug synthalin had trypanocidal action in mice and rats. In 1937, Yorke and Lourie at the Liverpool School of Tropical Medicine discovered that the anti-trypanosomal effect of synthalin had nothing to do with lowering the blood glucose level in the infected animals but that synthalin itself was trypanocidal. When Harold King at the National Institute of Medical Research in London learnt about the trypanocidal action of synthalin, he synthesised and tested related compounds and found that diamidino-1,11-*n*-undecane was particularly active against *T. b. rhodeseinse* in mice. Meanwhile, the English chemist Arthur James Ewins of the pharmaceutical company May and Baker prepared a large number of aromatic diamidines in which the polar amidine groups were separated by two phenyl groups rather than by a polymethylene group. Many of these compounds displayed trypanocidal activity, especially stilbamidine and pentamidine. Both compounds were also highly effective against human trypanosomiasis. Whereas stilbamidine was later abandoned, because it caused serious neurological effects in some patients, pentamidine is still used for treatment of the first stage of *T. b. gambiense* sleeping sickness. Pentamidine is also used in the treatment of leishmaniasis and *Pneumocystis jirovecii* pneumonia, mostly in AIDS patients(*314*)."

From the discoverer(s):

"In the first place a series of homologues of synthalin was prepared and tested. It will be observed that the trypanocidal action in vitro rises as the number of methylene groups in the alkylene chain increases, until, when these number 10 to 14, the action in vitro is comparable with that shown by the aromatic trivalent arsenicals-e.g., Halarsol. With lengthening of the alkylene chain there is also an increase in toxicity for mice, but this increase is not strictly parallel with that of the trypanocidal activity; thus the decamethylene member (synthalin) is 256 times as trypanocidal as the tetra-methylene compound, but its toxicity for mice is only 16 to 32 times as great as that of the tetramethylene compound. The therapeutic effect in infected mice is seen to be dependent upon these two factors. With the lower members of the series, which exhibit a relatively low trypanocidal power in vitro, there is no appreciable therapeutic effect; this first becomes manifest with the octamethylene member, maximum tolerated doses of which clear the blood of infected mice for a number of days. With the 10- to 14- methylene members the therapeutic action is considerable; for example, in the case of synthalin 0.05 mg. per 20 g. mouse (about a third of the maximum tolerated dose) sufficed to make the blood negative for 5 or 6 days; and permanent cures were occasionally obtained with the maximum tolerated doses, and also with repeated smaller doses(*315*)."

"In previous papers the results are recorded of the examination for trypanocidal activity of a considerable number of guanidines, isothioureas, amidines and amines with alkyl and alkylene chains.

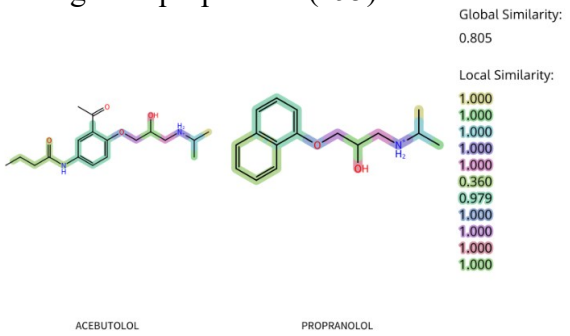
It was found that some of these compounds exhibited a powerful trypanocidal action in vitro and that with certain of them, notably n. undecane-1: 11-diamidine, it is possible to produce permanent cures in approximately 100 per cent. of mice and rabbits infected with our laboratory strain of *T. rhodesiense*(*316*)."

Interestingly, Yorke, Adams, and Murgatroyd had previously, in 1929, reported a method they had developed for 24-hour maintenance of trypanosomes in order to test the trypanocidal activity of different chemicals *in vitro*(*317*).

ACEBUTOLOL

1984

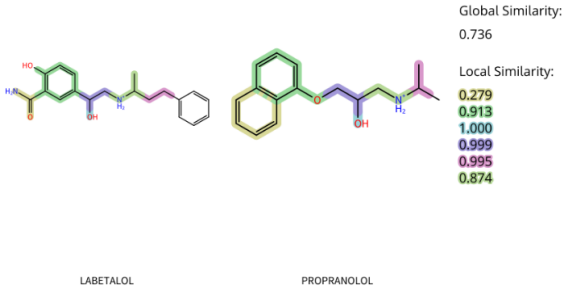
Analogue of propranolol(*253*)




LABETALOL

1984

Analogue of propranolol




"Labetalol (AH5158) [5-(1-hydroxy-2)1-methyl-3-phenylpropyl (amino)-ethyl(salicylamide)] was the first of a new class of antihypertensive agents with both α- and β-adrenoceptor blocking properties (Farmer et al., 1972)(*318*)"

The following quotations in this entry are from a few papers of the discoverer(s):

The structure of labetalol is based on AH 3474 whose mix alpha and beta blocking activity had previously been investigated by the team:

"This paper describes the properties of AH 5158, 5- salicylamide, a drug which differs from currently available adrenoceptor blocking drugs in blocking both α- and β-adrenoceptors. AH 5158 is related chemically to the previously reported β-adrenoceptor blocking drug, AH 3474, 5-(2-t-butylamino-1-hydroxyethyl) salicylamide (Blackburn, Byrne, Cullum, Farmer & Levy, 1969)(*319*)."

No reports explicitly outlining the process leading to the discovery could be found, yet the earliest paper reporting the effects of AH 5158, only comprises *in vivo* or isolated tissue bioassays:

"AH 3474 is a specific β-adrenoreceptor antagonist, devoid of stimulant activity. When given by mouth to conscious guinea-pigs and dogs, AH3474 and propranolol are equiactive in antagonizing isoprenaline-induced tachycardia. In anaesthetized animals AH 3474 was 2-4 times less active than propranolol when given intravenously. A similar potency ratio was found in volunteer studies in which the drug was taken orally. On isolated tissues AH 3474 was much less active than propranolol. AH 3474 had 1/l0th the activity of propranolol in blocking the inhibitory action of isoprenaline on the rat uterus and was at least 100 times less active in antagonizing the tachycardia induced by adrenaline on the guinea-pig atria. *In vitro*, equilibrium conditions for AH 3474 were obtained in 15 min, whereas 45 min were required for propranolol. AH 3474 antagonized the cardiac arrhythmias induced by ouabain in the anaesthetized dog. The amount required far exceeded the β-adrenoreceptor blocking dose. AH 3474 possessed no 'quinidine-like' actions on cardiac muscle of dog or guinea-pig(*320*)."

IOHEXOL

1985

Contrast agent

IOPAMIDOL

1985

Contrast agent

NABILONE

1985

“The cannabis plant has been used for several centuries for a number of therapeutic applications, including the attenuation of nausea and vomiting. Ineffective treatment of chemotherapy-induced nausea and vomiting prompted oncologists to investigate the antiemetic properties of cannabinoids in the late 1970s and early 1980s, before the discovery of the 5-$HT_3$ antagonists. The first cannabinoid agonist, nabilone (Cesamet), which is a synthetic analogue of $\Delta^9$-THC was specifically licensed for the suppression of nausea and vomiting produced by chemotherapy(*321*).”

“Healers identified marijuana’s antiemetic and appetite-enhancing effects at least by the 1500s(*322*).”

“[c]ancer patients undergoing chemotherapy experience several disconcerting and unpleasant side effects of treatment such as vomiting and nausea. By chance, one such patient happened to use marihuana after receiving chemotherapy and he found that the vomiting he usually experienced was alleviated. He reported this effect to his doctors, and subsequent testing at the Harvard Medical School proved so satisfactory that marihuana has become a routine adjunct to cancer chemotherapy at some hospitals(*323*).”

From the discovery paper cited in the previous quotation:

“Anecdotal accounts from patients suggested that smoking marihuana before receiving intravenous anti-tumor drugs resulted in diminution of nausea and vomiting, and, in contradistinction to the usual post-therapeutic anorexia, some were able to take food shortly after therapy(*324*).”

DRONABINOL

1985

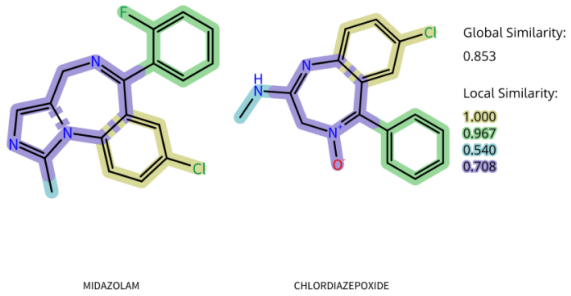
An active ingredient of cannabis

See the nabilone entry.

MIDAZOLAM

1985

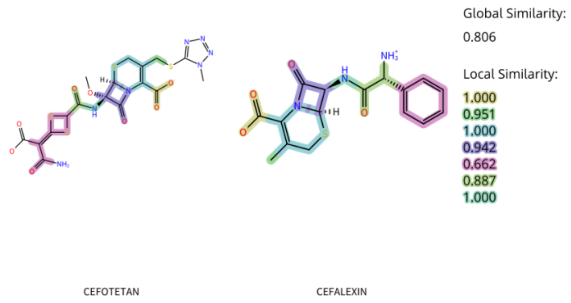
Analogue of chlordiazepoxide(*21*)




CEFOTETAN

1985

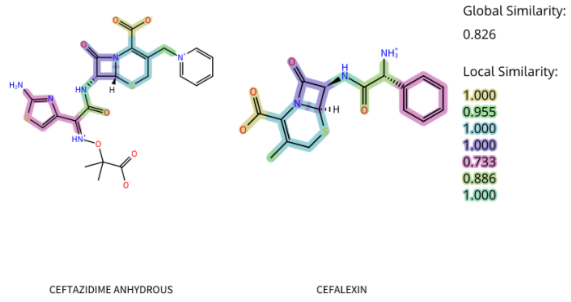
Analogue of cefalexin




CEFTAZIDIME

1985

Analogue of cefalexin(*21*)




TRIENTINE

1985

Copper-chelating agent

BUPROPION MALEATE

1985

It was at first was investigated for cardiovascular indications, yet, in general pharmacology tests, it showed better potential for depression in antidepressant animal tests.

From the discoverer(s):

"We therefore sought an agent that would be active in antidepressant screening models, but differ chemically and pharmacologically from the tricyclics, and not be sympathomimetic, cholinolytic nor an inhibitor of monoamine oxidase. Bupropion (Wellbatrin) which was synthesized by one of the authors (N.B.M.) (Baltzly & Mehta, 1968; Mehta, 1974, 1975) […]

The pharmacological properties of bupropion have to date been reported only in abstract form (Soroko, Mehta & others, 1970) as has its clinical effectiveness as an antidepressant in an open study by Fann, Schroeder & others (1974) and in a double-blind, placebo-controlled study by Fabre, McLendon & Mallette (1977). A description of the pharmacology of the drug follows. Actions on cns. Bupropion in doses from 6.15-25 mg $kg^{-1}$ (i.p.) produced a dose-dependent prevention of tetrabenazine-induced sedation in mice.

It also prevented tetrabenazine-induced blepharospasm and fall in rectal temperature, and it corrected the 'hunched' posture characteristic of tetrabenazine action. The compound was approximately half as potent by the oral route as by the intraperitoneal route(*325*)."

From another paper of the discoverer(s) cited above in which the synthesis of bupropion was first reported:

"Methoxamine [erythro-α- (2,5-dimethoxyphenyl) -β-aminopropanol] has been regarded pharmacologically as a pure a-adrenergic stimulant. Interest having been expressed as to the fashion in which this property would be altered by, e.g., S-isopropyl substitution. A considerable number of such derivatives were prepared by reductive alkylation of methoxamine base in the presence of available aliphatic ketones, cycloalkanones, and aromatic aldehydes(*326*)."

These synthesized compounds were investigated for several potential activities such as antiarrhythmic activity, antihypertensive activity, and their ability to lower blood sugar and lipids:

"Some of these compounds exhibited the physiological properties of 'β-blockers' and antiarrhythmic agents. Several had a marked tendency to lower the blood levels of glucose and free fatty acids. In vivo N-sec-alkyl compounds were found to be degraded metabolically to the parent methoxamine (among other products) but the N-t-alkyl system was stable as regards this degradation […]

The compound first prepared, N-isopropylmeth-oxamine, was first regarded as a β-adrenergic blocker. Further investigation revealed more com-plicated behavior and interest centered on two properties. The first of these was the ability to restore normal sinus rhythm to hearts in which this had been disturbed by a number of stimuli. […]

The second physiological property of interest was a blocking of the hyperlipoidemia and hyperglycemia evoked by catecholamines(*326*)."

From the relevant patent whose inventor is one of the members of the discovering team who was one of the authors of in both of the previous two articles cited in this entry (Nariman B. Mehta):

"This is a division of application Ser. No. 93,852, filed on Nov. 30, 1970, now U.S. Pat. No. 3,819,706. The present invention relates to o-alkylaminopropiophenones. It has been found that the two novel compounds represented by the general formula (I) and acid

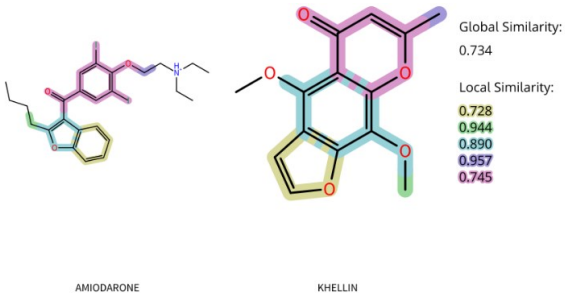
addition salts thereof, in which X is chlorine or fluorine, possess valuable properties as antidepressants when tested by standard techniques used in the art for determining antidepressant activity, for example the tetrabenazine-induced sedation test in rodents(*327*)."

AMIODARONE

1985

Analogue of khellin

Also see the nifedipine entry.




"Although synthesized as a coronary dilator for use as an antianginal agent over 20 years ago, amiodarone hydrochloride has recently drawn much attention as a potent antiarrhythmic compound for the control of a variety of cardiac dysrhythmias(*328*)."

"*Ammi visnaga* is an annual or biennial plant of the Apiaceae family (aka Umbelliferae) mostly found in Mediterranean countries. The shrub is about one meter high with an umbelliform inflorescence. It is known in Arabic as khella. Other notable names include Spanish carrot, Zahnstocherkraut, and khelale dendane or toothpick herb. *Ammi visnaga* is traditionally used for medical purposes in the form of decoction of its dried seeds or tincture of its fruits. However, limited clinical evidence is available to support its use in traditional medicine. The majority of early experiments with *A. visnaga* came from Egypt, where it had been used in practice to treat urinary stones. Egyptian clinicians such as Dr Ibrahim, the dean of the medical school at the University of Egypt in 1933, had many years of clinical experience with khella—known to the public as bisrel-khelle. Back in 1879, Mostapha et al. investigated the chemistry of khella and isolated an impure crystalline substance. At a later date, Samaan et al. extracted six distinct crystalline principles from *A. visnaga.* He stated that among these, visammin is the most active compound. In subsequent papers, visammin was called khellin. Limited animal and human studies confirmed its muscle relaxant activity on all smooth muscles in addition to a mild diuretic effect. Further attempts on isolation and purification of khellin were conducted by Fantland Salim (1930) and Malik(1932).

By the 1940s, khellin attracted attention for its effects on the cardiovascular system. Anrep et al. examined the substance as a coronary vasodilator in the treatment of angina and compared it with other known anti-anginal agents such as nitrates. Khellin's main advantage over other drugs was its selectivity for coronary arteries. Therefore, it was thought to exert its effects without causing systemic vasodilation and therefore a drop in blood pressure. In the 1960s, the search for new anti-anginal agents, and in particular coronary vasodilators, led to the production of amiodarone. The Labaz group in Belgium (which was later acquired by Sanofi) synthesized an array of agents based on the benzofuran portion of khellin, among which amiodarone prevailed due to its potency and fewer adverse effects. A reference to amiodarone's anti-arrhythmic action in animals was made in 1969(*329*)."

"Preliminary clinical trials with benziodarone promptly revealed its proclivity to induce jaundice and hepatotoxicity in man. It was soon superseded by amiodarone, a more potent coronary vasodilator. In a series of comprehensive pharmacologic studies Charlier et al in a variety of isolated tissue preparations and in intact conscious dogs clearly demonstrated somewhat unusual properties of the compound(*330*)."

## RIBAVIRIN

1985

From the discovery paper(*331*):

"The first synthetic broad-spectrum, noninterferon-inducing, antiviral agent 1-β-D-ribofuranosyl- 1,2,4-tri- azole-3-carboxamide **(1)** has been prepared and tested against a variety of both RNA and DNA viruses in tissue culture. […]

Reproducible broad-spectrum antiviral activity both in vitro and in vivo at nontoxic dosage levels is shown by **1**. […]

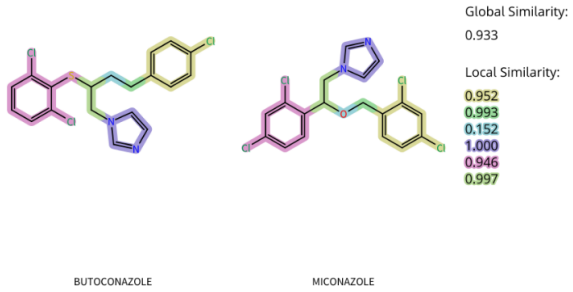
In searching for a broad-spectrum antiviral agent an effort was made to concentrate on the synthesis of compounds which have the potential to affect enzymatic processes which are common to all known viruses such as viral-induced nucleic acid and protein synthesis. These processes are carried out by enzymes specifically coded for in the viral genome. Another common feature of all viruses is their lack of protein-synthesizing capability. It is conceivable that initiation of virus-specific protein synthesis and/or RNA synthesis may utilize unique viral enzymes which could be specifically inhibited. Several nucleosides such as 5-iodo-2'-deoxyuridine and 1-β-D-arabinofuranosylcytosine have been used with limited success against herpes virus infection in man. One of the more potentially clinically useful agents, 9-β-D-arabino-furanosyladenine, possesses marked antiviral activity *in vitro* and *in vivo* against herpes and vaccinia viruses. More recently the ribofuranosyl nucleoside antibiotic pyrazomycin, 3-β-D-ribofuranosyl-4-hydroxypyrazole-5-carboxamide **(2)**, has been shown to have antiviral activity against rhinovirus, measles, herpes simplex, and vaccinia viruses in tissue culture. Apparently inhibition of viral replication *in vivo* and toxicity to the host could be only partially separated in studies of **2**. Another ribonucleoside antibiotic, formycin, has also demonstrated *in vitro* antiviral activity. These considerations led us to concentrate on the synthesis of a substantial number of β-D-ribo-furanosyl derivatives as potential wide-spectrum antiviral agents(*332*)."

These analogues were then investigated in tissue cultures infected with adenovirus, herpes, virus type 1 and type 2, vaccinia virus, myxoma virus, parainfluenza virus, rhinovirus, Coxsackie virus, influenza A2 virus, and influenza B virus.

## BUTOCONAZOLE

1985

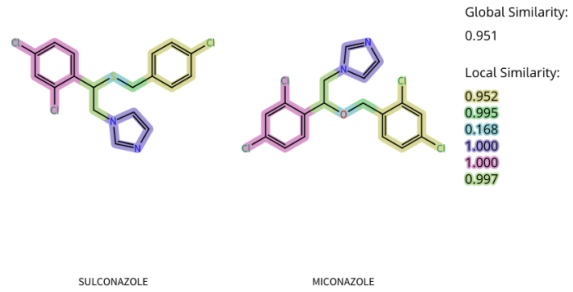
Analogue of miconazole




## SULCONAZOLE

1985

Analogue of miconazole




## LEVOCARNITINE

1985

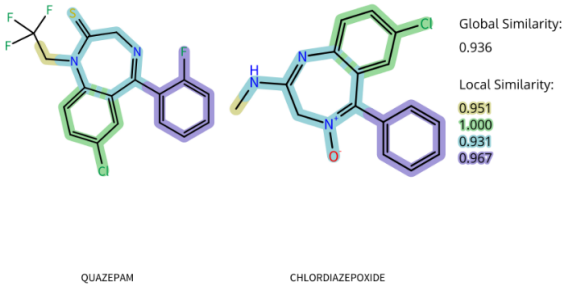
"Levocarnetine also known as L-carnitine is a naturally occurring substance required in mammalian energy metabolism that functions by facilitating long-chain fatty acid entry into cellular mitochondria, thereby

delivering substrate for oxidation and subsequent energy production. Levocarnetine was approved by FDA for the treatment of carnetine deficiency(*1*).”

## QUAZEPAM

1985

Analogue of chlordiazepoxide(*21*)




## IMIPENEM

1985

“Thienamycin, a β-lactam antibiotic with the unique structure shown in Fig. 1 was discovered in the course of screening soil microorganisms for production of inhibitors of peptidoglycan synthesis in Gram-positive and Gram-negative bacteria(*333*).”

“Although thienamycin possesses high potency against an unusually broad spectrum of bacteria, its further development was prevented by the instability it exhibited in concentrated solutions and in the solid state. As the concentration of thienamycin is increased, reaction of the side chain amine with the beta-lactam of a second molecule to form inactive dimer is accelerated. An extensive chemical derivatization program was undertaken to stabilize the molecule. A series of amidine derivatives was prepared. The best of the amidines was crystalline N-formimidoyl thienamycin (MK0787), which was subsequently assigned the generic name imipenem(*334*).”

From the paper cited in the previous quotation as the first paper reporting imipenem:

“Thienamycin is a recently discovered β-lactam anti- biotic of unique structure and exceptional breadth of antibacterial activity. Of particular interest is its exceptional potency against *Pseudomonas spp.* and its β-lactamase stability. The novel carbapenem nucleus and amino-ethylthio side chain of thienamycin, however, contribute to its chemical instability. […]

It has been postulated that the concentration-dependent instability of thienamycin is due to the intermolecular aminolysis of the azetidinone by the cysteamine side chain. Derivatization of the amino group of thienamycin to a less nucleophilic species seems an attractive route to more stable thienamycin analogues. Since the naturally occurring N-acetyl derivative has greatly diminished antipseudomonal activity, retention of antipseudomonal activity appeared to require a basic functionality. It was therefore considered likely that conversion of the amine to a stronger base would, by virtue of its existence to a greater extent in a protonated form, result in a compound with increased stability in concentrated solution as well as high antipseudomonal activity. We also hoped to obtain a crystalline derivative which would facilitate purification. We now report that the N-acetimidoyl and particularly the N-formimidoyl derivatives fulfilled these expectations. […]

Preliminary studies showed the amorphous amidines to be five to ten times more stable at high concentration than a thienamycin sample of equivalent purity and represents a rough approximation of the effect of the chemical modification. […]

Furthermore, these amidines retain the antibacterial spectrum of thienamycin and exhibit enhanced activity against *Pseudomonas aeruginosa.* Extensive evaluations of in vitro antibacterial activity have shown a two- to fourfold increased potency against these species. Because of its improved stability and enhanced antipseudomonal activity, N-

formimidoylthienamycin has been selected for clinical studies(*335*).”

## AURANOFIN

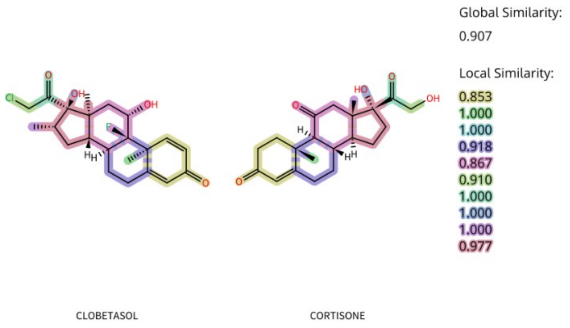
1985

“The observation by Robert Koch that gold cyanide was bactericidal to tubercle bacilli *in vitro*, led European investigators, over the next 40 yr, to experiment with the use of gold complexes in the treatment of human and bovine tuberculosis. The serendipitous assumption by Dr Jacques Forestier that rheumatoid disease was an infectious disease analogous to tuberculosis led him to use gold thiopropanol sodium sulphonate on 15 patients with inflammatory rheumatoid disease. The success of this initial experiment was the seed which steered researchers over the next 50 yr to investigate both the beneficial and the toxic effects of anti-arthritic gold complexes. It is important to note that although Forestier’s hypothesis was based on a so-called erroneous assumption, his observations of the histological similarity of ‘reactive’ rheumatoid synovium and tuberculous nodules are now known to bear more similarity to scientific truth than to fiction(*336*).”

## CLOBETASOL

1985

Analogue of cortisone(*21*)




## CILASTATIN

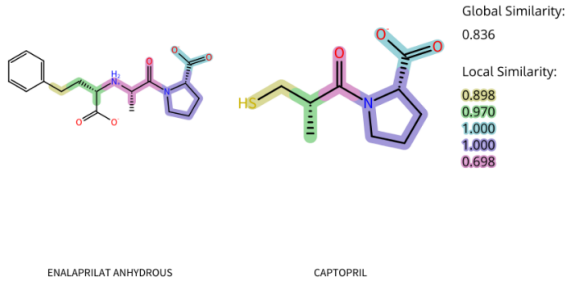
1985

Secondary

## ENALAPRILAT

1985

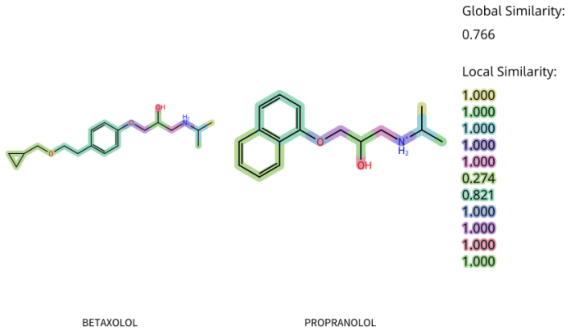
Analogue of captopril(*21*)




## BETAXOLOL

1985

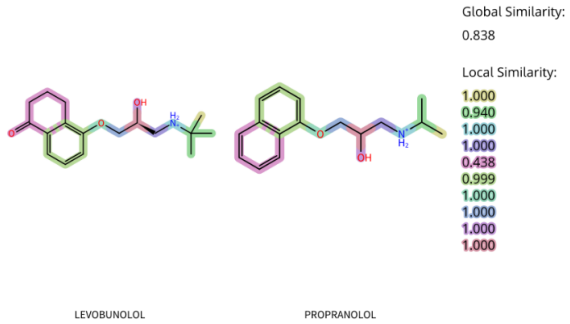
Analogue of propranolol(*253*)




## LEVOBUNOLOL

1985

Analogue of propranolol(*253*)



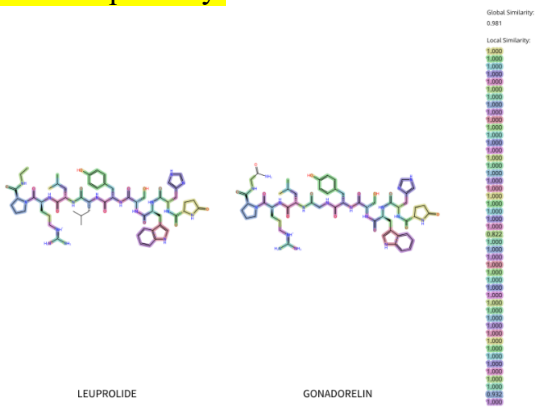

## LEUPROLIDE

1985

Analogue of the endogenous Gonadotropin Releasing Hormone (GnRH)(*21*)

Discovery of GnRH:

"The hypothalamus controls the release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH). The work of various investigators clearly demonstrated that there are, in hypothalamic extracts of animals, including man, substances, or one substance, capable of stimulating release of LH and FSH from the pituitary.




Much evidence also exists that sex steroids are involved in this regulation. Initially, it was thought that two different substances designated luteinizing hormone-releasing hormone (LH-RH) and follicle-stimulating hormone-releasing hormone (FSH-RH) were responsible for stimulating release of LH and FSH, respectively. However, it became necessary to question this belief when porcine LH-RH, obtained in a high state of purity, stimulated release of both LH and FSH in rats, chimpanzees, and human beings. Furthermore, after the addition of purified porcine LH-RH to an incubation system in vitro in which pituitaries of male rats were used, LH and FSH were released simultaneously with superimposable time courses. Stimulation of LH release by this material was also unequivocally established in sheep and rabbits, but because of the unavailability of specific radioimmunoassays, it was difficult to test for the effect on FSH secretion in these two species(*337*)."

From an early paper regarding the discovery of LH-releasing activity of GnRH:

"Release of luteinizing hormone (LH) from the pituitary appears to be under hypothalamic neurohumoral control. Since convincing evidence is now available indicating that a corticotrophin-releasing factor and vasopressin can release adrenocorticotrophin from the pituitary, it seems of interest to examine hypothalamic and median eminence extracts to determine if a substance originating in these structures may regulate release of LH. Ovarian ascorbic acid depletion (OAAD) from heavily luteinized ovaries of suitably prepared immature rats has been shown by Parlow to be an extremely sensitive and specific assay for LH, a finding that we have confirmed. In the present study this assay has been used to assess LH-releasing activity of hypothalamic extracts. […]

The results indicate that unilateral ovariectomy alone failed to elicit a significant OAAD. When an extract prepared from the SME region of 2 hypox. or normal rats was injected into each assay rat, a highly significant OAAD resulted. On the contrary, an extract of rat cerebral cortex equivalent in wet weight to that from SME failed to elicit a significant OAAD(*338*)."

From the discovery paper of the effect of GnRH analogues on tumors:

"With the discovery of the structure of gonadoliberin [gonadotropin-releasing factor or luteinizing hormone/follicle stimulating hormone-releasing-hormone], the decapeptide gonadotropin-releasing hormone, a number of synthetic analogs were found to have luteinizing hormone/follicle stimulating hormone-releasing activities several times that of the natural hormone. Further studies indicated that at higher doses, some of the analogs, especially those with a D-amino acid substituted in position 6, show antagonist properties. In particular the Abbott compound A-43818, (D-leucyl$^{6}$, desglycyl-NH$^{10}$, prolyl-ethylamide$^{9}$)go nadoliberin, has been shown to be 50 to 80 times as potent as the natural hormone in causing ovulation in the

diestrus rat, whereas large doses of A-43818 inhibited the uterotropic and ovariogenic effects of human chorionic gonadotropin. Chronic administration of large doses of A-43818 to immature rats inhibited ovarian and uterine growth, delayed vaginal opening, and prevented normal estrus cycles. In the mature animal, such treatment with A-43818 effected cessation of cycling and atropy of the ovaries and uterus, consistent with its antagonist role toward gonadoliberin and the consequent decreased levels of circulating ovarian steroids. Such results mimicking ovariectomy would therefore be expected to effect regression of ovary-dependent mammary tumors.

In a preliminary study, a spontaneous mammary tumor in an albino rat regressed on treatment with A-43818. When A-43818 administration was stopped, the tumor again grew; subsequent ovariectomy-induced tumor regression showed the spontaneous tumor to be hormone dependent. Therefore, this study was undertaken to test the ability of A-43818 at 2 dose levels to effect tumor regression in the DMBA-induced breast cancer model. […]

In the principal part of the study, A-43818-treated, vehicle treated, and ovariectomized, tumor-beaming rats were observed during a 6-week treatment period(*339*)."

From a paper cited in the previous quotation regarding the effects of chronic administration of GnRH analogues:

"We have reported that the analog [D-Leu$^{6}$,des-Gly-$NH_2$$^{10}$,Pro-ethylamide$^{9}$]-gonadotropin-releasing hormone (GnRH) (A-43818) (I) is 3 to 5 times as active as the natural hormone, GnRH, in the release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from rat pituitaries in vitro. In the same paper we reported that I is 50 to 80 times more potent that GnRH in causing ovulation in the diestrous rat. Subsequently we extended the evaluation of the strong gonadotropin-releasing and ovulation-inducing activities of I to the rabbit and the sheep. Meanwhile Vilchez-Martinez et al. have reported that I is 54 and 14.5 times more active than GnRH in its releasing activity for LH and FSH, respectively, in the immature male rat.

Recent work in our laboratory has shown that large doses of I inhibit the uterotropic and ovariogenic effects of human chorionic gonadotropin in the 21-day-old rat, suggesting that reversal of the well-documented ovulatory effects of I occurs when it is given at higher dose levels.

The studies reported here were designed to determine the specific effects of chronic administration of high doses of the highly potent releaser of gonadotropins on the maturation and maintenance of reproductive function in the female rat(*340*)."

Investigated phenotypes(*340*):

- Immature Animals
  - ✓ Delay of Vaginal Opening and Inhibition of Normal Cycling
  - ✓ Ovarian and Uterine Effects
  - ✓ Effect on Serum LH and FSH Levels
  - ✓ Effect on Body Weight
- Mature Animals
  - ✓ Effects on Cycle and Reproductive Organs
  - ✓ Effects of Interruption of Ovarian Function on Reproductive Performance

PERMETHRIN

1986

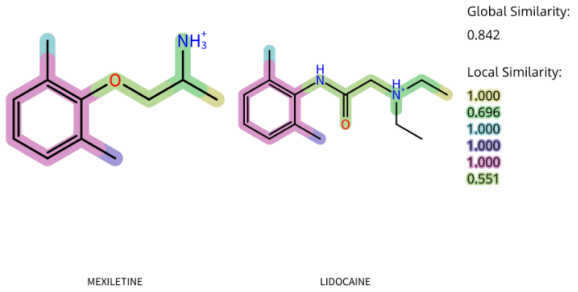
Insecticide activity of natural pyrethrins had been known previously. Inspired by their structures, Elliot and his team synthesized various structures during several years and tested, analysed and compared the insecticide activity of these compounds in bioassays like

toxicity against Houseflies (*Musca domestica* L.), Mustard beetles (*Phaedon cochleariae* Fab.), and *Drosophila melanogaster*(*341-345*).

MEXILETINE

1985

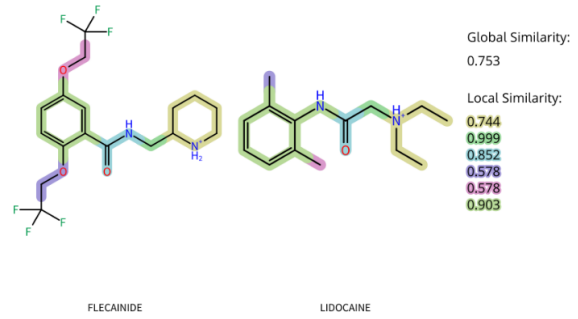
Analogue of lidocaine




FLECAINIDE

1985

Analogue of lidocaine




AZTREONAM

1986

From the monobactams' discovery paper(*346, 347*):

"In the long history of screening for antibiotics, fungi and actinomycetes have been the only producers of β-lactam antibiotics although several phytopathogenic bacteria have been reported to produce toxins with a β-lactam structure. We report here the first evidence that novel monocyclic β-Iactam antibiotics, sulfazecin and isosulfazecin, are produced by new species of *Pseudomonas*. Screening for β-lactam antibiotics was carried out using a selective and sensitive method involving *Pseudomonas aeruginosa* PsC$^{ss}$ and *Escherichia coli* PG8 (lacking chromosomal β-lactamase and penicillin-binding protein 1B. […]

Several bacterial strains producing p -lactam antibiotics were isolated from soil, mostly using agar plates acidified to pH 4.5(*348*)."

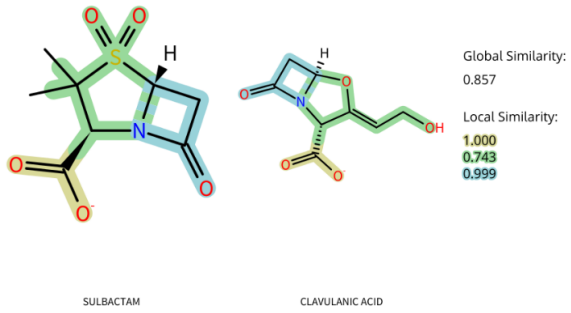
From another relevant early paper:

"Antimicrobial activities of selected monobactams are shown in Table 1. Although the compounds are weakly active against a range of bacteria, the methoxylated compound III shows greater activity against Gram-negative organisms, especially *Pseudomonas*, compared with the non-methoxylated derivative IV. Compounds VII-XI showed similar antimicrobial properties to those observed for compounds III and IV(*349*)."

SULBACTAM

1986

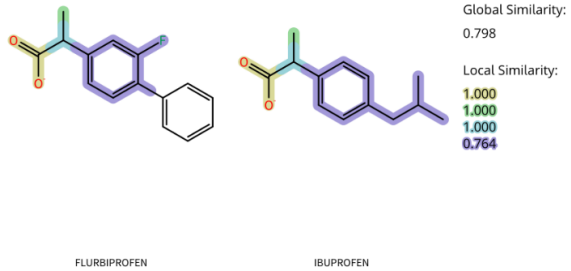
Analogue of clavulanic acid




FLURBIPROFEN

1986

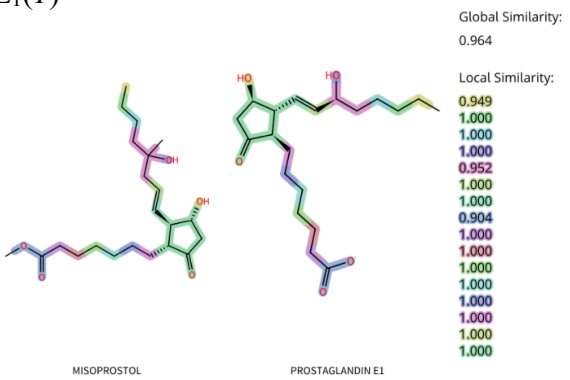
Analogue of ibuprofen(*21*)



MISOPROSTOL

1986

Analogue of the endogenous prostaglandin $E_1$(*I*)




See the dinoprostone entry.

From one of the discoverer(s) of misoprostol:

"The discovery that naturally occurring prostaglandins of the E series inhibit gastric acid secretion was made in 1967 by Robert et al. Because of the prevailing theory of 'no acid-no ulcer,' they became immediate candidates for ulcer therapy. Three critical drawbacks of the natural prostaglandins soon surfaced, however, which have thwarted the therapeutic entry of the natural prostaglandins and whose circumvention has been the objective of many synthetic modification programs. These problems were (1) rapid metabolism manifested as a lack of oral activity and a short duration of action when given parenterally, (2) incidence of numerous side effects, and (3) chemical instability. […]

In the early 1970s we began a chemical program to synthesize analogs of PGE, with the objective of improving its pharmacological profile. The specific goals of the program were oral activity, longer duration of action, and selectivity of biological action. Though mindful of the chemical stability problem, we did not fully appreciate its magnitude at the time and chose not to address it through chemical modification.

The probable reason for the lack of oral activity of $PGE_1$ is the very rapid metabolic oxidation of the C-15 hydroxy group to the corresponding ketone. In fact, other investigators achieved oral activity by blocking the oxidation of this hydroxy with placement of either a methyl group at C-15 or two methyl groups at C-16 (steric inhibition). The resulting compounds were potent, orally active, and long-acting inhibitors of gastric acid secretion. Unfortunately, the selectivity of these compounds was not improved. […]

[W]e decided to synthesize a derivative of $PGE_1$ in which the lower side chain hydroxy group is located at the adjacent C-16 position instead of at C-15. We were gratified to find that this analog possessed gastric antisecretory potency equivalent to $PGE_1$, yet the typical prostaglandin side effects such as rhinorrhea, emesis, and diarrhea were greatly diminished. However, this compound was only weakly active by oral administration, and its duration of action was quite short. […]

In view of the dramatic increase in oral potency and duration of action achieved by placement of a methyl group at C-15 in natural prostaglandins, we decided to add a methyl group to carbon-16 of our synthetic 16-hydroxy prostaglandin. This structural change produced misoprostol, which was approximately 35 times more active than the 16-hydrogen compound by intravenous administration, possessed good oral activity, and increased duration of action(*350*)."

From the 1967 discovery pape of Robert *et al.* cited in the previous quotation:

"PROSTAGLANDINS (PGs) are a group of long-chain, unsaturated, oxygenated fatty acids, first discovered in 1935 by Goldblatt and Von Euler in semen and seminal vesicles. Since then, these substances have been identified in several other tissues, including the gastrointestinal tract of the frog, the rat, the guinea pig, and the rabbit, s and have been found to stimulate smooth muscles (e.g., gastric and intestinal strips) in vitro. These

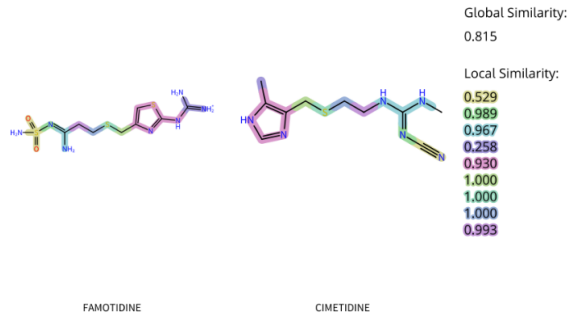
findings suggest a possible role for PGs in gastrointestinal function. In this paper we report the effect of four PGs on gastric secretion in the dog. […]

These two PGs inhibited gastric secretion (volume, acid, and pepsin outputs) stimulated by either food or histamine, and the response was dose dependent(*351*).”

## FAMOTIDINE

1986

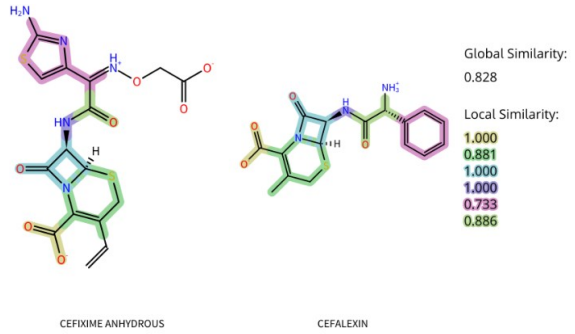
Analogue of cimetidine(*21*)




## CEFIXIME

1986

Analogue of cefalexin(*21*)




## METHACHOLINE CHLORIDE

1986

Diagnostic

## SOMATROPIN

1986

Recombinant human growth hormone (somatotropin)(*2*)

## INTERFERON ALFA-2B

1986

Endogenous(*352*)

“Type I interferons (IFNs) were discovered in 1957 by Isaacs and Lindenman who reported that cells infected with an inactivated virus release a soluble factor exerting an antiviral action. We now know that IFN is a key cytokine of the innate immune response which is produced upon recognition of many pathogens and damage-associated molecular patterns released by infected cells or dying cells(*352*).”

From the discovery paper cited in the previous quotation:

“During a study of the interference produced by heat-inactivated influenza virus with the growth of live virus in fragments of chick chorio-allantoic membrane it was found that following incubation of heated virus with membrane a new factor was released. This factor, recognized by its ability to induce interference in fresh pieces of chorio-allantoic membrane, was called interferon. Following a lag phase interferon was first detected in the membranes after 3 h incubation and thereafter it was released into the surrounding fluid(*353*).”

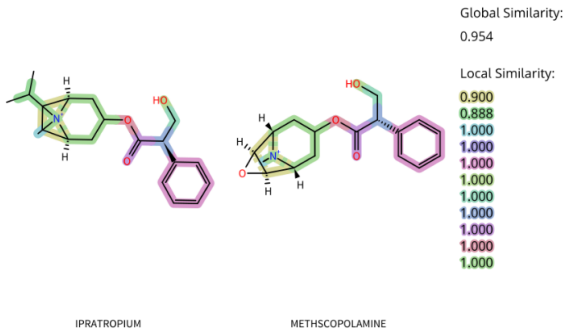
## CHROMIC CATION

1986

## IPRATROPIUM

1986

Analogue of methscopolamine(*21*)



## BUSPIRONE

1986

"Buspirone is derived from the N-[(4-heteroaryl-1-piperazinyl)alkyl]-substituted imide class of compounds which were developed in the early 1970s in the laboratories of Bristol-Myers(*354*). […]

The focus of the early work in this chemical class was on the development of effective tranquilizers lacking the sedative or adrenergic side effects commonly associated with the phenothiazines. The hierarchical organization of biological screens was therefore structured to identify compounds that had a minimum of depressive side effects. The two principal biological assays employed were the conditioned avoidance response (CAR) test in rats and the antagonism of amphetamine-induced aggregation stress in mice. The CAR was used to differentiate the tranquilizing activity of a compound from a less specific sedative-hypnotic effect. This differentiation was achieved by determining the ratio of the $ED_{50}$ values for the test compound in the unconditioned escape response (UER) versus the CAR. The larger the UER/CAR ratio, the more selective was the psychosedative activity. The antagonism of amphetamine-induced aggregation stress in rats was used to evaluate the compound's potential for treating stressful conditions in humans. […]

Usually the most potent activities in the CAR were achieved with a 4 carbon methylene chain linking the phenyl-piperazine group to the imide ring. This dominant effect was independent of the substitution pattern on the phenyl ring. Substituents located at meta or para positions on the phenyl ring generally reduced activity in the CAR, as seen in compounds 7 and 8, which are positional isomers of compound 6. In contrast, ortho substitution in compounds 11-16 led to equipotent or superior CAR activity relative to the parent structure 4. The o-OCH3 derivatized phenylpiperazine, 12, was the most potent analog of the series in both the CAR and the antagonism of amphetamine-induced aggregation stress(*354*)."

From the discovery paper:

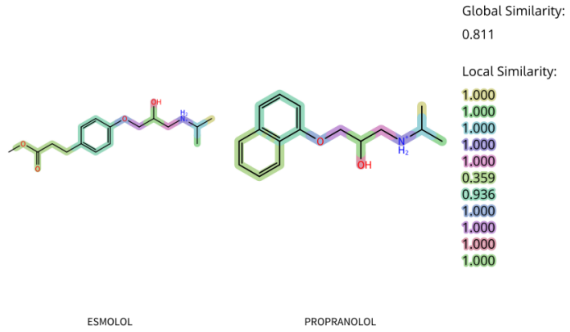
"**Biological Data. Screen for Tranquilizing Properties.** We screened compounds for their tranquilizing effects by two primary tests: (1) suppression of conditioned avoidance response (CAR) in rats, and (2) antagonism of amphetamine-aggregation stress in mice, as outlined in our previous paper(*355*)."

"**Testing for Sedative Side Effects.** Ideal tranquilizing agents should have as little depressive side effects as possible. To determine their sedative side effects, we subjected the selected compounds (3, 6,8) to 3 different tests in mice: (1) spontaneous motor activity, (2) hexobarbital hypnosis potentiation, and (3) motor incoordination(*355*)."

## ESMOLOL

1986

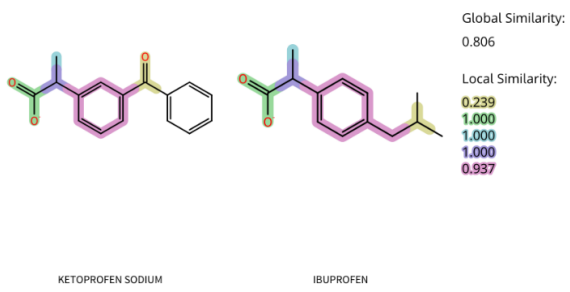
Analogue of propranolol(*253*)




## KETOPROFEN SODIUM

1986

Analogue of ibuprofen(*21*)

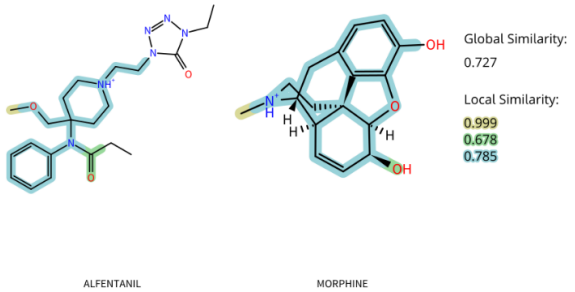


## ALFENTANIL

1986

Analogue of morphine and fentanyl

Also see the fentanyl entry and refer to Paul Janssen's article cited there.




## TRANEXAMIC ACID

1986

From the discovery paper(*356*):

"The very preliminary examination was first made, and the spontaneously activated fibrinolytic system obtained from human serum was used in order to know whether AMCHA might be promising for clinical application. The measurement of the inhibitory effect of AMCHA was made by admixing a certain amount of the active ingredients with the fibrinolytic system which contained active euglobulin, fibrinogen, thrombin and an adequate amount of 1/20 M of phosphate buffer, and by measuring the time required for the complete dissolution of the formed fibrin clots incubated at 37°C(*357*)."

## GUANFACINE

1986

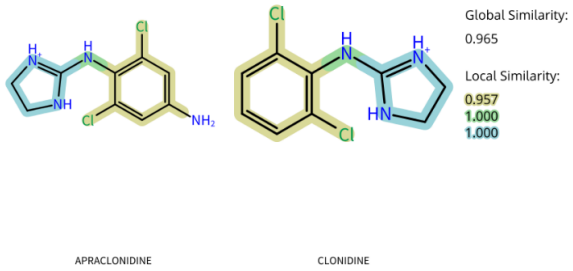
"The lignum vitæ or guaiacum wood of commerce is derived from *Guaiácum officinale* Linn., and *G. sanctum* Linn., family Zygophyllaceæ, both evergreen trees, the former a native of the West Indian Islands and the north coast of South America, the latter of southern Florida and the Bahamas. Both occur in Cuba and Hayti, whence the wood is largely exported. The Spaniards became acquainted with the drug when conquered San Domingo; it was soon brought to Europe, where it acquired an immense reputation in the sixteenth century as a cure for syphilis and certain other diseases, the resin extracted from the trunk being introduced subsequently. […]

Guaiacum has a local stimulant action which is sometimes useful in sore throat. The resin is used in sore throat. The resin is used in chronic gout and rheumatism, whilst the wood is an ingredient in the compound concentrated solution of sarsaparilla, which was formerly much used as an alternative in syphilis(*358*)."

## APRACLONIDINE

1987

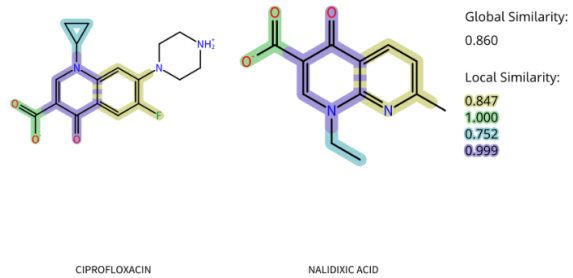
Analogue of clonidine




## CIPROFLOXACIN

1987

Analogue of nalidixic acid




## BECLOMETHASONE

1987

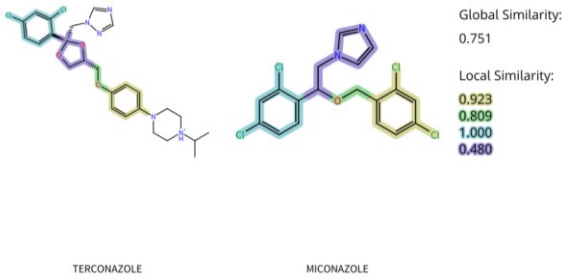
Analogue of cortisone(*21*)

Error in similarity calculation by FTrees

## TERCONAZOLE

1987

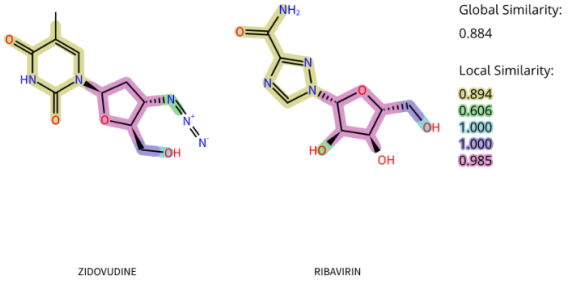
Analogue of miconazole




## ZIDOVUDINE

1987

Analogue of ribavirin




"After the discovery of HIV in 1983, Burroughs Wellcome began a screening programme for compounds that would be effective against the virus. In November, 1984, zidovudine, first synthesised in 1964, was found to inhibit the replication of animal retroviruses in vitro. Predicting that the drug would be active against HIV, the company applied for a patent. Because the company's facilities for handling HIV were still under construction, it contracted the US National Cancer Institute (NCI) to do further testing. Those tests were designed and directed by Burroughs Wellcome scientists, who wrote the protocols to be applied in the NCI laboratories. When those tests confirmed that zidovudine was highly active against HIV-1 Burroughs Wellcome began preclinical toxicology and pharmacology testing, leading to clinical trials and approval of zidovudine by the US Food and Drug Administration in March, 1987(*359*)."

"From the time Dr. George Hitchings began the research program at Wellcome Research Laboratories in 1942 to search for antagonists of nucleic acid bases, viruses were among the potential chemotherapeutic targets. A number of 5-substituted uracil derivatives and 2,6-diamino-purine, which had been identified as inhibitors of bacterial nucleic acid synthesis in *Lactobacillus casei*, were found to also interfere in tissue culture with the multiplication of vaccinia virus […]

Research on nucleosides at Wellcome was concentrated during the 1950s and 1960s on purine analogues in the search for new anticancer drugs. The discovery of the antiviral activity of adenine arabinoside reawakened interest in searching for antiviral agents among the nucleosides. This initiative stimulated a close collaboration between the Wellcome Research Laboratories in the United States and at Beckenham in the United Kingdom, where antiviral testing was conducted. The first successes came with the finding that 2,6-diaminopurine arabinoside and guanine arabinoside had good activity against the herpes simplex viruses and vaccinia virus, in vivo as well as in vitro. There was, however, no firm commitment to pursuing the search for antiviral nucleosides at that time. […]

Compound 22U81 was the *threo*-analogue with the 3' -azido substituent above the plane of the sugar ring, and compound 509U81 (later named zidovudine; also known as azidothymidine or AZT) was the *erythro*-analogue with the 3-azido below the plane of the sugar ring where thymidine would have a hydroxyl group. Both compounds were synthesized by published procedures and were tested at Wellcome Research Laboratories in the United States and the United Kingdom. Although zidovudine had initially been synthesized by Dr. Jerome Horwitz and associates in 1964 at the Michigan Cancer

Foundation as a potential anticancer agent, studies with the compound were abandoned shortly thereafter because of a lack of activity against animal cancers. […]

Both compounds were active in microbiological screens, but the minimum inhibitory concentrations (MICs) obtained with bacterial strains sensitive to zidovudine were less than 10- to greater than 100-fold lower than those obtained for 22U81. Extensive in vitro studies of zidovudine showed a limited spectrum of activity, with inhibition against a variety of gram-negative enteric bacteria, but the gram-positive bacteria were naturally resistant. The MICs in vitro were in the range of 0.1-4 g/mL for *Escherichia coli* B, *Salmonella typhimurium*, *Shigella flexneri*, *Klebsiella pneumoniae*, and E*nterobacter aerogenes*, but gram-positive bacteria such as *Streptococcus pyogenes* and *Pseudomonas aeruginosa*, as well as anaerobic bacteria, mycobacteria, and various fungi, were not inhibited. […]

In vivo, antibacterial studies with zidovudine at the US facilities and at Wellcome, Berkhamsted, in the United Kingdom demonstrated activity in experimental models. Mice were protected from life-threatening septicemic infections of Escherichia and acute ascending pyelonephritis. Veterinary models showed that calves were protected from fatal infections of Salmonella dublin. Other experimental models utilized chickens and weaning pigs. No toxicity to the compound was noted during these short-term experiments.

Other Bioactivity Assessments

Zidovudine, based upon its microbiological activity and lack of toxicity, was further assessed. Inactivity against a wide variety of DNA and RNA viruses was demonstrated: herpes simplex virus types 1 and 2, varicella virus, adenovirus type 5, influenza A, respiratory syncytial virus, rhinovirus B, yellow fever virus, measles virus, coronavirus, and bovine rotavirus. Zidovudine was also inactive against vaccina virus, vesicular stomatitis virus, and the murine leukemia, L1210, in vitro. Ultimately, tests showed it was inactive against human cytomegalovirus. Some activity is reported for zidovudine against Epstein-Barr virus […]

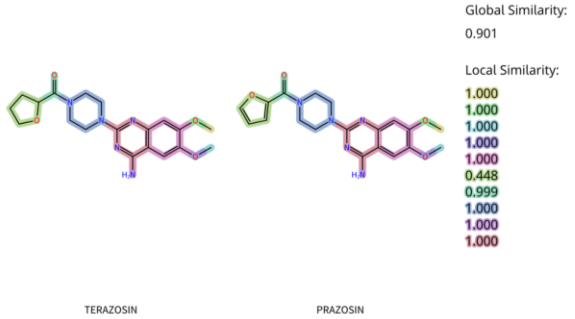
In October 1984, the newly discovered retrovirus HIV, then termed HTLV III or LA V, was the subject of a series of seminars given at Wellcome Research Laboratories in the United States by Drs. Francoise Barre-Sinoussi, Robert Gallo, and Samuel Broder. These discussions served as a catalyst to ensure Wellcome's involvement in the discovery and development of therapies for the new disease syndrome devastating thousands of patients, mainly in the prime of their lives. An early decision was to further develop a plaque reduction assay already in place since 1980 for an animal retrovirus, which then would be used to screen potential anti-HIV compounds. Friend leukemia virus (F-MuLV, a murine retrovirus), Harvey sarcoma virus (HaSV, another murine retrovirus), and FG-10 (murine) cells were acquired from Kent Weinhold at Duke University. Since both F-MuLV and HaSV form plaques in FG-10 cells, the basis for the initial Wellcome assay was that if a compound inhibits the ability of the virus to grow, the number of plaques formed will be reduced. Once the murine plaque reduction assay was functioning, known antiviral com- pounds, such as Wellcome's acyclovir, were screened. When no exciting activities were observed with these initial candidates, the focus shifted to the dideoxynucleoside group of compounds, such as dideoxycytosine, dideoxyadenosine, dideoxyguanosine, and dideoxythymidine. While activities in the 10-20 M range were demonstrated with these compounds in the assay, the Wellcome scientists were optimistic that a compound could be identified with even greater anti-HIV activity. Wellcome's senior organic chemists supplied 10-20 compounds representative of their synthetic

expertise and established drug development programs for testing in the new plaque reduction assay. Among 12 such compounds furnished on November 2, 1984, was zidovudine. Not knowing what excitement would befall the laboratory, the compounds were analyzed at the next available opportunity. When counting the plaques from that assay, it became obvious that none of the 18 plates with zidovudine had plaques. None at all!(*360*)"

TERAZOSIN

1987

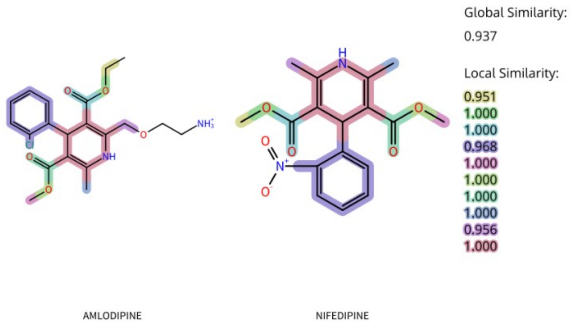
Analogue of prazosin(*21*)




AMLODIPINE

1987

Analogue of nifedipine(*21*)




MOMETASONE

1987

Analogue of cortisone

Error in similarity calculation by FTrees

MESNA

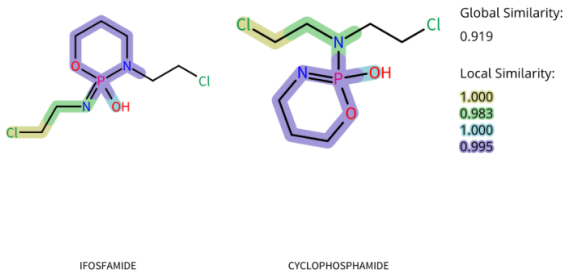
1987

Secondary

IFOSFAMIDE

1987

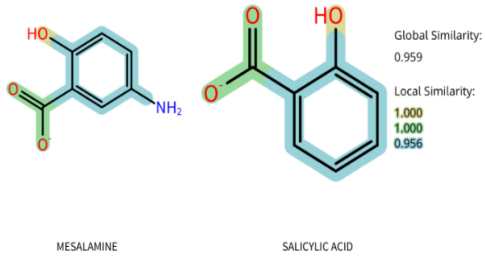
Analogue of cyclophosphamide




MESALAMINE

1987

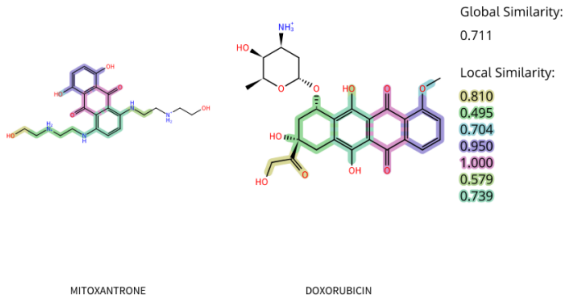
Analogue of salicylic acid




MITOXANTRONE

1987

Analogue of doxorubicin(*21*)




TERIPARATIDE

1987

Recombinant human parathyroid hormone (1-34)

MUPIROCIN

1987

"Early observations of the antimicrobial activity exhibited by *Pseudomonas fluorescens* eventually led to the isolation and characterisation of a novel family of structurally related antibiotics, pseudomonic acids A, B, C and D. Pseudomonic acid A which is now referred to as mupirocin is the major antibacterial component of the group and is produced by submerged fermentation of *P. fluorescens*(*361*)."

"THE antagonistic effects of *Pseudomonas fluorescens* were first recorded by Garre in 1887. Several reports since have dealt with the biological activity of cultures and extracts of *P. fluorescens*. We wish to report the production and purification of these inhibitory substances and the characterization of a metabolite responsible for a significant proportion of the antibacterial activity. […]

The mixture of sodium salts showed a wide antibacterial spectrum against Gram positive and Gram negative bacteria, showed low toxicity and was bacteriostatic against S. aureus (NCTC 6571) and E. coli (MRE 600)(*362*)."

Discovery of nalidixic acid:

"The first antimicrobial quinolone was discovered about 50 years ago as an impurity in the chemical manufacture of a batch of the antimalarial agent chloroquine. It demonstrated anti Gram-negative antibacterial activity, but its potency and antimicrobial spectrum were not significant enough to be useful in therapy. Building on this lead, however, subsequently nalidixic acid was commercialized(*363*)."

From the discovery paper cited in the previous quotation:

"As part of a general investigation of new antibacterial agents, we have prepared a series of l-alkyl-l,8-naphthyridin-4-one-3-carboxylic acid derivatives. Several members of the series were found to be highly effective antibacterial agents both *in vitro* and *in vivo*.

The outstanding compound of this series is l-ethyl-7-methyl-1,8-naphthyridin-4-one-3-carboxylic acid.

The antibacterial activity of nalidixic acid has been demonstrated against a variety of microorganisms causing disease in man and animals.

The *in vivo* activity of the compound is most pronounced against Gram-negative bacteria, while Gram-positive organisms are generally more resistant. Chemotherapeutic studies of nalidixic acid in acute experimental infections of mice have shown a similar pattern of activity. Maximal activity was observed against systemic infections caused by *E. coli*, *A. aerobacter*, *Proteus mirabilis*, *Shigella flexneri*, *Past. multocida* and *Salm. typhimurium*. Under similar experimental conditions, the compound exhibited no therapeutic effect in mice against lethal infections with *Staph. aureus*, *Strep. pyogenes*, *D. pneumoniae* and two strains of *Brucella*. In all instances, therapeutic response was related to the dose, and no toxic side-effects were observed upon single or multiple dose medications at dose levels ranging from 25 to 400 mg./kg. The activity was evident upon both oral and parenteral administration, indicating absorption by both routes of medication. Other compounds in the series had a similar spectrum of activity, but required larger doses to obtain the same therapeutic effect(*364*)."

"Eventually, nearly 30 years after Lesher's initial work on the class, a brief description of the events leading up to the discovery of nalidixic acid was communicated. As stated by David Greenwood: 'Details of the circumstances surrounding the discovery remained unclear until 1986 when George Lesher gave an account of the events at a symposium on quinolone agents in Chicago.' A Sterling scientist who had worked with George Lesher (although after the discovery of nalidixic

acid) wrote a tribute to Lesher after Lesher's death in 1990 that contained the following description, taken from the 1986 symposium:

'As part of a study at Sterling in the late 1950s aimed at the identification of by-products of the synthesis of the important antimalarial drug chloroquine, he [Lesher] and his co-workers isolated and characterized 7-chloro-1-ethyl-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid. This by-product was a regioisomer of the normal intermediate in the process, ethyl 7-chloro-1,4-dihydro-4-oxo-3-quinolinecarboxylate. The by-product exhibited modest in vitro antibacterial properties and served as the lead structure of the design and synthesis of additional analogs. Among those new derivatives was the 1,8-naphthyridine analog nalidixic acid.'

This description, published in a book in 1993, is consistent with the 1962 Lesher footnote, inasmuch as both refer to the Sterling lead structure having a quinolone (rather than naphthyridone) core, now identified specifically as 7-chloro-1-ethyl-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid. Further, the 1986 lecture by Lesher and the 1993 written account of that lecture for the first time identified the synthesis of the antimalarial chloroquine as the general source of that antibacterial quinolone lead compound. Sterling Drug was actively involved with chloroquine synthesis and manufacture during the 1940s and 1950s, so the serendipitous detection of such a byproduct would not be surprising from a drug discovery perspective(*365*)."

## PHENYLACETIC ACID

1987

Endogenous(*217*)

"A second compound which could be used to promote waste nitrogen excretion is phenylacetic acid. In primates this substance acetylates glutamine to form phenylacetylglutamine, which is rapidly excreted by the kidney. Acetylation and excretion of glutamine rather than glycine has three advantages-(i) glutamine contains two nitrogen atoms per molecule, (ii) it accumulates in urea-cycle enzymopathies, and (iii) it is in equilibrium with glutamate, the nitrogen donor for urea synthesis.

Shiple and Sherwin showed that phenylacetylglutamine synthesis in man utilises nitrogen that otherwise would appear as urinary urea. Ambrose et al found that 98% of orally administered phenylacetic acid (5 to 7 gm/day for 3 months in man) was excreted in the urine as phenylacetylglutamine. James gave 85 mg/kg of phenylacetic acid to a man and found that 91% of this dose was excreted in the urine as phenylacetylglutamine.

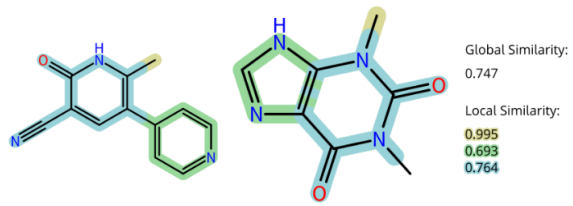
No adverse effects were noted in either of these studies, but an earlier paper reported thirst, nausea, and dizziness after a single dose. This acetylation system is similar to that described for hippuric-acid synthesis, for it involves phenylacetic thiokinase and a glutamine-specific transacetylase.

We have given a 16-year-old girl with carbamyl-phosphate-synthetase deficiency 6-4 g phenylacetic acid for 7 days. Urinary nitrogen excretion rose 45%, all of which could be accounted for by an increase in phenylacetylglutamine. No side-effects were noted(*366*)."

## MILRINONE

1987

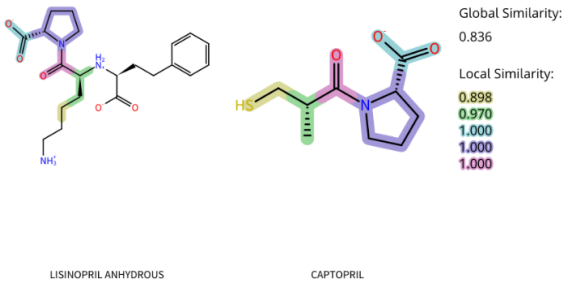
Analogue of theophylline and caffeine(*1*)




## LISINOPRIL

1987

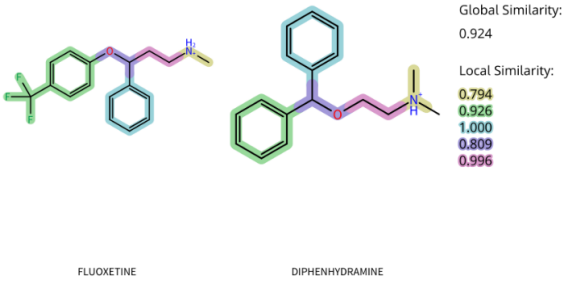
Analogue of captopril(*21*)

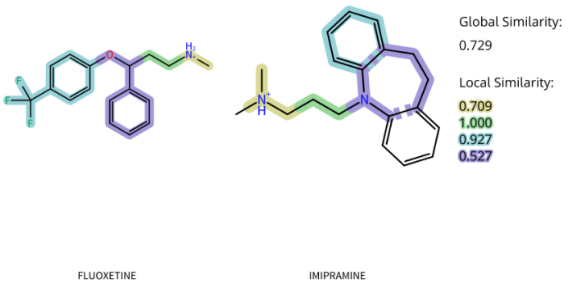



FLUOXETINE

1987

Analogue of imipramine and diphenhydramine



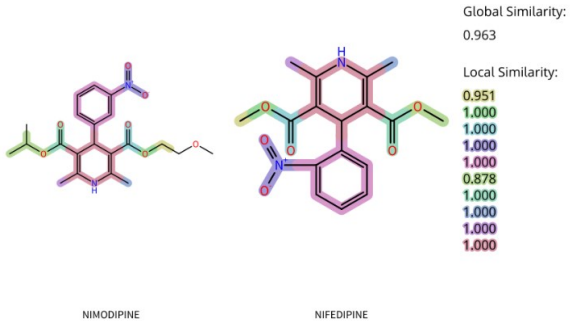

From the discoverer(s):

"In 1970, Molloy (a medicinal chemist) and Rathbun (a pharmacologist) began their collaboration, which aimed to develop an agent that would retain the therapeutic activity of the TCAs, but which would be devoid of their undesirable effects on cardiac conduction as well as anticholinergic activity. They used a test scheme that involved the reversal of apomorphine-induced hypothermia in mice — a test in which the TCAs were active as antagonists. Diphenhydramine was known to enhance the pressor response to NA, and was observed by Carlsson and colleagues at the University of Goteborg in Sweden to inhibit monoamine uptake in addition to antagonizing histamine receptors. The inhibition of monoamine uptake implied a potential usefulness in treating depression. Molloy, along with colleagues Schmiegel and Hauser, synthesized many analogues of the antihistamine drug diphenhydramine. Kattau, in the Rathbun laboratory, then tested the newly synthesized molecules for their capacity to reverse apomorphine-induced hypothermia in mice. LY86032, which is a phenoxy analogue, was highly effective in antagonizing apomorphine hypothermia in mice. Analysis of the structure–activity relationship (SAR) led to the identification of a molecule, DL-N-methyl-3-(o-methoxyphenoxy)-3-phenylpropylamine HCl (later called nisoxetine hydrochloride; LY94939), which was as effective as the TCAs in reversing the apomorphine-induced hypothermia(*367*)."

NIMODIPINE

1988

Analogue of nifedipine(*21*)




GADOXETATE DISODIUM

1988

Contrast agent

GADOBENATE DIMEGLUMINE

1988

Contrast agent

GADOTERATE MEGLUMINE

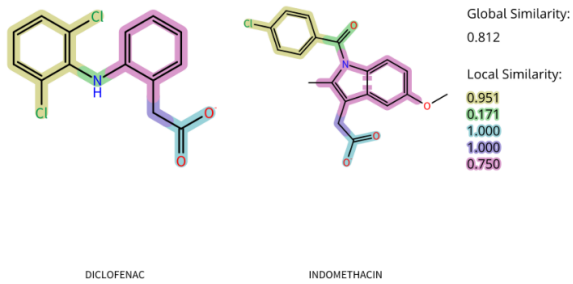
1988

Contrast agent

## DICLOFENAC

1988

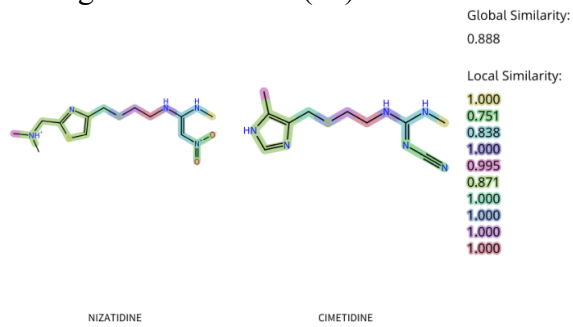
Analogue of indomethacin(*21*)




## NIZATIDINE

1988

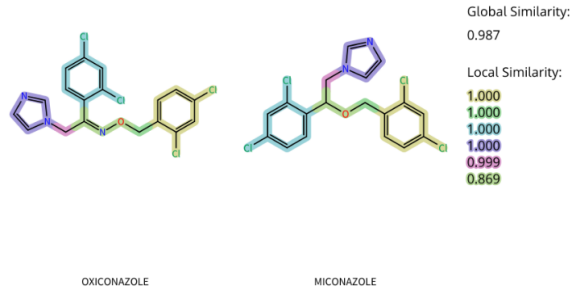
Analogue of cimetidine(*21*)




## OXICONAZOLE

1988

Analogue of miconazole(*21*)




## GADOBUTROL

1988

Contrast agent

## NAFTIFINE

1988

"The discovery of the first representative of this new class of antifungal agents, naftifine, was basically accidental. In 1974, this compound was obtained as the result of an unexpected chemical reaction during a program at Sandoz-Wander, Berne, for the synthesis of compounds active in the central nervous system. Because it was a novel compound, it was also tested as part of a general screening program at the Sandoz Research Institute in Vienna, where it was found to be highly active in vitro and in vivo against a number of pathogenic fungi(*368*)."

## AVOBENZONE

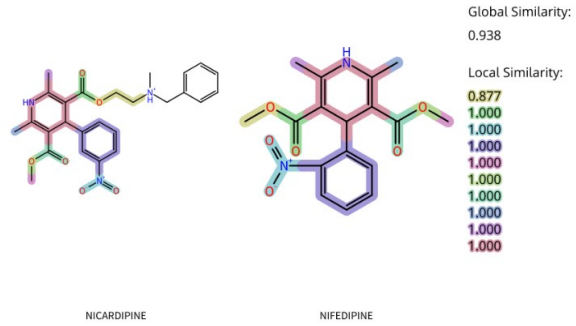
1988

"Avobenzone is an oil soluble ingredient used in sunscreen products to absorb the full spectrum of UVA rays. It helps prevent sunburn. Avobenzone works by absorbing the rays and converting them to energy that is less damaging to the skin(*1*)."

## NICARDIPINE

1988

Analogue of nifedipine(*21*)




## ETHANOLAMINE OLEATE

1988

Calcium chelating agent

## IOVERSOL

1988

Contrast agent

OCTREOTIDE

1988

Analogue of the endogenous somatostatin

Error in similarity calculation by FTrees because of the unsupported macrocycle

Discovery of somatostatin:

From one of the discoverer:

“It can be said, with no qualification, that everything about the discovery of somatostatin, including somatostatin itself, was unexpected. […] I should have named that novel peptide not somatostatin but serendipin or serendipitin - and the name would be just as good today as it would have been 20 years ago. […]

I asked him to set up a radioimmunoassay for rat growth hormone (GH) as it was obvious that the search for the putative GRF could not proceed with the classic ‘tibia test’ bioassay for GH. After 2 years of efforts with Wilson Rodger, later in collaboration with the group of John Beck in Montreal we had gone nowhere even to prove the existence of a GRF in hypothalamic extracts using the tibia test […] Paul Brazeau set up the RIA for rat GH, and had it working routinely within a couple of months. […]

It was time to approach the isolation of the postulated GRF combining the short-term incubation of the cultured dissociated pituitary cells and the RIA for GH in the culture fluid. Moreover, we had plenty of fresh, untouched fragments of (ovine) hypothalamus and, better still, side fractions from the earlier isolations of TRF and LRF corresponding to several hundred thousands of processed hypothalamic fragments.

Very early in the project it became obvious that things were not working as expected. Based on the RIA for GH run by Paul Brazeau, Wylie Vale had noticed that simply changing the culture fluid in the short-term incubation of pituitary cells would stimulate by 15-20% the basal secretion of GFI, in a highly reproducible manner. Now aware of the fact, we thought we could live with it in the search for GRF, taking it in consideration for calculating the (expected) release of GH upon addition of the hypothalamic extract to the cultured cells. The early results were showing no increase in the release of GH over and above that one to the fluid exchange. Indeed, with hypothalamic extracts there appeared to be inhibition of that ‘mechanically induced’ release of GH and as the dose (concentration) of the hypothalamic extract was increased there was an unmistakable decrease in the basal secretion (release) of GH that was dose-related(*369*).”

From a discovery paper cited in the article of the previous quotation:

“Searching to demonstrate the presence of this still hypothetical somatotropin releasing factor in the crude hypothalamic extracts used in the isolation of TRF (thyrotropin releasing factor) and LRF (luteinizing hormone releasing factor), we have regularly observed that their addition in minute doses ($\geqslant .001$) of a hypothalamic fragment equivalent) to the incubation fluid of dispersed rat pituitary cells in monolayer cultures significantly decreases the resting secretion of immunoreactive growth hormone by the pituitary cells. This inhibition is related to the dose of hypothalamic extract added and is specific. […]

After purification, the synthetic peptide had the biological activity of the native SRIF at concentrations $\geqslant$ 1 nM, native or synthetic SRIF inhibits the secretion of growth hormone from monolayer cultures of dispersed cells of rat adenohypophysis. In one experiment, native SRIF, at a concentration of 20 nM, inhibited significantly the spontaneous secretion of growth hormone by enzymatically dispersed cells derived from the

pituitary gland of a patient with confirmed active acromegaly(*370*).”

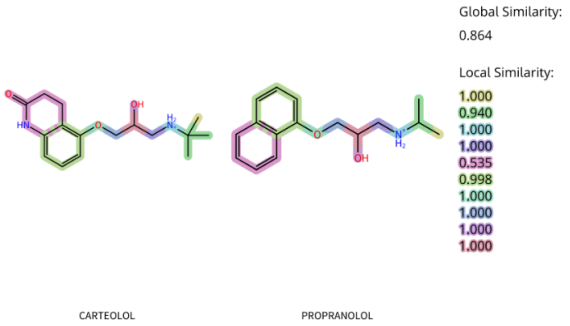
From the discovery paper of Krulich and McCann cited in the article of the two preceding quotations:

“Pituitaries were incubated in vitro for 5 hr and the quantity of GH released into the medium and remaining in the glands was bioassayed by the ‘tibia test.’ […] GH-inhibiting factor (GIF) inhibited the release of GH as indicated by a decrease in the quantity released into the medium, but had no definite effect on that remaining in the glands(*371*).”

## CARTEOLOL

1988

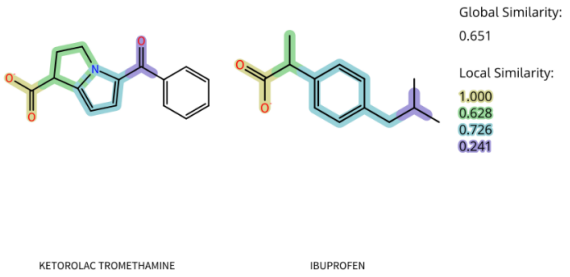
Analogue of propranolol(*253*)




## KETOROLAC TROMETHAMINE

1989

Analogue of ibuprofen(*21*)




## INTERFERON ALFA-N3

1989

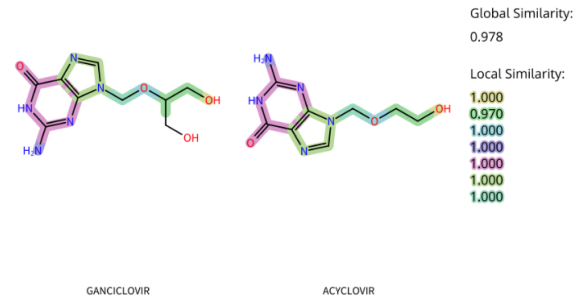
Endogenous-based biopharmaceutical

“Purified, natural (n is for natural) human interferon alpha proteins (consists of 3 forms or polymorphisms including 2a, 2b and 2c). 166 residues, some are glycosylated(*2*).”

## GANCICLOVIR

1989

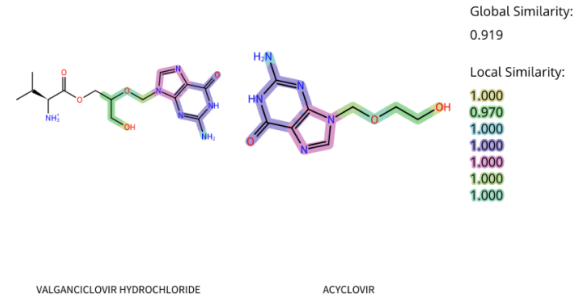
Analogue of acyclovir




## VALGANCICLOVIR HYDROCHLORIDE

1989

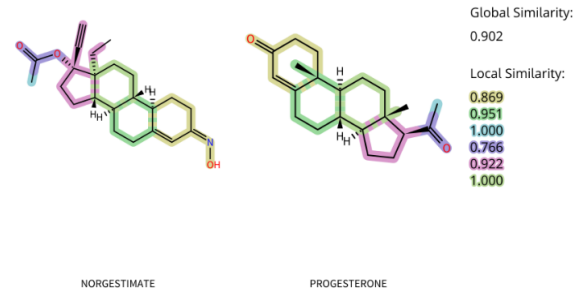
Analogue of acyclovir




## NORGESTIMATE

1989

Analogue of progesterone




## ERYTHROPOIETIN

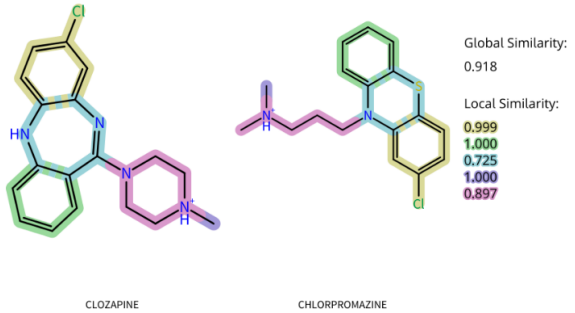
1989

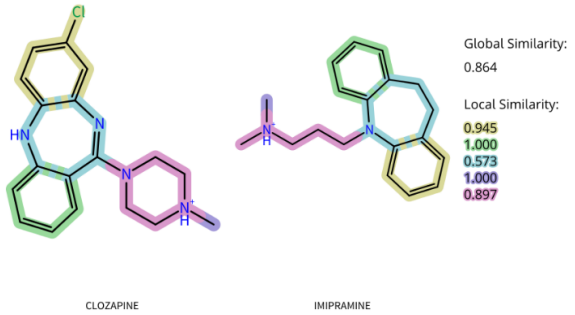
Endogenous-based biopharmaceutical

## CLOZAPINE

1989

Analogue of chlorpromazine




"In 1958 a group of tricyclic compounds based on the chemical structure of the antidepressant imipramine was synthesized by Swiss pharmaceutical company Wander AG, described as 'tricyclic antidepressants but with neuroleptic properties'. One of the compounds in this group, identified in 1959, was named 'clozapine'(*372*)."

From the discoverer(s):

"Initial interest in a drug such as clozapine arose from speculations and possible connections between chemical structure and therapeutic effectiveness. After the discovery of imipramine by Kuhn in 1957, the molecules of all pharmacologically defined and clinically applied tricyclic psychotropic drugs were built as, 'calotte models' in the Research Department of the Psychiatric Department of the Free University of Berlin. This was done in the manner proposed by Pauling and, in retrospect, this method was a very naive and old-fashioned procedure. The aim was to discover consistent differences between neuroleptic and antidepressant drugs and by this procedure to develop a new method for drug-screening - independent of pharmacological screening. At that time, we came to the conclusion that the angle between the planes of the rings of tricyclic drugs was flat, and that the drug should have a neuroleptic profile. If the angle was sharper and the planes of the rings twisted relative to each other, the drug should have an antidepressant effect.

These speculations, which in hindsight seem strange, were published at the beginning of the 1960s. The summary of this work, published in 1964 (Bente et al. 1964), resulted in us having a number of discussions with chemists and pharmacologists, including a chemist and a pharmacologist from a company based in Berne, Switzerland (Wander). These scientists offered us a group of newly developed tricyclic drugs with a 7-membered central ring. Given the stereostructure of these molecules, all of these drugs should have been antidepressants.

The first drug investigated in this group, a dibenzapine, was an antidepressant, which is still a very reliable antidepressant used widely in the clinical setting. Investigation of other drugs appeared to confirm our theory concerning the connection between chemical structure and therapeutic profile. However, clinical investigation of three compounds produced by Wander completely undermined our theory. As far as the chemical structure was concerned, the drugs should have been antidepressants, but clinical investigations showed them to be neuroleptics. We reported these findings on the three compounds at the C.I.N.P. conference in Washinton in 1966 as an obituary to our theory (Bente et al. 1966b).

One of these compounds was clozapine. Just as we were coming to terms with the fact that our elegant theory on the relationship between chemical structure and therapeutic

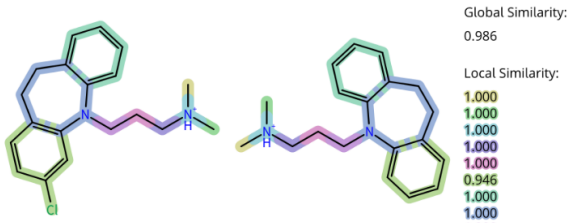
effect had been destroyed, we discovered to our surprise that clozapine, in contrast to all other compounds, had no extrapyramidal effects despite being a fully effective antipsychotic. This finding was almost unbelievable, because at that time it was a part of psychopharmacological dogma that extrapyramidal effects went in tandem with antipsychotic efficacy.

In the same year (1966) the Austrian psychiatrists Gross and Langner described in detail the excellent antipsychotic efficacy of clozapine, but because the drug had no extrapyramidal side-effects either in animal experiments or in clinical use, they did not call it a real neuroleptic. The Wander Company, the manufacturers at that time, found themselves in a bizarre situation. They were hesitant to introduce the drug, not because of its effectiveness, but because it lacked an adverse side-effect!(*373*)"

## CLOMIPRAMINE

1989

Analogue of imipramine

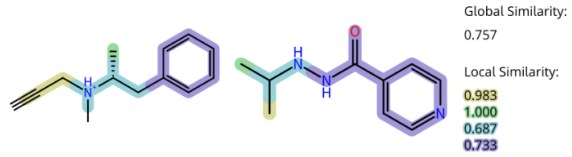



CLOMIPRAMINE IMIPRAMINE

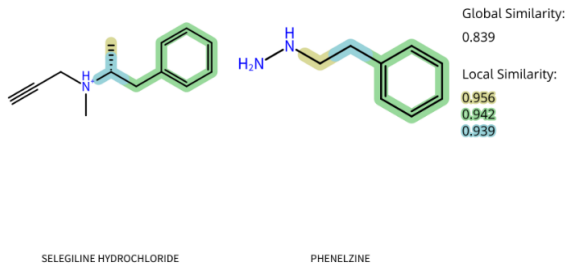
## SELEGILINE HYDROCHLORIDE

1989

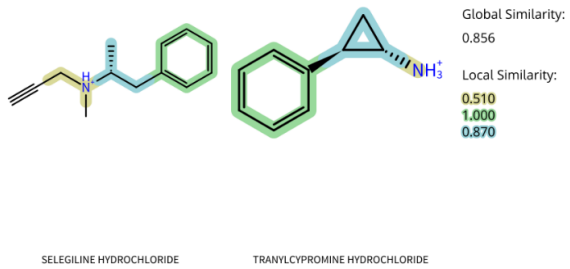
Analogue of iproniazid




SELEGILINE HYDROCHLORIDE IPRONIAZID




SELEGILINE HYDROCHLORIDE PHENELZINE

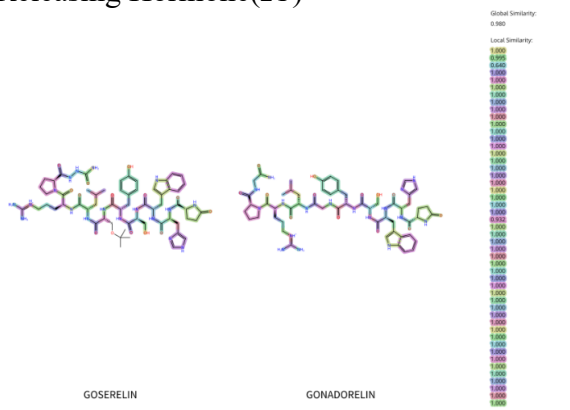



SELEGILINE HYDROCHLORIDE TRANYLCYPROMINE HYDROCHLORIDE

## GOSERELIN

1989

Analogue of the endogenous Gonadotropin Releasing Hormone(*21*)

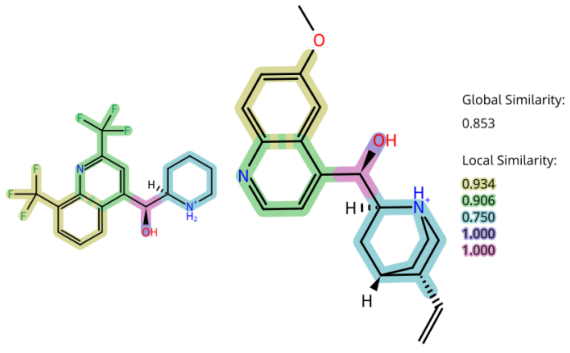


GOSERELIN GONADORELIN

## MEFLOQUINE

1989

Analogue of quinine




MEFLOQUINE QUININE

OMEPRAZOLE MAGNESIUM

1989

"**Background:** In the late 1960s,the pharmaceutical company Hässle decided to start a gastrointestinal research division with the aim of finding a potent drug for the inhibition of gastric acid secretion to be used in patients with peptic ulcers. To this end, a gastrointestinal laboratory was created, and the first project in this laboratory resulted in an antisecretory compound that was very effective in the rat, which was used as a screening model. However, the compound was completely ineffective in man, indicating that new screening models were needed.

**The omeprazole project**: In 1972, the gastric acid inhibitory project was restarted with a new approach. Anesthetized dogs were used as an initial screening model, followed by tests on conscious GASTRIC FISTULA DOGS. A literature search found a paper describing an antisecretory compound (CMN 131) developed by the pharmaceutical company Servier; this compound, however, showed severe acute toxicity, and further research into this compound was consequently cancelled. As it seemed a reasonable assumption that the thioamide group in the chemical structure of CMN 131 was responsible for the toxicity, the new approach aimed to eliminate this group by incorporating it into, or in between, heterocyclic ring systems. By 1973, the first hit was discovered — the benzimidazole H 124/26, which was a powerful antisecretory compound without acute toxicity, and which therefore became the lead compound. […]

[A] metabolite of H 124/26, which was not included in the Hungarian patent, was found to be an even more potent antisecretory compound. The metabolite H 83/69 was the sulphoxide of H 124/26 — named timoprazole — and it became the new lead compound. At this stage, the site of inhibitory action in the pathway leading to acid secretion was not known. […]

**Compound optimization.** Simpler *in vitro* techniques were essential in order to test a large number of different substituted benzimidazoles for the optimal inhibition of gastric acid secretion. The isolated gastric-acid-secreting mucosa of the guinea pig was introduced as an appropriate *in vitro* model. Later on, isolated rabbit acid- secreting glands were used, and a micromethod for isolating acid-secreting glands from human gastric biopsies was developed. These techniques allowed the testing of a large number of compounds, including tests on the human target tissue(*374*)."

The activity bioassay used in the article cited in the previous quotation as the first paper reporting the discovery of the lead compound, CMN 131:

"**Gastric Antisecretory Activity in the Rat.-**Gastric antisecretory activity was evaluated in the 4 hr polyrus-ligated rat, using the technique of Shay. The compds were suspended in 20% gum syrup, and were administered intraduodenally immediately after pyloric ligation to groups of 6 male Sprague Dawley/CD rats weighing 221 ± 1.77 g. Free acid output was calcd for each rat(*375*)"

ESOMEPRAZOLE

1989

enantiopure omeprazole

PROPOFOL

1989

"In May 1973, hypnotic activity was detected in 2,6-diethylphenol, one of a selection of poorly water-soluble agents selected by James, a project chemist from ICI's compound collection. Because its onset of effect was slow this compound was discarded, but it provided a lead for the systematic evaluation of related alkyl substituted phenols. Among these Glen selected propofol (2,6-

diisopropylphenol[ICI 35 868], previously synthesized as a potential antibacterial agent) as the only compound with the optimum balance of properties and acceptable effects on respiration and circulation(*376*)."

From the article cited in the previous quotation as the paper reporting the discovery of propofol:

"Following our discovery of the intravenous (iv) anesthetic activity of 2,6-diethylphenol in mice, a series of alkylphenols was examined in this species and the most active analogues were further evaluated in rabbits. The synthesis of compounds which were not commercially available was accomplished by adaptations of standard ortho-alkylation procedures for phenols. Structure-activity relationships were found to be complex, but, in general, potency and kinetics appeared to be a function of both the lipophilic character and the degree of steric hindrance exerted by ortho substituents. The most interesting compounds were found in the 2,6-dialkyl series, and the greatest potency was associated with 2,6-di-sec-alkyl substitution. In particular, 2,6-diisopropylphenol (IC1 35 868) emerged as a candidate for further development and has subsequently been shown to be an effective iv anesthetic agent in man. […]

Hypnotic activity ($HD_{50}$) and acute toxicity ($LD_{50}$) were estimated in mice for standard anesthetics and the phenols examined. Sleeping times and the speed of induction and recovery were noted together with a qualitative assessment of muscle relaxation, analgesia, and any excitatory effects. Compounds with an $HD_{50} \leq 20$ mg/kg and a therapeutic ratio (LD50/HD50)$\geq 4$ which were free from undesirable side effects were considered for further evaluation of the quality of anesthesia produced in rabbits.

General trends in the primary mouse results were apparent when derivatives were arranged according to the pattern and type of substitution in the phenol ring as in Tables 11-V(*377*)."

"Anaesthetic activity has been discovered in a series of hindered phenolic compounds which exist as oils at room temperature. These compounds can be administered i.v. in aqueous solution with the solubilizing agent Cremophor EL. Animal tests were designed to detect a compound which produced anaesthesia characterized by rapid onset, short duration, lack of cumulation on repeated administration, and a lack of excitatory effects on induction and during maintenance and recovery. Of the compounds examined only ICI 35 868 was found to have a desirable anaesthetic profile in animals(*378*)."

## FLUTAMIDE

1989

"The pioneering work by Huggins and Hodges in 1941 demonstrated that prostate tumor growth is dependent on the male sexual hormone testosterone, thus providing a rationale for reduction of serum testosterone concentration as a therapeutic approach, either by surgical or medical castration. Although initially effective, the disease progresses in the majority of patients, even when serum testosterone is on castrate level (castration-resistant prostate cancer). Yet, at this stage of the disease, prostate cancer is still dependent on androgen receptor (AR) signalling. […]

Flutamide was first described as a member of a series of N-acyl anilides synthesized at Monsanto in the 1960s during a compound finding program aiming at bacteriostatic agents. Soon after, at Schering Corp., the compound was characterized pharmacologically and further developed as SCH-13521(*379*)."

From the earliest article describing the compound along its antibacterial activity:

"The *in vitro Staphylococcus aureus* activity

of the nitro-trifluoromethylanilides was obtained. Active structures included those which were substituted in the meta and para positions of the N-phenyl ring with a nitro and trifluoromethyl group and in which the acid-derived moiety incorporates alkyl, haloalkyl, cycloalkyl, alkenyl, haloalkenyl, alkyldienyl, and phenethyl groups and contains 5-12 carbon atoms. The benzyl and phenoxymethyl derivatives were inactive. N,N-Disubstituted and ortho-substituted derivatives were also inactive. Those anilides disubstituted in the α position possessed a lower order of activity. All of the complexes were derivatives of active anilides and exhibited the same order of activity on a weight basis as the anilides themselves(*380*)."

The earliest study reporting its antiandrogenic effect does not discuss explicitly the rationale for the selection of flutamide, yet its reported experiments are(*381*):

investigating the effects of the compound on:

- ✓ intact male rats
- ✓ castrate rats
- ✓ hypophysectomized rats
- ✓ prenatal development
- ✓ fertility in male rats
- ✓ gonadotropin inhibition in female rats parabiotically joined to male rats
- ✓ spayed rats
- ✓ female immature mice
- ✓ progestational and antiprogestational activities in immature female rabbit

The mechanism that flutamide antagonizes the receptor binding of dihydrotestosterone was first reported in an article published in 1974, 2 years after the publication year of the article of the previous quote(*382*):

The citation in the following quotation refers to the article of the previous quotation.

"Recently, a nonsteroidal compound, flutamide, was found to have a high antiandrogenic activity on male accessory sex organs. This report shows that the new antiandrogen, although non- steroidal, also antagonizes the receptor binding of DHT and the nuclear retention of DHT-receptor complex *in vivo* and *in vitro*(*382*)."

## CARBOPLATIN

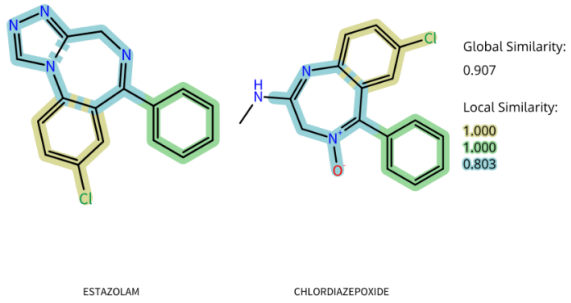
1989

Analogue of cisplatin(*21*)

## ESTAZOLAM

1990

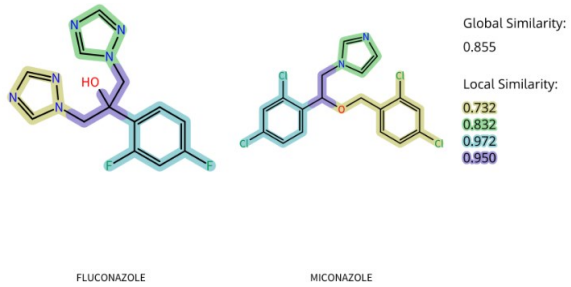
Analogue of chlordiazepoxide(*21*)




## FLUCONAZOLE

1990

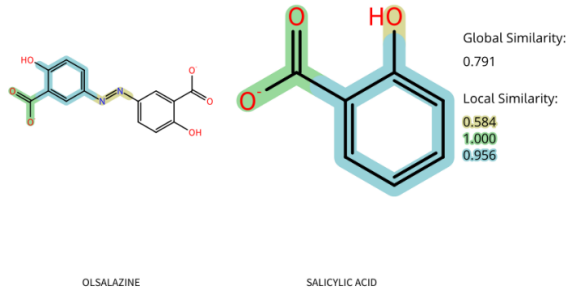
Analogue of miconazole(*21*)




## OLSALAZINE

1990

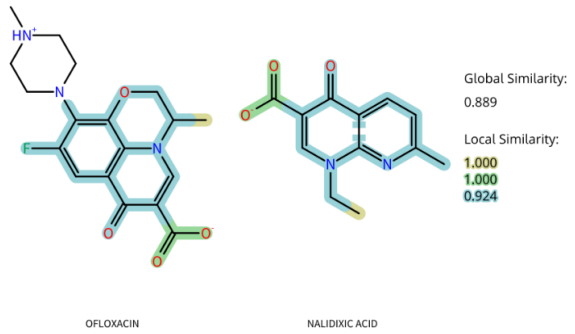
Analogue of salicylic acid



## OFLOXACIN

1990

Analogue of nalidixic acid(*21*)




## PODOFILOX

1990

"The first literature report on the extraction of *Podophyllum* was that of King in 1844, who called the resin he obtained from alcohol extraction podophyllin. He also described the effects of podophyllin administered to one of his patients. On the basis of evidence about the traditional therapeutic uses of these extracts, investigators were interested in discovering which of the chemical entities present in podophyllin were responsible for its 'anticancer' activity. […]
Podwyssotzki managed to achieve the difficult crystallization of the major component of the extract which he named 'podophyllotoxin'(*306*)."

"He tasted his own extracts and stated: 'When chewed, podophyllin developed a bitter taste. A peculiar, almost acrid sensation could be perceived.' He also showed that the preparation was toxic in cats. […]

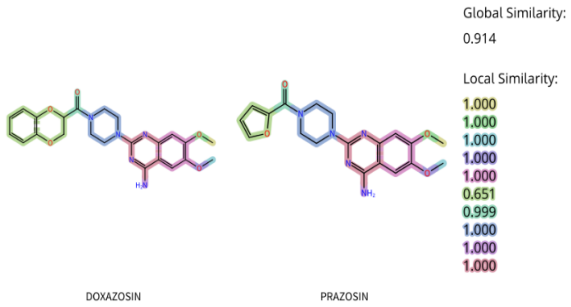
Neuberger crystallized podophyllotoxin and investigated its activity in animals such as frogs, cats, dogs and rabbits. He observed toxic effects similar to those induced by colchicine, with the effects being more marked in carnivores than in herbivores. […]

The first key step was a 1942 publication by Kaplan, describing the successful use of podophyllin applied topically to treat venereal warts (*Condylomata acuminata*). This success kindled interest in the use of podophyilin against tumor tissues. in parallel, the chemical analysis of its components was undertaken on a wide front. The next major advance was the 1946 publication of the results of King and Sullivan that showed that, when tested against dividing cells, podophyllin was as powerful an antimitotic agent as was colchicine(*306*)."

## DOXAZOSIN

1990

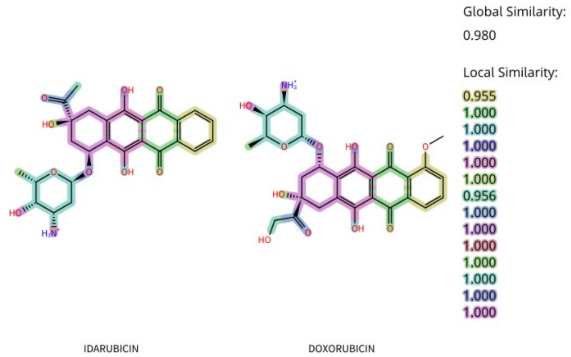
Analogue of prazosin(*21*)




## IDARUBICIN

1990

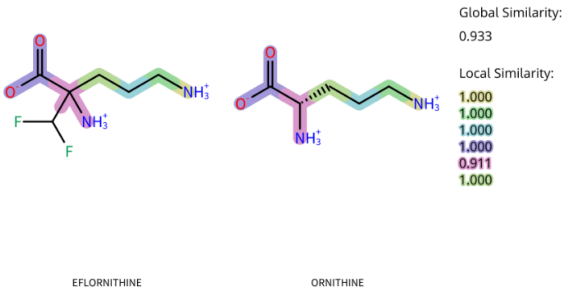
Analogue of doxorubicin(*21*)




## EFLORNITHINE

1990

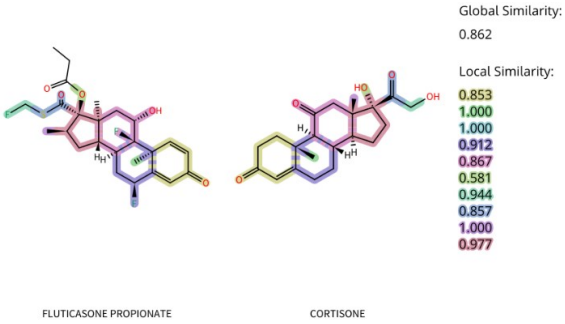
Analogue of the endogenous compound, ornithine. It irreversibly binds to ornithine decarboxylase and physically prevents the natural substrate, ornithine from accessing the active site(*1*).




## FLUTICASONE PROPIONATE

1990

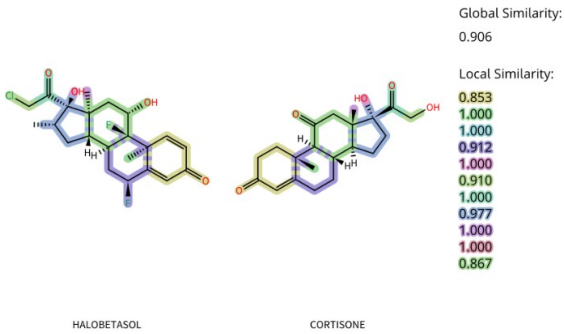
Analogue of cortisone(*21*)




## HALOBETASOL

1990

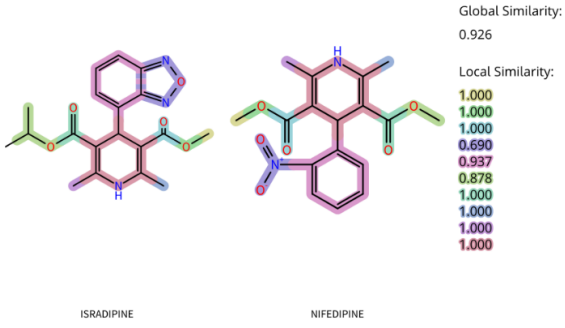
Analogue of cortisone(*21*)




## ISRADIPINE

1990

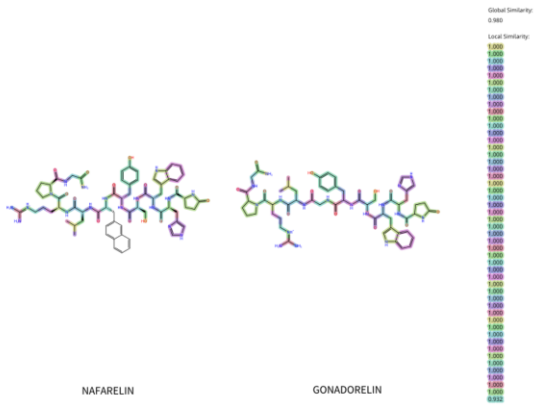
Analogue of nifedipine(*21*)




## NAFARELIN

1990

Analogue of GnRH(*1*)




## TITANIUM HYDRIDE

1990

Natural oxide of titanium, inorganic

## NABUMETONE

1991

From the discovery paper(*383*):

"Numerous arylacetic and arylpropionic acids have been synthesized in the search for nonsteroidal antiinflammatory agents. Although many of these acids have been shown to possess good activity, they invariably cause harmful irritation to the gastrointestinal tract. It is thought that this property could be related to the acidic nature of such compounds. In order to overcome this important drawback we decided to screen a variety of compounds lacking a carboxyl group, and from this investigation we have now prepared a structurally novel class of antiinflammatory compounds. This class consists of 2,6-disubstituted naphthylalkanones and derivatives thereof. […]

The antiinflammatory activity of some of the compounds was initially discovered using an acute model of inflammation, namely, the carrageenan-induced edema test of the rat paw. Cotton pellet induced granuloma formation in the rat served as a chronic model of

inflammation for further evaluation of the series(*384*)."

## ONDANSETRON

1991

Quoting from Sanger, one of the important figures in the discovery of antiemetic 5-$HT_3$ antagonists:

"The identification of 5-$HT_3$ receptor antagonism as a means of preventing cisplatin-evoked emesis began with the discovery that, unlike other dopamine $D_2$ receptor antagonists, high intravenous doses of metoclopramide reduced cisplatin-evoked emesis in cancer patients. On this evidence, we suggested that a mechanism unrelated to $D_2$ receptor antagonism was responsible for the antiemetic activity of high dose metoclopramide.

Examination of the pharmacology of metoclopramide showed that high concentrations had several actions that were additional to the ability to increase gut cholinergic activity and antagonize dopamine D2 receptors. Among these actions was a weak activity as a 5-$HT_3$ receptor antagonist (see Fozard 1984a). We tested for the possibility that antagonism of 5-HT3 receptors might prevent cisplatin-evoked emesis using ferrets as our animal model. […] we tested BRL 24924, a potent stimulant of gut motility and a 5-$HT_3$ receptor antagonist at higher doses. Our studies with BRL 24924 enabled us to suggest that 5-$HT_3$ receptor antagonism might prevent cisplatin-evoked emesis, but we could not. entirely rule out the unlikely possibility that selective stimulation and reordering of disordered gut motility might also contribute to the antiemetic activity. To complete our proposal, we, therefore, tested the first selective 5-$HT_3$ receptor antagonist MDL 72222 (Fozad 1984b). The result was a complete prevention of cisplatin-induced emesis in ferrets. […]

As a result sf our experiments, we developed BRL 43694 (granisetron), a highly potent and selective 5-$HT_3$ receptor antagonist and antiemetic agent. Other 5-$HT_3$ receptor antagonists (ICS 205-838, GR 38032F), originally developed for other indications, were also shown to have antiemetic properties(*385*)."

The rationale for the design and selection of the compound is not mentioned in the discovery paper of granisetron, yet its effect on the following assays are reported(*386*):

- ✓ Isolated gastrointestinal tissues
  - guinea-pig ileum
  - rat forestomach
  - human stomach
- ✓ potentiation of electrically evoked contractions caused by 5-HT
- ✓ Antagonism by BRL 43694 of 5-HT-evoked tachycardia in rabbit isolated heart
- ✓ Antagonism by BRL 43694 of the Bezold-Jarisch reflex in anaesthetised rats
- ✓ Inhibition of $^3$H-radiofigand binding to rat brain membranes *in vitro*

Another name of MD-72222 is bemesetron.

"Bemesetron was not progressed for treatment of emesis, the company preferring its follow-up molecule MDL73147 or dolasetron(*241*)."

Ondansetron and tropisetron were previously designed for other disorders, but due to this evidence on the relationship between 5-$HT_3$ antagonism and antiemesis activity, they were repurposed for antiemesis, quoting from Sanger:

"With respect to ondansetron and tropisetron, these can therefore be regarded as examples of 're-purposing'(*241*)"

"Glaxo (GR38032F or ondansetron, a racemate designed for 'a variety of disorders including migraine' before being specifically patented for treatment of depression, schizophrenia, anxiety and cognitive disorders 7 ); Sandoz (ICS 205-930 or tropisetron, designed for treatment of migraine and later

found to have some ability to antagonize at the 5-$HT_4$ receptor)(*241*)."

Regarding the discovery of MD-72222, quoting from Fozrad, its designer and the discoverer of its 5-$HT_3$ antagonistic effect(*241, 385*):

"Recently, a series of substituted benzoic acid esters of tropine was synthesised (Fozard and Gittos, 1983) several of which proved to be both potent and highly selective antagonists at the 5-HT receptor mediating excitation of sympathetic postganglionic neurones. The most active compound, MDL 72222 blocked, at nanomolar concentrations, release of noradrenaline evoked from the rabbit heart by activation of the excitatory 5-HT receptors present on the sympathetic terminal fibres(*387*)."

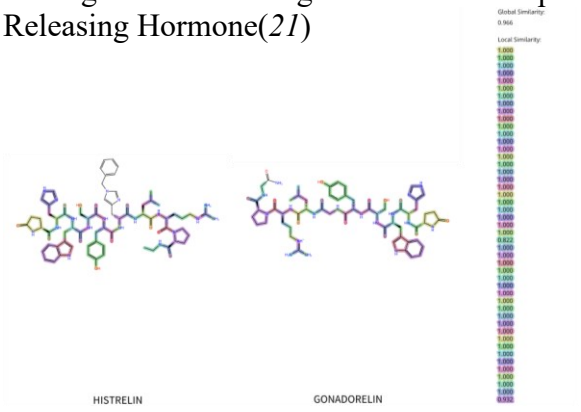
From another related article of Fozrad:

"The interaction of MDL 72222 with 5-HT has been investigated on the rabbit isolated heart, where stimulation of 5-HT receptors results in noradrenaline release from the terminal sympathetic fibres, on the guinea-pig ileum, where excitatory 5-HT receptors mediate acetylcholine release from the intramural cholinergic nerves, and in the anaesthetized rat, where activation of receptors on vagal fibres initiates afferent the Bezotd-Jarisch effect of 5-HT(*388*)."

## HISTRELIN

1991

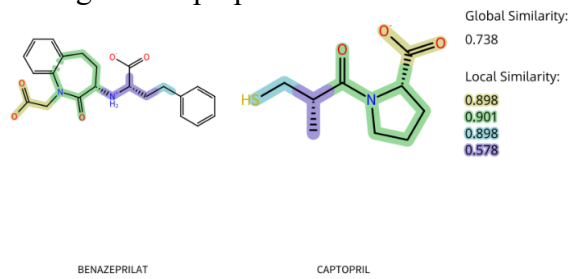
Analogue of the endogenous Gonadotropin Releasing Hormone(*21*)




## BENAZEPRILAT

1991

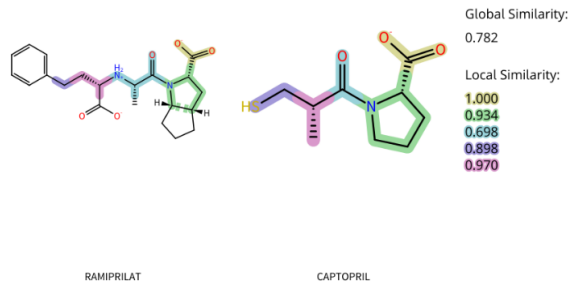
Analogue of captopril




## QUINAPRILAT

1991

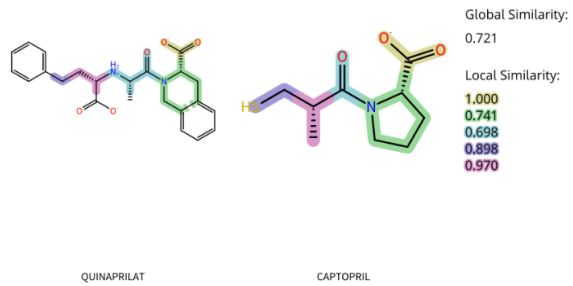
Analogue of captopril(*21*)




## RAMIPRILAT

1991

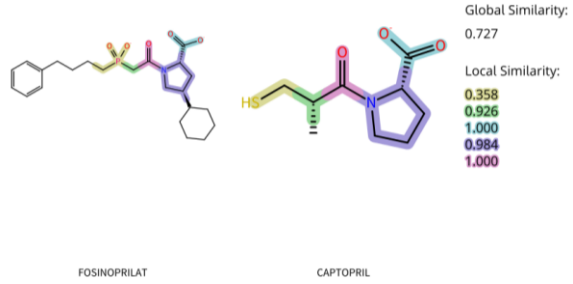
Analogue of captopril(*21*)




## FOSINOPRILAT

1991

Analogue of captopril

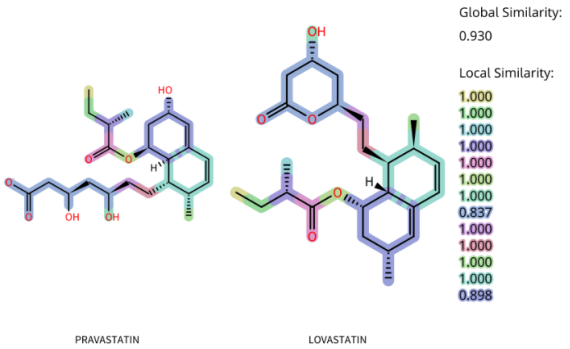


## PRAVASTATIN

1991

Analogue of lovastatin(*21*)

From the discoverer(s):




"We first searched for microbial culture broths that inhibited the incorporation of [$^{14}$C]acetate into nonsaponifiable lipids. The active broths were then tested for their ability to inhibit lipid synthesis from [$^{3}$H]mevalonate. Culture broths that were active in the first assay but not active in the second determination were suspected to contain a compound (or compounds) that inhibited the early stages between acetate and mevalonate in the cholesterol synthetic pathway. The principal active component(s) in these culture broths were then isolated. Rat liver enzymes were used for these assays(*389*)."

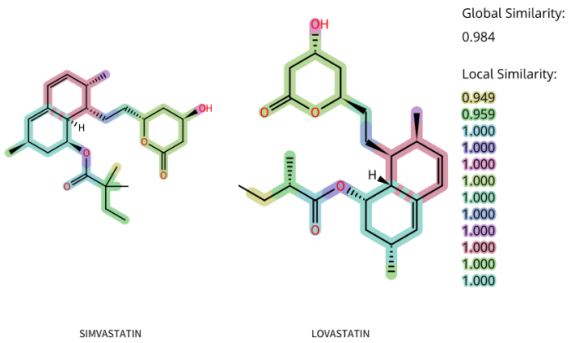
Quoting from the paper cited by the discoverer(s) regarding their bioassay:

"*Preparation of Enzyme System*-Freshly excised rat livers were perfused a few seconds in the cold buffer of Bucher and Mc Garrahan, minus glutathione and sucrose, and then homogenized in two volumes of the buffer in a Potter-Elvehjem type homogenizer of 1-mm clearance. Only six strokes were used for homogenization, for more vigorous treatment resulted in a greatly reduced activity of the preparation. The centrifugation procedure described by the above authors was used to obtain microsomal and supernatant fractions. The supernatant solution was then fractionated with neutral ammonium sulfate solution at 0° into the following fractions: A, 0 to 25%; B, 25 to 40%; C, 40 to 55% and D, 55 to 80% of saturation. Each fraction was dissolved in 0.1 M phosphate buffer and dialyzed 2 hours at 0° against 2 liters of 0.003 M phosphate buffer of pH 7.0. After dialysis, the fractions were adjusted to the desired volume, and then these fractions and microsomes were stored separately in 0.1 M phosphate, pH 7.0, for varying periods of time, up to 20 days, on Dry-Ice(*390*)."

## SIMVASTATIN

1991

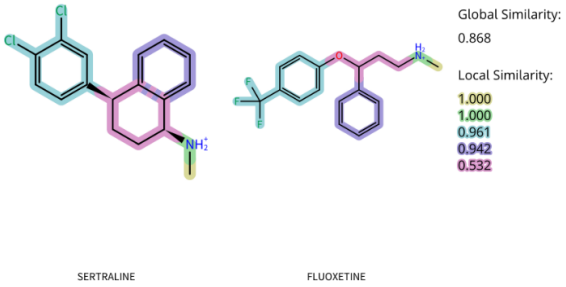
Analogue of lovastatin(*21*)

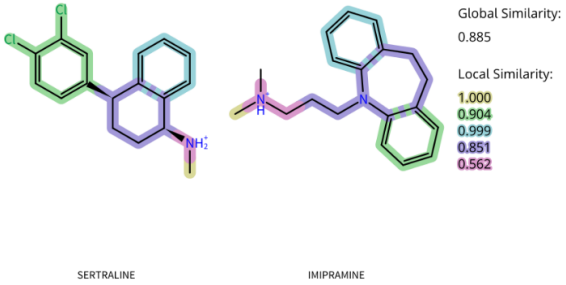



## SERTRALINE

1991

Analogue of fluoxetine



## TICLOPIDINE

1991

From the discoverer(s):

Title of the paper is: “The story of clopidogrel and its predecessor, ticlopidine: Could these major antiplatelet and antithrombotic drugs be discovered and developed today?”

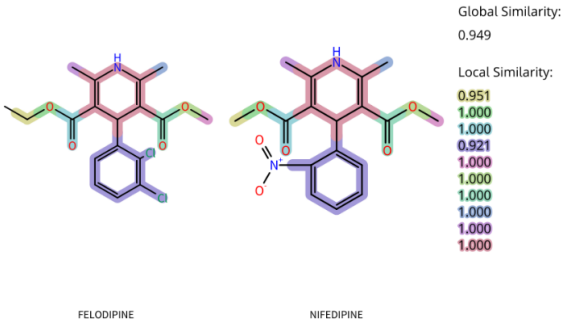
“Clopidogrel has a more favorable side effect profile than ticlopidine. These two molecules could not be discovered today through an in vitro high throughput screening because they are prodrugs, which must be transformed in the body into an active metabolite. The active metabolite is very unstable and cannot be obtained by chemical synthesis or stored. Moreover, its structure cannot be predicted by rational drug design. Even if these two prodrugs were discovered today by chance, they would probably not be developed by the majority of R&D teams because of a number of drawbacks associated with their strong metabolic transformation in the body and their irreversible effect on platelets. […]

The story started in 1972 when my manager, Dr Fernand Eloy, decided to search for new anti-inflammatory drugs related to Tinoridine, a thienopyridine compound whose anti-inflammatory and analgesic properties were published 2 years previously by the Yoshitomi Company. Exploiting our knowledge in thienopyridine chemistry, we synthesized a number of derivatives in gram quantities to screen them on a wide battery of animal models exploring different physiological systems or mimicking human pathologies. Almost all these tests were performed in vivo or ex-vivo, in the mouse and the rat. It appeared that none of the thienopyridine compounds synthesized had anti-inflammatory or analgesic effects but, fortunately, some of them displayed unexpected antiplatelet and antithrombotic activities after oral administration to rats. It is worth mentioning that it was uncommon, at that time, to search for new antiplatelet agents. The link between platelet aggregation, thrombosis and cardiovascular events was still ignored or disputed by some cardiologists and in actual fact, vascular spasm was considered as the major cause of the clinical complications of atherosclerosis. One of the most active compounds found, ticlopidine, was rapidly selected for development(*391*)”

## FELODIPINE

1991

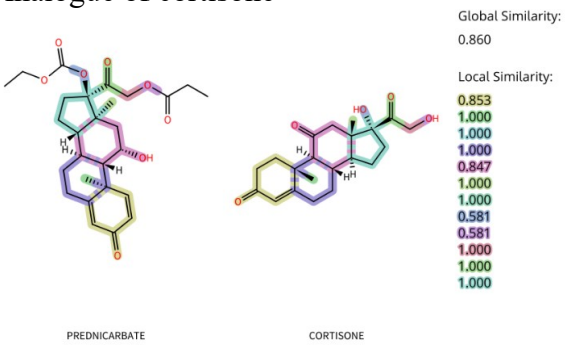
Analogue of nifedipine(*21*)




## PREDNICARBATE

1991

Analogue of cortisone




## AZITHROMYCIN

1991

Analogue of erythromycin(*21*)

Error in similarity calculation by FTrees because of the unsupported macrocycle

## STIBOCAPTATE

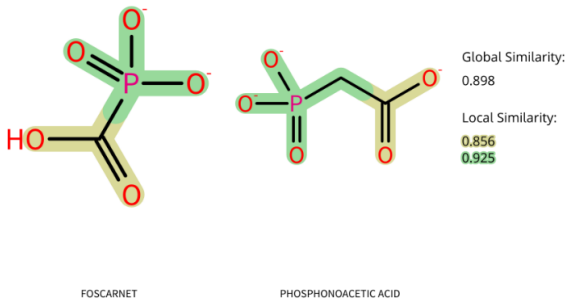
1991

Chelating agent

## FOSCARNET

1991

Analogue of phosphonoacetic acid




From the first report, a case report, of its use in humans:

"SIR,-We have successfully treated a patient in terminal hepatic coma with foscarnet (trisodium phosphonoformate). […]

Initial treatment was standard with intravenous cefotaxime given for possible septicaemia but he continued to deteriorate. 48 h after admission, intravenous foscarnet was started. The rationale was the known in-vitro inhibition of DNA polymerase. A 20 mg/kg loading dose was followed by continuous infusion of 1 mg/kg per hour increasing to 1 mg/kg. He received a total of 30 g over 13 days. 48 h after the start of foscarnet, motor function was normal, and verbal communication was unimpaired. Complete recovery followed(*392*)."

From the article cited in the previous quotation regarding the DNA polymerase inhibitory activity of foscarnet:

"Mao et al. (1975) reported that phosphonoacetic acid inhibits herpesvirus DNA polymerase, and this explained the earlier observed antiherpes activity in cell-culture and in animals (Shipkowitz et al., 1973). Trisodium phosphonoformate, through independent experiments by Helgstrand et al. (1978) and Reno et al. (1978), was also found to inhibit herpesvirus DNA polymerase and herpesvirus replication in a manner similar to that of phosphonoacetic acid. […]

In the literature, trisodium phosphonoformate, phosphonoformate, phosphonoformic acid, PFA and foscarnet sodium have been used to denote the same compound(*393*)."

The discovery of phosphonoacetic acid

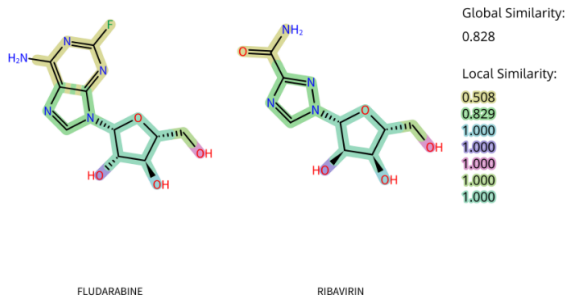
From the discovery paper:

"Random testing of compounds with a tissue culture screen designed to detect antiviral compounds revealed that PAA inhibited replication of herpesvirus types 1 and 2. The activity was consistently obtained at a concentration of 100 µg/ml. Our in vitro data suggested the possibility of achieving a favorable in vivo therapeutic index against herpesvirus. We present data on our animal studies(*394*)."

## FLUDARABINE

1991

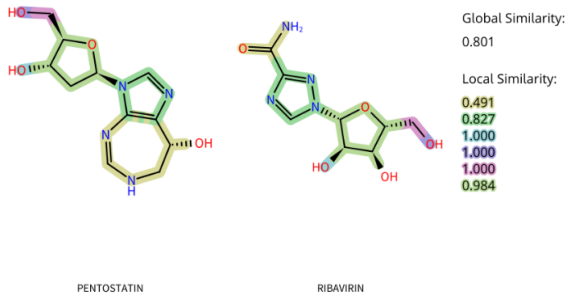
Analogue of ribavirin




## PENTOSTATIN

1991

Analogue of ribavirin




## SUCCIMER

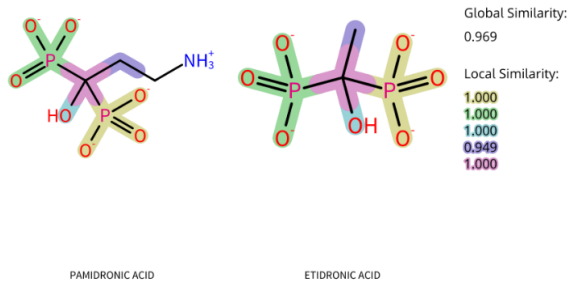
1991

Chelating agent

PAMIDRONIC ACID

1991

Analogue of etidronic acid




From the discoverer(s):

"The bisphosphonates, in the past erroneously called diphosphonates, have been known to chemists since the middle of the 19th century, the first synthesis dating back to 1865 in Germany. Their use was industrial (mainly in the textile, fertilizer and oil industries) and, because of their property of inhibiting calcium carbonate precipitation, as preventors of scaling. Our knowledge of the biological characteristics of bisphosphonates dates back 30 years, the first report about them, actually by the present author's group, having been presented in 1968. The concept was derived from earlier studies in our laboratory on inorganic pyrophosphate, in which it was found that plasma and urine contained compounds inhibiting calcium phosphate precipitation *in vitro* and it was found that part of this activity was due to inorganic pyrophosphate, a substance that had not been described previously in these fluids. We then found that pyrophosphate also inhibited calcium phosphate dissolution *in vitro*. *In vivo*, this compound prevented ectopic calcification but had no effect on normal mineralization and on bone resorption, possibly because it was destroyed locally by phosphatases. This prompted us to look for analogs of pyrophosphate that were not destroyed enzymatically. The bisphosphonates fulfilled these conditions(*395*)."

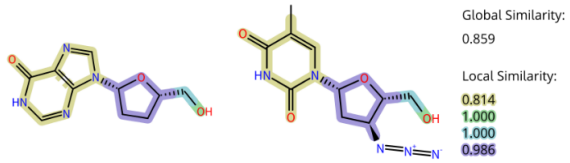
From an early article of the discoverer(s):

"Various diphosphonates were found to inhibit vitamin D3-induced calcification of the aorta and the kidney of rats. In addition, these diphosphonates also inhibit the dissolution of apatite crystals in vitro and inhibit bone resorption both in tissue culture and in living animals. We have now shown that dichloromethylenediphosphonate ($Cl_2MDP$), with the structure shown, prevents immobilization osteoporosis induced experimentally in rats(*396*)."

DIDANOSINE

1991

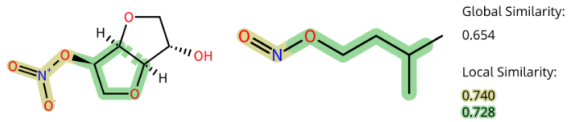
Analogue of zidovudine(*21*)




ISOSORBIDE MONONITRATE

1991

Analogue of Isoamyl nitrite(*21*)




OCTOCRYLENE

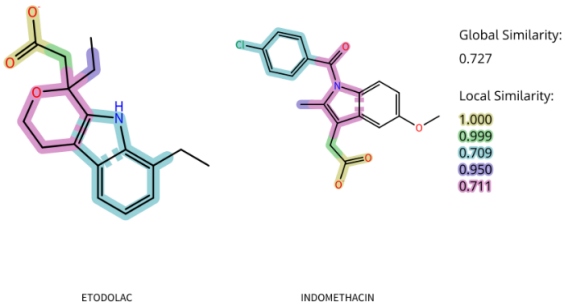
1991

"Octocrylene is a compound often used as an additive in sun screen, and is thought to have skin moisturizing effects because of its emollient properties(*1*)."

## ETODOLAC

1991

Analogue of indomethacin(*21*)




## CLARITHROMYCIN

1991

Analogue of erythromycin(*21*)

Error in similarity calculation by FTrees because of the unsupported macrocycle

## SARGRAMOSTIM

1991

"Sargramostim is a human recombinant granulocyte macrophage colony-stimulating factor (GM-CSF) expressed in yeast. It is a glycoprotein that is 127 residues. Substitution of Leu23 leads to a difference from native protein(*2*)."

## FILGRASTIM

1991

"Filgrastim is a recombinant, non-pegylated human granulocyte colony stimulating factor (G-CSF) analog(*2*)."

## BERACTANT

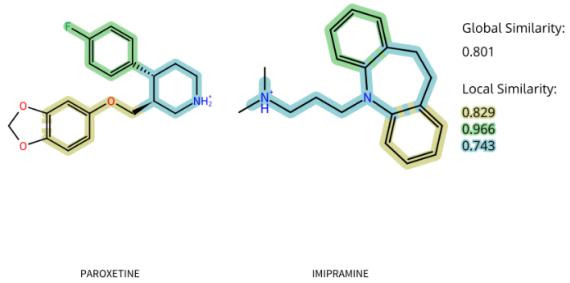
1991

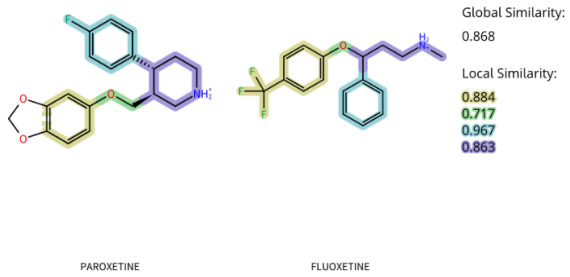
"Beractant is a pulmonary surfactant used for the treatment of Respiratory Distress Syndrome (RDS) in premature infants. Considered a natural source of surfactant as it is made from bovine lung extract, beractant contains a mixture of phospholipids, neutral lipids, fatty acids, and surfactant-associated proteins such as SP-B and SP-C(*2*)."

## PAROXETINE

1992

Analogue of fluoxetine

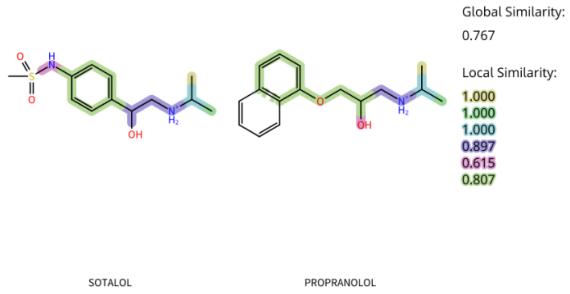



## SOTALOL

1992

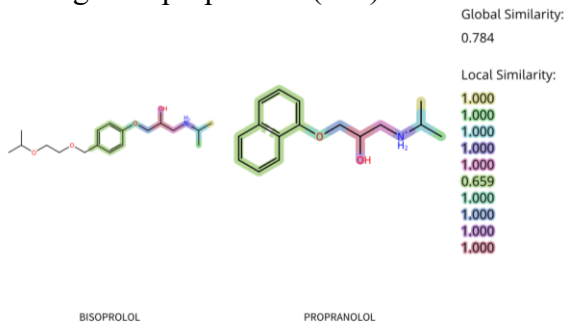
Analogue of propranolol(*21*)




## BISOPROLOL

1992

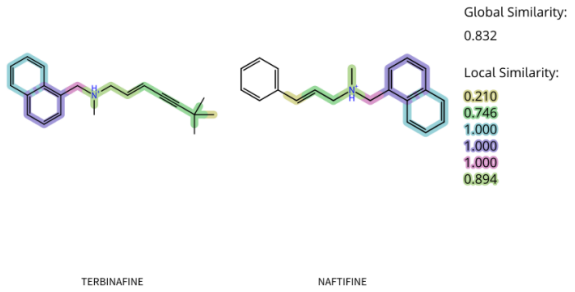
Analogue of propranolol(*253*)



## TERBINAFINE

1992

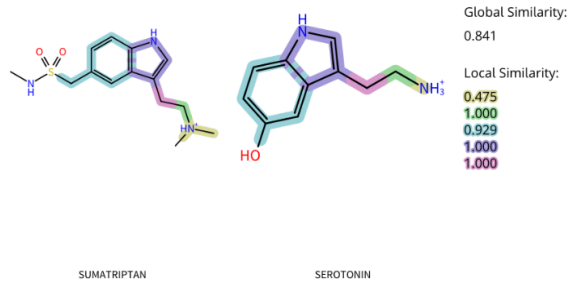
Analogue of naftifine




## SUMATRIPTAN

1992

From the discoverer(s):




"Our early research focus was on the perceived involvement of serotonin in the pathophysiology of migraine, with the weight of evidence at that time on the possibility of a causative involvement of serotonin depletion from blood platelets leading to loss of cranial vascular tone. Regardless, vasoconstrictor agents, including serotonin, had been shown to work in alleviating migrainous headaches in a number of clinical settings. In the 1960s, Lance's research team confirmed an earlier observation of Kimball and colleagues that intravenously infused 5-hydroxytryptamine(serotonin) was effective in alleviating the pain of migraine, albeit very aware that its side effects made its therapeutic use totally impractical. More than a decade later, our research team at Glaxo, in England, set about trying to find the serotonin receptor type responsible for serotonin's beneficial effect. Our research led us to identify a then unknown serotonin receptor type (now called 5-$HT_{1B}$) that is largely located in cranial rather than peripheral blood vessels. We then went on to design novel agonists that specifically stimulated these receptors to produce selective vasoconstriction of cranial vessels, such as meningeal arteries, which can become distended and inflamed(*397*)."

"Eventually we found this compound, sumatriptan, which is structurally similar to 5-HT, but a small modification to the molecule is enough to change its pharmacology radically, so that sumatriptan is remarkably selective for the 5-$HT_1$ receptor. It does not activate the 5-$HT_2$ through to 5-$HT_7$ receptors, and even within the 5-$HT_1$ subgroup it only activates some subtypes. It constricted excised intracranial blood vessels just like 5-HT, yet did not constrict blood vessels from the legs, the gut or even from the heart. As we now know, the latter contain predominantly 5-$HT_2$ but not 5-$HT_1$ receptors.

Well, that is all very well in isolated tissues, but we had to find out what happened in the whole animal. Pramod Saxena played a major part in teaching Wasyl Feniuk and I the use of radio-labelled microspheres to measure blood flow in all the organs of the body in one experiment. In the cat we found that ergotamine at low doses, say 30 µg/kg, led to an increase in resistance in every vascular bed, including the brain, whereas sumatriptan, even with the huge dose of 1 mg/kg, had no effect on the heart, brain or kidney vasculature(*398*)."

"So we set out to make an analog of 5-HT that would selectively stimulate the 5-$HT_1$ receptor. To some extent we were lucky that it did not stimulate all these other 5-HT receptor types that were identified later at the molecular level. So, we developed sumatriptan, which is a relatively simple analog of 5-HT, but remarkably selective for the 5-$HT_{1B}$ receptor(*399*)."

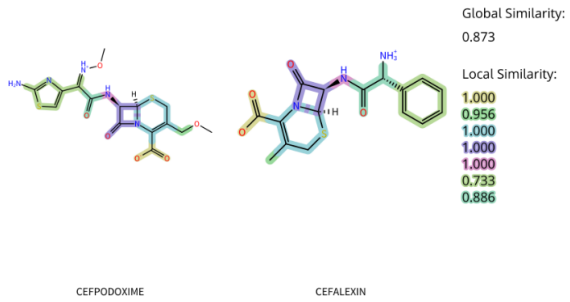
From the discovery paper:

1. “We describe the actions of a novel and selective 5-$HT_1$-like receptor agonist, GR43175, in a range of isolated tissue preparations containing different 5-hydroxytryptamine (5-HT) receptor types.
2. GR43175 was a potent agonist at 5-$HT_1$-like receptors mediating contraction of the dog isolated saphenous vein and also at those inhibiting neuronally mediated contractions in the same preparations. For both actions, GR43175 was approximately four times weaker than 5-HT.
3. GR43175 was devoid of agonist properties at 5-$HT_1$-like receptors mediating relaxation of the cat isolated saphenous vein.
4. GR43175 was devoid of agonist properties at 5-$HT_2$ receptors mediating contraction of the rabbit isolated aorta, pig coronary artery, greyhound coronary artery and beagle femoral artery.
5. GR43175 was devoid of agonist properties at 5-$HT_3$ receptors mediating depolarization of the rat isolated vagus nerve.
6. The contractile response to GR43175 in the dog isolated saphenous vein was selectively antagonized by methiothepin but was resistant to antagonism by the 5-$HT_2$ receptor blocking drug ketanserin and the 5-$HT_3$ receptor blocking drug MDL 72222. Methiothepin antagonized the contractile action of 5-HT and GR43175 to an equal extent suggesting that both agonists act at the same receptor.
7. The results demonstrate that GR43175 is a highly selective agonist for the 5-$HT_1$-like receptors found in the dog saphenous vein. The absence of an action of GR43175 at 5-$HT_1$-like receptors mediating relaxation of the cat isolated saphenous vein provides further evidence that 5-$HT_1$-like receptors are heterogeneous(*400*).”

## CEFPODOXIME

1992

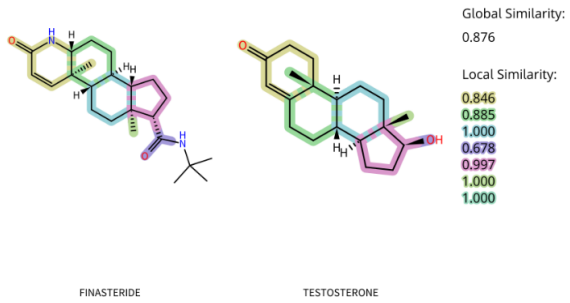
Analogue of cefalexin




## FINASTERIDE

1992

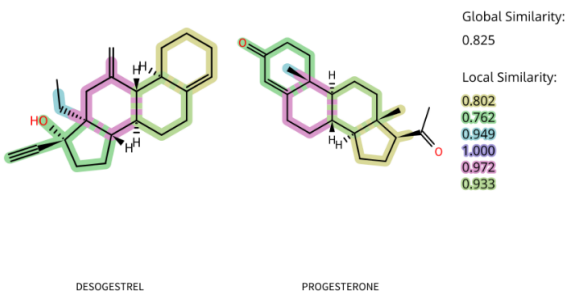
Analogue of the endogenous testosterone




## DESOGESTREL

1992

Analogue of progesterone(*21*)




## ALDESLEUKIN

1992

“Aldesleukin, a lymphokine, is produced by recombinant DNA technology using a genetically engineered E. coli strain containing an analog of the human interleukin-2 gene(*2*).”

## PACLITAXEL

1992

From the discoverer(s):

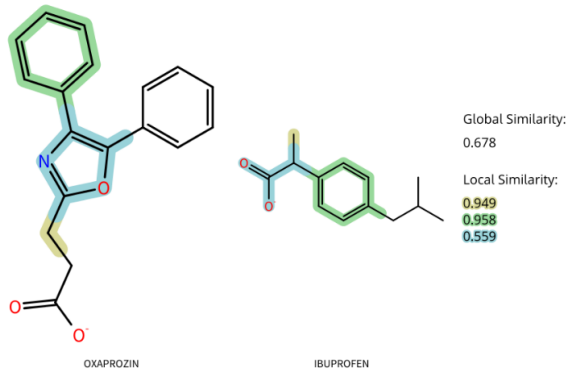
"A screening program for antitumor agents in the plant kingdom was initiated in 1960 under Dr. Jonathan L. Hartwell of the National Cancer Institute (NCI). Plant samples collected at random were supplied to the NCI by the U.S Department of Agriculture (USDA) under an interagency agreement. In August 1962, USDA botanist Arthur S. Barclay, Ph.D., and three college student field assistants collected 650 plant samples in California, Washington, and Oregon, including bark, twigs, leaves, and fruit of Taxus *brevifolia* (Pacific or Western Yew) in Washington State. *T. brevifolia* is a slow growing tree which is found primarily in the coastal areas of the Northwest of the United States. Potential medicinal properties of the plant had never been investigated. The assignment of the plant to the Research Triangle Institute (RTI) International by Dr. Hartwell was not entirely serendipitous. When the original cytotoxicity tests were conducted with crude extracts by NCI contractors, some of the samples demonstrated cytotoxicity against 9KB cell cultures that had been derived from a human cancer of the nasopharynx. Drs. Wall and Wani, medicinal chemists who worked at RTI International, had noted an excellent correlation between L1210 (lymphoid leukemia in mice) in vivo activity and the 9KB cytotoxicity assay when studying camptothecin. Accordingly, they had requested Dr. Hartwell to assign to them as many 9KB active plant extracts as possible. […]

approximately 0.5 g of Taxol® was isolated starting with 12 kg of air dried stem and bark from *T. brevifolia*. The yield was approximately 0.004%. All the various steps were monitored by an *in vivo* bioassay which involved the inhibition of the solid tumor known as Walker-256 intramuscular rat carcinosarcoma. [...], increased purification was accompanied by increased antitumor activity at lower doses(*401*)."

## OXAPROZIN

1992

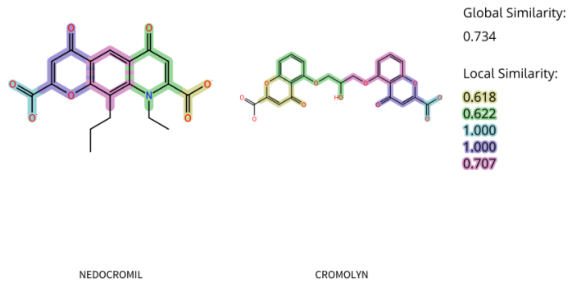
Analogue of ibuprofen(*21*)




## NEDOCROMIL

1992

Analogue of cromolyn

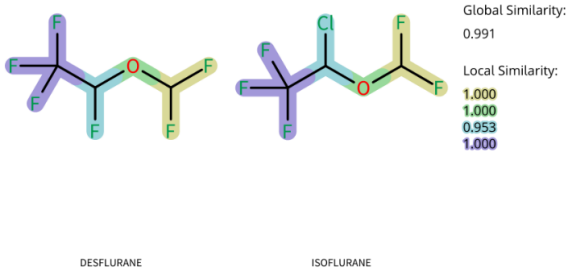



## DESFLURANE

1992

Analogue of isoflurane(*269*)

See the isoflurane entry.




## RIFABUTIN

1992

Analogue of rifampin

Error in similarity calculation by FTrees because of the unsupported macrocycle

ATOVAQUONE

1992

From the discoverer(s):

"In 1946, it was noted that certain 2-hydroxy-3-alkyl-naphthoquinones inhibited the respiratory processes of *Plasmodium* species. Subsequently, these findings were substantiated by Fieser and his collaborators, though no drug suitable for human use was discovered. A variety of naphthoquinones were also found to have activity against other protozoa, including trypanosomes, *Theileria parva*, *Toxoplasma* spp., and certain *Eimeria* and *Plasmodium* species. Hydroxynaphthoquinones block protozoal respiratory chain electron transport at complex III, probably by functioning as analogs of ubiquinone. […]

The studies to be described here represent a collaborative effort of investigators at St. Jude Children's Research Hospital in Memphis, Tenn., and the Wellcome Research Laboratories in Beckenham, United Kingdom. The hydroxynaphthoquinone 566C80 was under development at Wellcome as an antimalarial drug, and studies were in progress at St. Jude to identify new compounds effective against *P. carinii.* One of the Beckenham investigators (W.E.G.) suggested that 566C80 be tested in the St. Jude laboratory for efficacy, since *P. carinii* has been found to be susceptible to certain drugs with antiprotozoal activity. After demonstration of efficacy in the initial animal studies at St. Jude, similar studies were done at Wellcome for confirmation. Subsequently, these studies were expanded in both laboratories(*402*)."

From the discoverer(s):

"The compound 566C80, which is in development by the Wellcome Research Laboratories, has shown particular promise as a potential anti-malarial agent. It exhibits potent blood schizontocidal activity against *P. falciparum in vitro* and in *Aotus* monkeys and also against *P. yoelii* in mice. Furthermore, it has been shown to be active against chloroquine, pyrimethamine and mefloquine resistant strains of *P. yoelii* and *P. berghei*. Good causal prophylactic properties have been demonstrated against the liver or exo-erythrocytic (EE) stages of *P. berghei* in rats. In contrast to earlier compounds from this class which exhibited disappointing activity in human clinical trials, 566C80 is metabolically stable and orally bioavailable in man. […]

The present study extends our previous observations of the activity of 566C80 against the EE stages of *P. berghei* in which we demonstrated *in vivo* the ability of the drug to prevent or delay the appearance of the erythrocytic forms generated by rupture of the liver forms (Davies et al. 1989 a). […]

In the present study *in vitro* cultures of *P. berghei* liver stages in HepG2 cells were employed to carry out a quantitative examination of the influence of 566C80 on exo-erythrocytic development(*403*)."

I could not find the full-text of two relevant papers: PMIDs: 2489391, 20999490

ZOLPIDEM

1992

From the patent disclosing it:

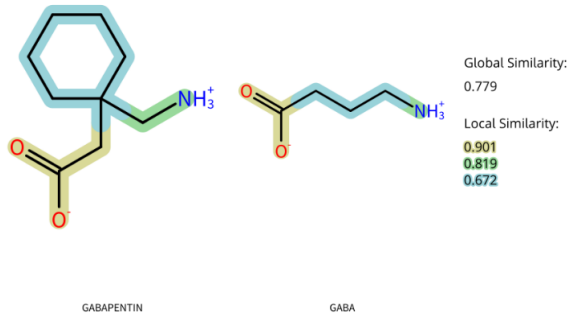
"The anxiolytic activity was determined according to the eating test. In this test, the doses which increases the food consumption of the mice vary from 0.1 to 10 mg/kg, administered intraperitoneally. […]

The sedative or hypnotic activity was determined by observing the action of the compounds on the EEG of curarised rats and also on the wake-sleep states in freely moving, implanted rats and cats(*404*)."

## GABAPENTIN

1993

Analogue of GABA



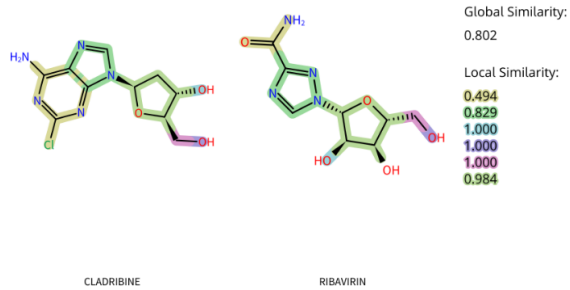

"A strategy common to the design of all of these compounds was to manipulate the molecule of GABA so as to increase its lipophilicity and thereby allow it to gain access to the CNS. This principle was applied in perhaps its most simple and elegant form in the design of anticonvulsant agent gabapentin wherein the third carbon atom of GABA is incorporated into a cyclohexane ring(*405*)."

"Gabapentin is an anticonvulsive medication which first discovered in the 1970s in Japan. Its original use was as a muscle relaxer and anti-spasmodic medication, but later, it was discovered the potential of the medication as anticonvulsive medication and as an adjunct to stronger anticonvulsants(*406*)."

## CLADRIBINE

1993

Analogue of ribavirin




## STRONTIUM CATION SR-89

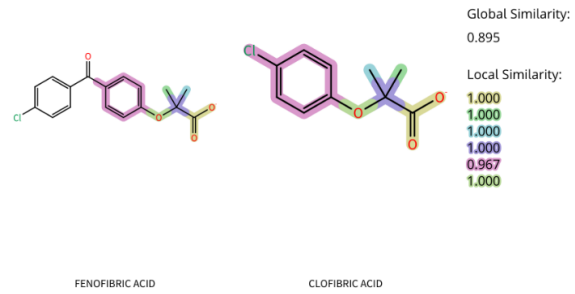
1993

Inorganic

## FENOFIBRIC ACID

1993

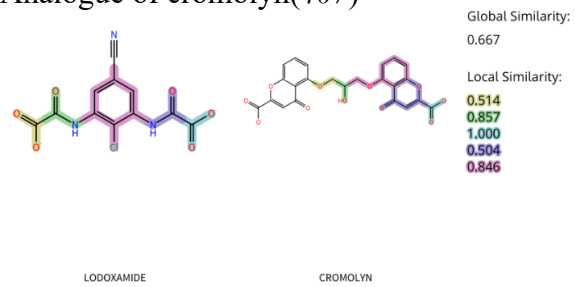
Analogue of clofibrate(*21*)

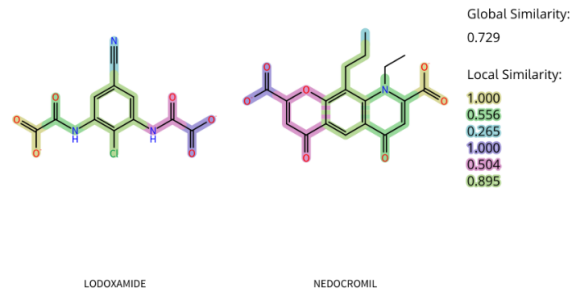



## LODOXAMIDE

1993

Analogue of cromolyn(*407*)

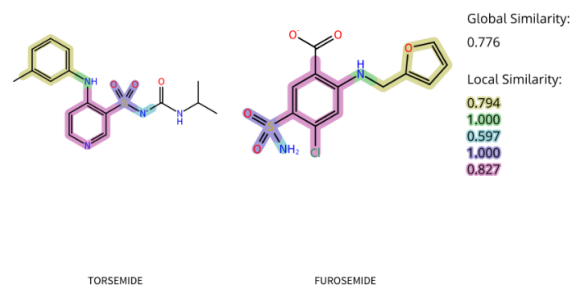



## TORSEMIDE

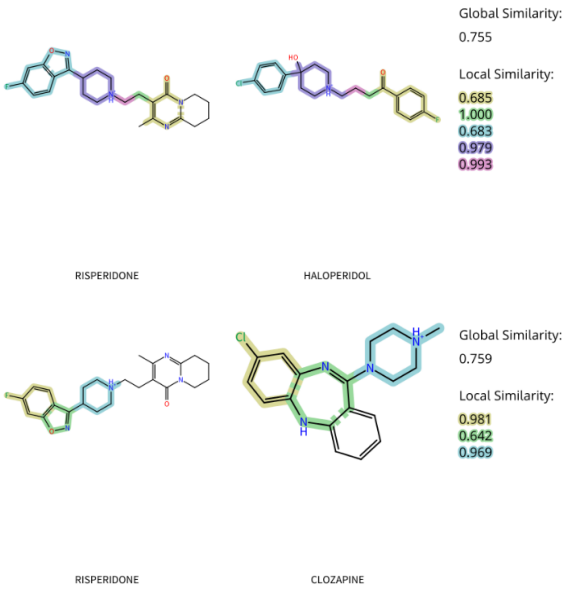
1993

Analogue of furosemide



RISPERIDONE

1993




From one of the members of the discovering laboratory:

"In stark contrast to the then-prevailing wisdom, and igniting a controversy that would simmer for decades, we suggested that this technology no longer measured the state-dependence of memory. Instead, it provided a measurement of the ability of animals to discriminate between the subjective experiences induced by one pharmacological treatment as opposed to another, and the new technology was named Drug Discrimination (DD).

In a typical DD experiment, rats are initially trained to press one of two levers in order to obtain food. Thereafter, discrimination training is instituted; before the session, the animal is injected with either drug or saline. On drug days, pressing only the left lever is rewarded; on saline days, pressing only the right lever is rewarded. After a number of discrimination training sessions, rats learn to perceive the 'subjective' effects of the drug, determine the difference from (that is, discriminate those from) saline injection, and choose the appropriate lever. By this lever choice, the rats categorically indicate whether they received the training drug; in an analogy to quantum physics, this categorical choice arguably constitutes an elementary particle of behaviour(*408*)."

"With the DD analysis of partial receptor activation in mind, these data led us to the hypothesis that the discriminative effects of LSD arise from a low and narrow range of 5-HT receptor activation. The data also made us realise that no available agent was capable of adequately blocking LSD's subjective effects, and provided the impetus to devise a drug discovery strategy that molecular pharmacology also adopted decades later. We and others had long been aware of the 5-HT antagonist activity that DA-antagonist antipsychotic agents also exert, but a 'clinical correlate of this activity in schizophrenia [remained] unknown.'

These 5-HT-antagonist properties were measured, *in vivo*, by the agents' ability to counteract tryptamine-induced convulsions in the rat, as well as by their *in vitro* ability to displace $^{3}$H-spiperone from a binding site that had been identified as the 5-$HT_2$ receptor. After initial screening of DA antagonists using these latter two assays as measures of the 5-HT antagonist activity of DA antagonists, the hunt for a pure LSD antagonist yielded the first such compound, pirenperone. However, the kinetic features of pirenperone in humans were found to be inadequate, and in 1985 we discovered risperidone, a longer-acting benzisoxazole derivative(*408*)."

Regarding the used bioassays, from two references cited in the preceding quotation which are also affiliated with the discovering laboratory (Janssen Pharmaceutica Research Laboratories):

"These conclusions were reached from a study of the relative binding affinities of a series of serotonin or dopamine agonists or antagonists for rat frontal cortex and striatal receptors. Significant correlations were obtained between the binding activities in the

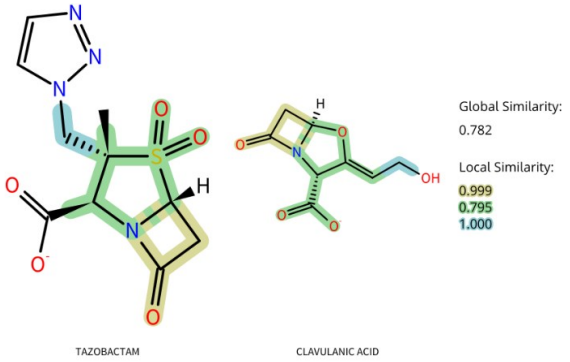
rat frontal cortex and in vivo potencies in the pharmacological anti-tryptamine test. Similarly, binding activities in the striatum were significantly correlated with the potencies in the anti-apomorphine test. We therefore suggest that serotonergic, as well as dopaminergic, receptors are involved in the mechanism of action of neuroleptic drugs(*409*)."

"The selected compounds belong to different chemical classes. They have been studied in rats and dogs over a large dose range and at different time intervals in a series of standardized tests, covering a variety of pharmacological activities. In rats: apomorphine, amphetamine, tryptamine, norepinephrine and compound 48/80 antagonism; inhibition of conditioned reactions and intracranial self-stimulation; cataleptogenic, palpebral ptosis-inducing and anticholinergic properties; oestrus delay and acute toxicity. In dogs: antagonism of apomorphine-induced emesis by different routes of administration and inhibition of conditioned reactions. In these different tests, various methods of evaluation were applied, but for each test an 'all or none' criterion was adopted, according to which less than 5 % false positives occurred among the control population. Based on these criteria, ED50 values and 95 % confidence limits were calculated(*410*)."

## TAZOBACTAM

1993

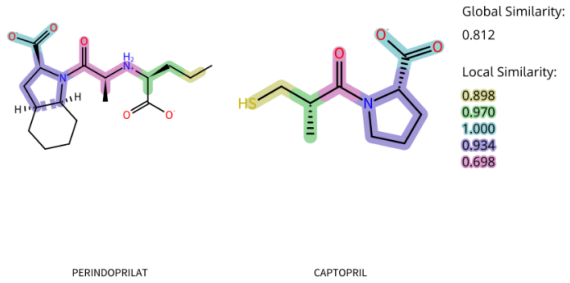
Analogue of clavulanic acid(*21*)




## PERINDOPRILAT

1993

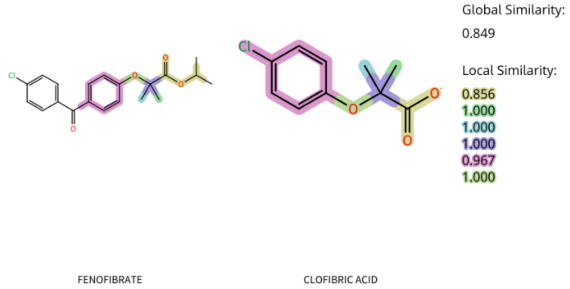
Analogue of captopril(*21*)




## FENOFIBRATE

1993

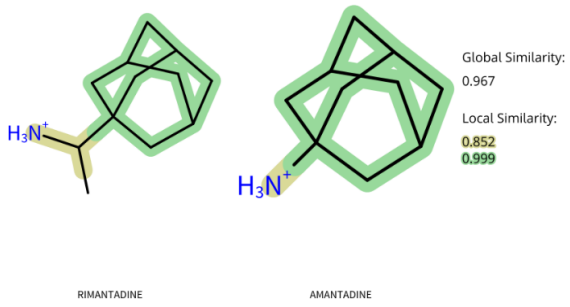
Analogue of clofibrate(*21*)




## RIMANTADINE

1993

Analogue of amantadine




## DORNASE ALFA

1993

"Dornase alfa is a biosynthetic form of human deoxyribunuclease I (DNase I) enzyme(*2*)."

## GADODIAMIDE

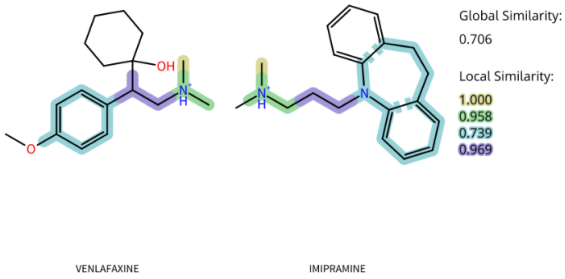
1993

Contrast agent

VENLAFAXINE

1993

Analogue of fluoxetine



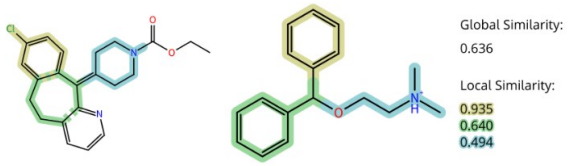

From the discoverer(s):

"**Identification of an Early Lead (WY-44362)** With the goal of identifying an antidepressant drug with a faster onset of action we initiated a medicinal chemistry program to identify reuptake inhibitors of both 5-HT and NE (serotonin/norepinephrine reuptake inhibitors, SNRIs). The program evolved from investigations into the mixed opiate agonist–antagonist analgesic ciramadol. In an effort to simplify the structure of ciramadol by removing two of its chiral centers, we translocated the hydroxyl group to give WY-44053. This compound displayed no analgesic activity *in vivo*. Insertion of a methylene group to yield WY-44362 (11) likewise resulted in a compound with no analgesic activity. However, structural similarities between 11 and a weak antidepressant agent, gamfexine, suggested evaluation of 11 for antidepressant activity. This compound displayed both weak SRI and NRI activity *in vitro* and weak antidepressant activity *in vivo* and became the lead structure for optimization(*142*)."

LORATADINE

1993

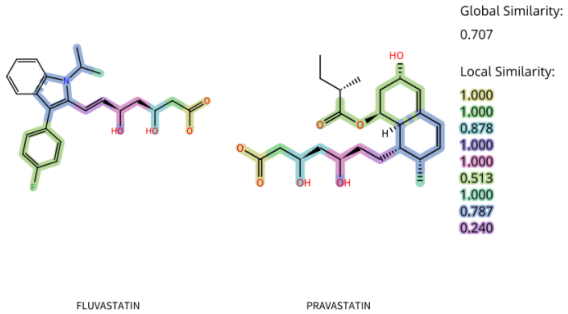
Analogue of diphenhydramine(*21*)




FLUVASTATIN

1993

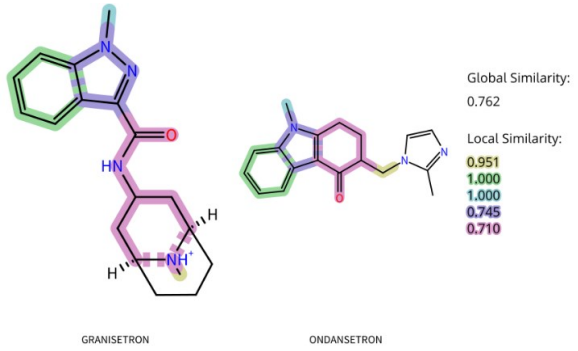
Analogue of lovastatin(*21*)



## GRANISETRON

1993

Analogue of ondansetron




Also see the ondansetron entry.

From the discovery paper:

From the discoverer(s):

"As a result sf our experiments, we developed BRL 43694 (granisetron), a highly potent and selective 5-$HT_3$ receptor antagonist and antiemetic agent. Other 5-$HT_3$ receptor antagonists (ICS 205-838, GR 38032F), originally developed for other indications, were also shown to have antiemetic properties(*385*)."

From the discovery paper:

The rationale for the design and selection of the compound is not mentioned, yet its effect on the following assays are reported(*386*):

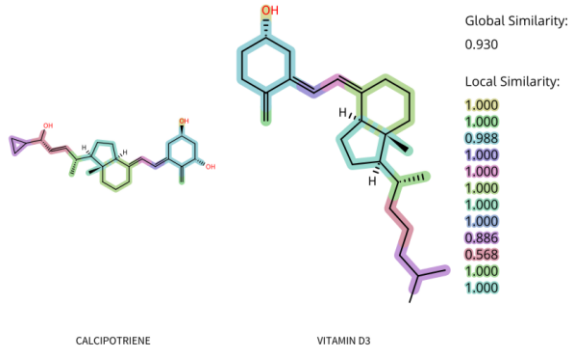
- ✓ Isolated gastrointestinal tissues
  - guinea-pig ileum
  - rat forestomach
  - human stomach
- ✓ potentiation of electrically evoked contractions caused by 5-HT
- ✓ Antagonism by BRL 43694 of 5-HT-evoked tachycardia in rabbit isolated heart
- ✓ Antagonism by BRL 43694 of the Bezold-Jarisch reflex in anaesthetised rats

Inhibition of $^3$H-radiofigand binding to rat brain membranes *in vitro*

## CALCIPOTRIENE

1993

A synthetic vitamin D derivative




From an early paper on using vitamin D in psoriasis:

"The discovery by Dowling, Prosser Thomas and Charpy of the treatment of lupus vulgaris with high doses of vitamin D2, suggested that other skin diseases responsive to heliotherapy, such as acne and psoriasis, might benefit by similar treatment.

A few cases of indurated acne so treated proved disappointing, an initial improvement being soon followed by recurrence.

Psoriasis promised better response. In America Krafka, Ceder and Zon, Brunsting, and Clarke, treated psoriasis with vitamin D, partly with encouraging results(*411*)."

From the discovery paper of the effect of vitamin D on lupus vulgaris cited in the previous quotation:

"We are presenting these cases of lupus vulgaris because of their good response to the oral administration of calciferol as virtually the only form of treatment. We have been treating lupus with calciferol since 1943. Including the six cases shown here to-day, we now have records of thirty-eight lupus patients who are being treated exclusively with

calciferol or being followed up after stopping it(*412*)."

ENOXAPARIN SODIUM

1993

A low molecular weight heparin(*2*)

GABAPENTIN ENACARBIL

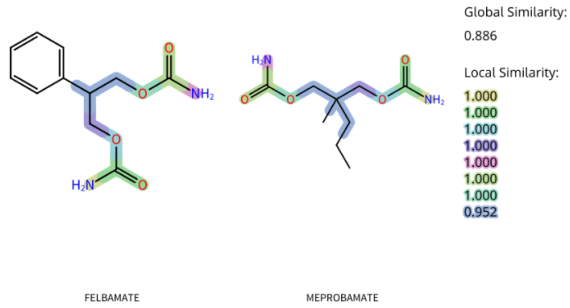
1993

Prodrug of gabapentin

FELBAMATE

1993

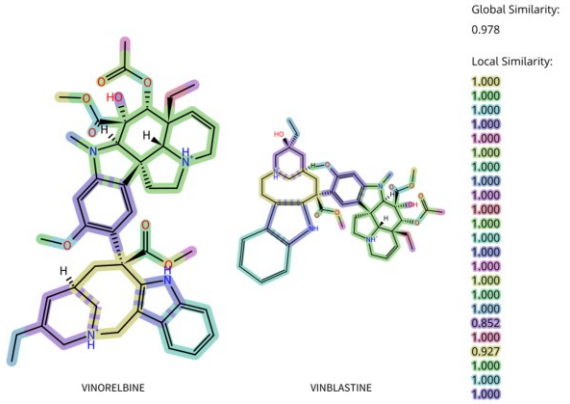
"Felbamate is a dicarbamate that is structurally similar to the antianxiety drug meprobamate(*413*)."




VINORELBINE

1994

Analogue of vinblastine




PEGASPARGASE

1994

Modified and pegylated asparaginase(*414*)

CYSTEAMINE

1994

"In spite of extensive investigations, the primary defect leading to cystine accumulation and renal failure is unknown. The accumulation of free cystine in fibroblasts cultured from cystinotic patients has provided a convenient in vitro test system for the evaluation of methods of lowering the intracellular nonprotein cystine content of these cells. Effective methods include growth in a low-cystine medium, treatment with dithiothreitol (DTT), and treatment with ascorbic acid. None of these methods has been proved effective clinically, although DTT treatment has been shown to lower the leukocyte nonprotein cystine content in vivo. This report shows the effectiveness of certain aminothiols in producing a rapid and complete depletion of nonprotein cystine from cystinotic fibroblasts without producing apparent morphological signs of cytotoxicity. The cystine released is utilized by the cell for GSH synthesis. A series of structural analogues of the aminothiol, cysteamine (2-aminoethanethiol), have been investigated and allow some tentative conclusions on the relative effectiveness of these compounds in depleting cystine from cystinotic fibroblasts. […]

Known standards included taurine, cysteic acid, GSH-NEM, cysteine-NEM, cystine, methionine, cysteamine-NEM, the mixed disulfide of cysteamine and cysteine, and cystamine. […]

At a concentration of 1 mM, cystamine, the disulfide of cysteamine, is equally as effective as cysteamine in producing intracellular nonprotein cystine depletion from cystinotic fibroblasts. […]

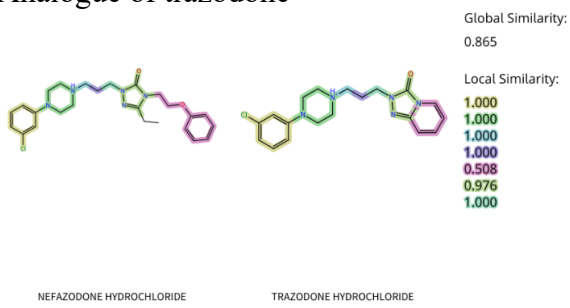
Table I lists analogues of cysteamine and their effect on the intracellular nonprotein cystine content of cystinotic cells, along with the effect of selected compounds on L-cystine in a simple cell-free chemical

reaction(*415*)."

## NEFAZODONE HYDROCHLORIDE

1994

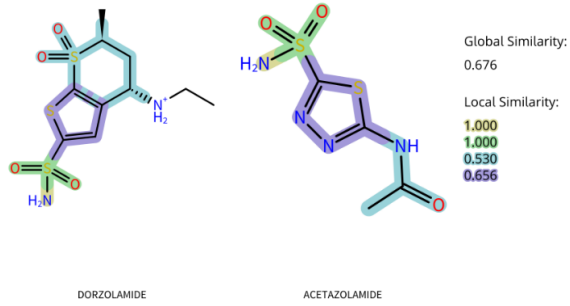
Analogue of trazodone




## DORZOLAMIDE

1994

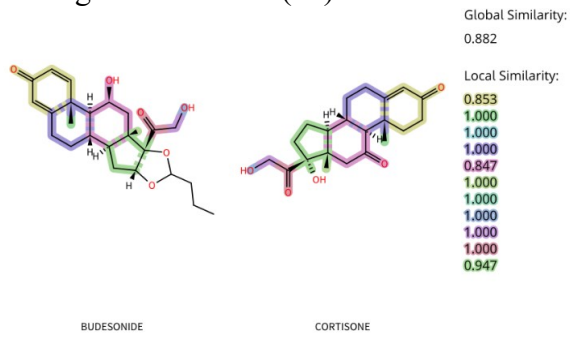
Analogue of acetazolamide




## BUDESONIDE

1994

Analogue of cortisone(*21*)




## TACROLIMUS

1994

Analogue of sirolimus

Error in similarity calculation by FTrees because of the unsupported macrocycle

## LAMOTRIGINE

1994

"Discovery and development of lamotrigine for bipolar disorder: A story of serendipity, clinical observations, risk taking, and persistence […]

The phenyltriazine lamotrigine was originally synthesized by scientists at Wellcome Laboratories in response to an unmet need for antiepileptic drug (AED) treatments with improved safety profiles and wider therapeutic indices (Risner,2001). At the time it was first synthesized in the early 1980s, no new drugs had been successfully developed for the treatment of epilepsy for over thirty years. Based on evidence dating from the mid-1960s that folate was proconvulsant and the suggestion that many AEDs in use at the time were folic acid antagonists, a rational drug discovery program was initiated with pyrimethamine, a drug previously developed for the treatment of malaria. Among the series of compounds developed, lamotrigine was found to have considerable anticonvulsant activity in animal models, although it ultimately proved to be only a weak inhibitor of dihydrofolate reductase. […]

The early epilepsy clinical trials also provided a signal of potential clinical utility outside of epilepsy, in the form of improved mood and communicativeness of patients receiving lamotrigine treatment. This was reminiscent of earlier observations with other anticonvulsants, especially valproate and carbamazepine, which had originally led to the suggestion that AEDs might be useful in the treatment of bipolar disorder. […]

The first recorded use of lamotrigine in bipolar disorder, presented at the 1994 annual meeting of the American Psychiatric Association provides an interesting example of serendipity and clinical observation in drug development(*416*)."

## IOBENGUANE I-131

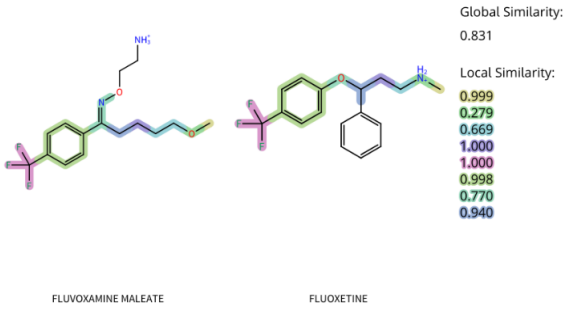
1994

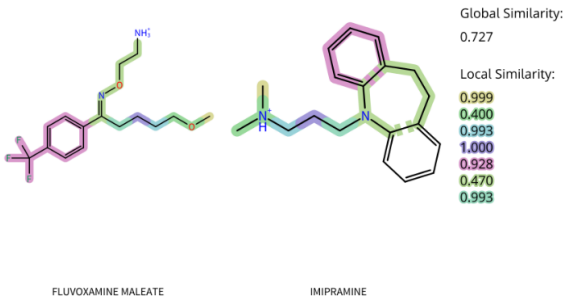
Radiopharmaceutical

FLUVOXAMINE MALEATE

1994

Analogue of fluoxetine

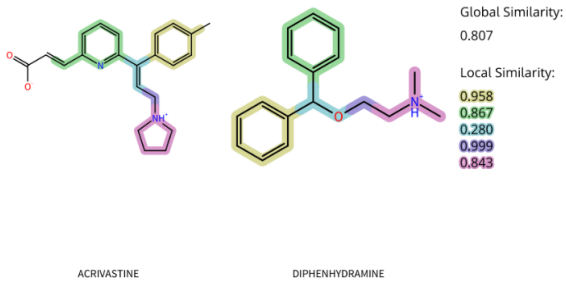



ACRIVASTINE

1994

Analogue of diphenhydramine(*21*)




IMIGLUCERASE

1994

Human Beta-glucocerebrosidase or Beta-D-glucosyl-N-acylsphingosine glucohydrolase(*2*)

ABCIXIMAB

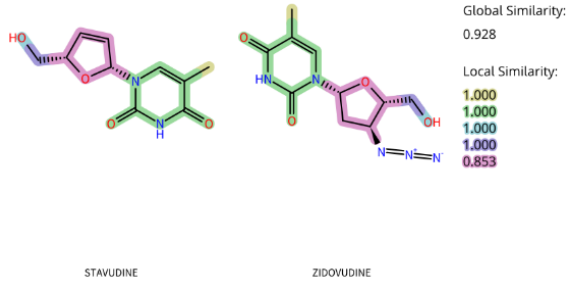
1994

Monoclonal Antibody

STAVUDINE

1994

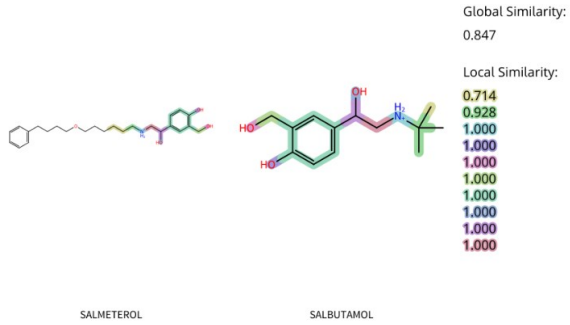
Analogue of zidovudine(*21*)




SALMETEROL

1994

Analogue of salbutamol(*21*)




FLUDEOXYGLUCOSE F-18

1994

Radiopharmaceutical

TECHNETIUM TC-99M BICISATE

1994

Radiopharmaceutical

DALTEPARIN SODIUM

1994

A low molecular weight heparin(*2*)

IOPROMIDE

1995

Contrast agent

DEXRAZOXANE HYDROCHLORIDE

1995

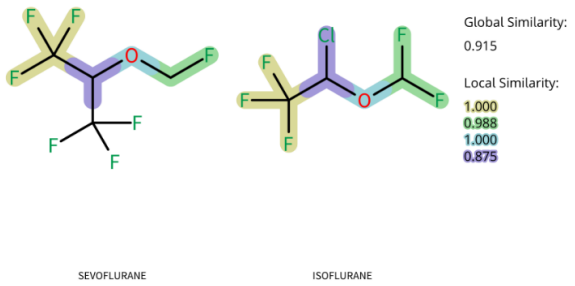
Contrast agent

SEVOFLURANE

1995

Analogue of isoflurane(*269*)

Refer to the isoflurane entry.




CISATRACURIUM

1995

"Chance, coincidence and atracurium […] Tubocurarine is now known to have a monoquaternary structure, but research in the 1940s erroneously suggested a bisquaternary structure. That error fortuitously focused the attention of chemists on compounds with two or more quaternary centres, leading to the rapid appearance of gallamine, decamethonium and then suxamethonium. […]

With tubocurarine still believed to have a bisquaternary structure, literature data on the relationship between its stereochemistry and potency was anomalous. Investigating this problem, the Glasgow team examined two simple monoquaternary compounds, l- and d-laudanosine methiodides, which are structurally related to the component moieties of the tubocurarine stereoisomers. […]

On his arrival in Glasgow in 1952, Professor Stenlake had been given responsibility for a project to isolate an alkaloid from the tubers of a Mediterranean plant. By a strange coincidence, the alkaloid was identified as a simple benzylisoquinoline quaternary salt closely related to the laudanosine methiodides. More significantly, the alkaloid was easily degraded in mild alkali at ambient temperature by the Hofmann elimination pathway — which usually requires strong alkali (pH 12-14) and high temperature (100C). The alkaloid's easy degradation triggered the idea of a new type of neuromuscular blocking agent, programmed by its chemical structure to undergo Hofmann elimination at physiological pH (7.4) and body temperature (37C)(*417*)."

It seems that the series was tested using vagal and neuromuscular tissues(*418*):

"Coincidentally he was also responsible for the research into an alkaloid from the tubers of a Mediterranean plant. This alkaloid was a simple benzylisoquinoline quaternary salt and was found to degrade in mild alkali by Hofmann elimination, a process which normally requires a strong alkali and a high temperature. This discovery triggered the idea for a new muscle relaxant which would undergo Hofmann elimination at physiological pH and body temperature.

Professor Stenlake's objective was to synthesize a bisquaternary compound with competitive action, high potency and selectivity which was degraded by Hofmann elimination within the body at an appropriate rate. In retrospect these were very specific goals which one would imagine posed quite a challenge. Stenlake investigated four series of compounds and found a suitable candidate in the fourth series, only the eighteenth compound they had tested. 18A, as it was known, showed promising separation between vagal blocking and neuromuscular blocking doses(*418*)."

From a discovery paper:

"It is one of a series of non-depolarising neuromuscular blocking agents designed to induce ready fragmentation to inactive moieties *in vivo* by a combination of enzymic ester hydrolysis and facile base-catalysed

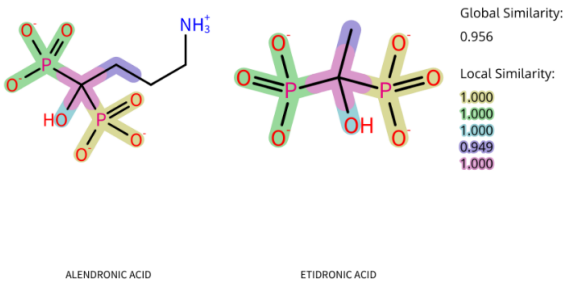
degradation of its quaternary ammonium groups initiated at physiological pH(*419*).”

I could not find an article cited in the previous quotation and authored by the discoverer(s) which seems to be helpful for obtaining a detailed report of the discovery (PMID: 6688014).

## ALENDRONIC ACID

1995

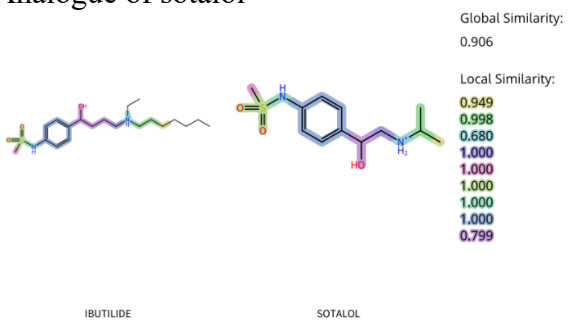
Analogue of etidronic acid(*21*)




## IBUTILIDE

1995

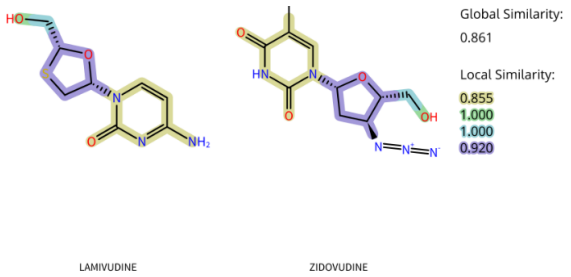
Analogue of sotalol




## LAMIVUDINE

1995

Analogue of zidovudine(*21*)




## METFORMIN

1995

“Its history is linked to *Galega officinalis* (also known as goat’s rue), a traditional herbal medicine in Europe, found to be rich in guanidine, which, in 1918, was shown to lower blood glucose. Guanidine derivatives, including metformin, were synthesised and some (not metformin) were used to treat diabetes in the 1920s and 1930s but were discontinued due to toxicity and the increased availability of insulin. Metformin was rediscovered in the search for antimalarial agents in the 1940s and, during clinical tests, proved useful to treat influenza when it sometimes lowered blood glucose. This property was pursued by the French physician Jean Sterne, who first reported the use of metformin to treat diabetes in 1957. […]

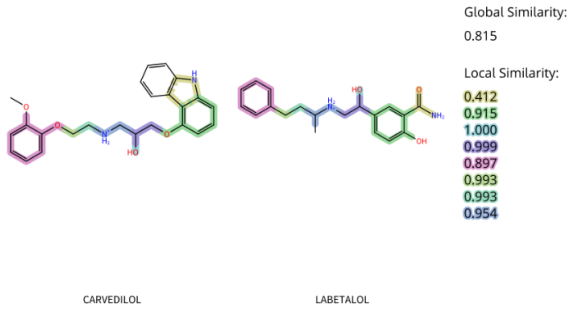
The herbal lineage of metformin can be traced from the use of *Galega officinalis* (a.k.a. goat’s rue, French lilac, Italian fitch, Spanish sainfoin or professor weed) as a traditional medicine in medieval Europe. Also known as *Herba rutae caprariae* in some herbals, *G. officinalis* was ascribed benefits against worms, epilepsy (‘falling-sickness’), fever and pestilence in *Culpeper’s Complete Herbal* of 1653, whilst in 1772, John Hill recommended *Galega* to treat conditions of thirst and frequent urination. In Europe, wild *G. officinalis* was widely recognised as an animal galactagogue from which it gained its name (‘*Galega*’ being derived from the Greek for ‘milk stimulant’). The plant was introduced into North America in 1891 and is now classed as a noxious weed in many states of the USA. Chemical analyses of *G. officinalis* dating from the mid-1800s found the plant to be rich in guanidine and related compounds, especially the immature seed pods. In 1918, guanidine was reported to reduce blood glucose in animals, and during the 1920s several mono-guanidine derivatives, notably galegine (isoamylene guanidine) and

diguanidines, such as synthalin (two guanidines separated by a methylene chain), were also shown to lower blood glucose in animals. This led to the introduction of galegine and the more potent synthalin in diabetes treatment(*420*)."

## CARVEDILOL

1995

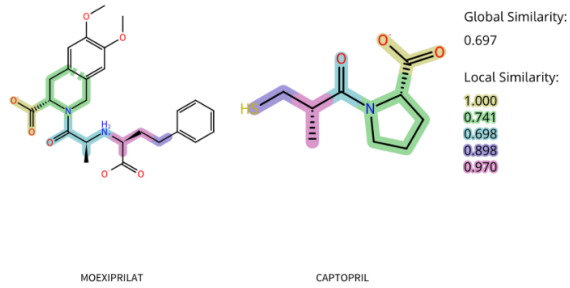
Analogue of labetalol(*21*)




## MOEXIPRILAT

1995

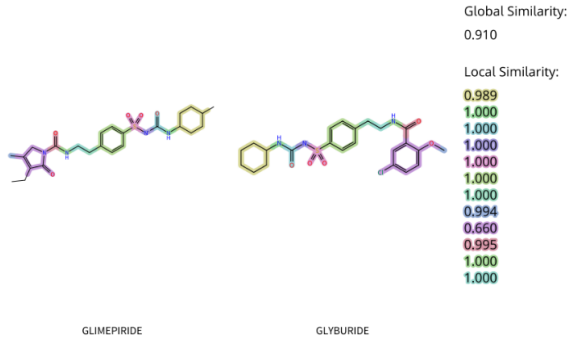
Analogue of captopril(*21*)




## GLIMEPIRIDE

1995

Analogue of glyburide(*21*)

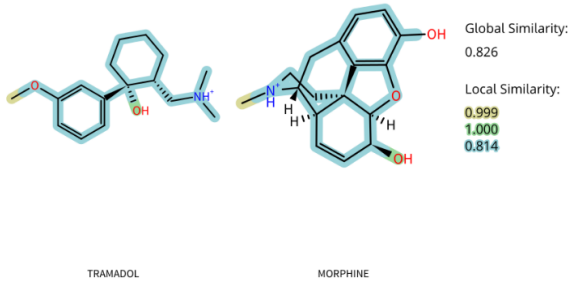



## TRAMADOL

1995

Analogue of morphine(*21, 421*)

"It is 4-phenyl-piperidine analogue of opioid drug codeine. It was discovered and synthesized in 1962 for the first time by German company (Grunenthal GmbH) for the treatment of pain while being introduced in the market by the name 'Tramadol' in 1977(*421*)."




## DISODIUM AZELATE

1995

"Initial discovery and recognition of the biological properties and therapeutic potential of AA lies firmly to the credit of Marcella Nazzaro-Porro, Siro Passi and their associates of the San Gallicano Dermatological Institute of Rome. Their starting-point was an academic interest in skin surface lipids and the pathogenesis of hypopigmentation in tinea versicolor. In cultures of the fungus *Pityrosporum* supplemented with unsaturated fatty acids with double bonds in the 6-12 position they observed that dicarboxylic acids of chain lengths $C_6$-$C_{12}$ were formed and that these dicarboxylic acids exhibited an ascending gradient of competitive tyrosinase inhibition in vitro. This led them to speculate that such dicarboxylic acids might be used to treat hyperpigmentary disorders, and they decided to test one of the reasonably soluble dicarboxylic acids with an intermediate range of anti-tyrosinase activity (namely, AA) clinically.

The beneficial effect of AA on acne was first observed when a number of patients being

treated for melasma in Rome reported a coincidental improvement in their 'spots'. This unexpected development was tangential to our then-current ideas and plans, but Dr Nazzaro-Porro insisted on following it up(*422*)."

## LOSARTAN

1995

I could not locate the full-text of two papers describing the discovery of losartan from its discoverers: PMIDs: 8583479 and 8583479

"Targeting ACE to prevent the formation of Ang II and subsequent steps leading to hypertension had been more successful by the early 1980s. The first ACE inhibitor, captopril from Squibb, had been approved by the FDA in April 1981. It was evidence that interfering with RAS could lower blood pressure […]

Industry attempts over many years had resulted in a few antagonists, peptide analogues of Ang II, that were active *in vitro*, but could not be made into drugs. They lacked oral absorption and had short half-lifes – some of just a few minutes. Some even showed agonistic activity

Chiu's receptor-binding assay results of the Takeda compounds synthesised by Carini caused disappointment. They were at odds with the patents' claims. S-8307 and the other molecules did bind with the Ang II receptor, but extremely weakly […]

Responsible for testing the Takeda compound *in vivo*, he injected a large quantity (100 mg/kg) of it into a rat. In a human weighing 70 kg, it would amount to an intravenous dose of 7000 mg. As a comparison, losartan taken orally by a human only has 50 mg of the compound. Taber observed, 'It was like adding the animal to the drug instead of adding the drug to the animal'. When Wong showed others his results, the immediate reaction was of dismay at the mistake. However, Taber, himself a pharmacologist, quickly noticed, this time with amazement, that although the molecule was extremely weak, it was selective. It was evidence of the mode of action they were seeking. A drug with such selectivity would have the desired effect with probably few side effects. As the compound was extremely weak, it took a vast quantity injected directly into the rat's bloodstream to show selectivity […]

He was unaware that such an amount was unacceptably large for drug discovery. Had he known that, he would have injected the 'right' (lower) amount. They would not have found selectivity and the Takeda compounds would have been dropped. […]

Through personal conversations, one of the DuPont scientists later learned that Takeda had tried unsuccessfully to increase the potency of their compounds. After a while, they gave up and turned their attention elsewhere. Given the interest in Ang II receptor antagonists, the Takeda compounds were no doubt pursued at many other companies. In conducting their tests correctly, they would not have found any results of promise. It took a mistake to discover selectivity.

Thrilled by the results, Taber suggested directing discovery efforts at the Takeda lead to design compounds that were similarly selective, but far more potent and which could be taken orally. […]

Carini began synthesising a series of structural variants of S-8307. […]

Duncia began by synthesising a couple of simple analogues and then moved to computer modelling to take a more rational approach. He wanted to overlap and compare the structures of Ang II and S-8307 to see how more potent analogues could be made by better mimicking the binding portion of Ang II. The chemists now believed S-8307 was weak because it was too small compared with most of the AngII they believed was involved in binding(*281*)."

By adding some functional groups, they

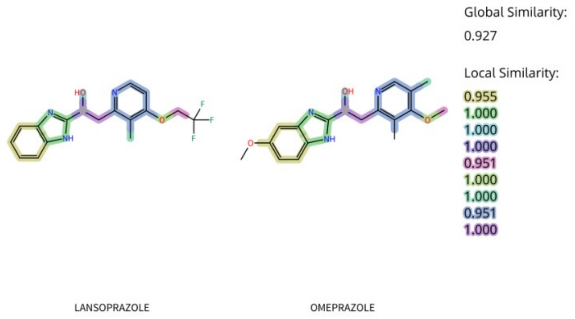
added the potency 100-fold, but the compound was not orally active. Then they could come up with "EXP-7711 that was orally active and it was able to lower blood pressure for an extended period. However, there was no increase in potency. The next series of molecules were modifications of EXP-7711

After synthesising a number of molecules, Duncia attached an unusual acidic functional group called tetrazole that led to yet another 10-fold increase in potency. They had losartan. It was March 1986(*281*)."

## LANSOPRAZOLE

1995

Analogue of omeprazole(*21*)




## DEXLANSOPRAZOLE

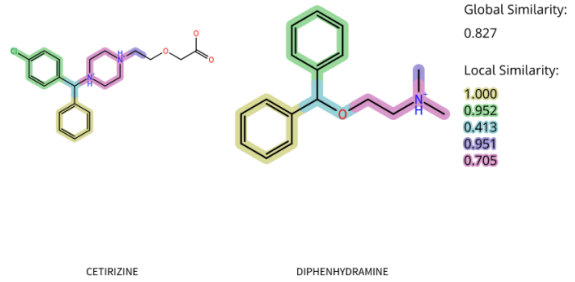
1995

enantiopure lansoprazole(*21*)

## CETIRIZINE

1995

Analogue of diphenhydramine(*21*)




## LEVOCETIRIZINE

1995

Enantiopure cetirizine

## EPOPROSTENOL

1995

Is the same as prostaglandin $I_2$, prostaglandin X or prostacyclin(*217*)

From the discovery paper:

"Recently a novel transformation of $PGG_2$ and $H_2$ to a non-prostaglandin compound 'thromboxane $A_2$' ($TXA_2$) has been reported, and a microsomal thromboxane synthetase system in blood platelets has been identified and characterised Most of the activity associated with 'rabbit aorta contracting substance' or RCS is now thougr.t to be due to $TXA_2$. $TXA_2$ shares with prostaglandin endoperoxides two important biological properties; they both contract strips of rabbit aorta, and cause platelet aggregation *in vitro*.

We have discovered that blood vessel microsomes contain an enzyme that transforms PO endoperoxides to an unstable principle which relaxes some blood vessels and prevents platelet aggregation. […]

Activity of PGs and products of the PG endoperoxides was assayed using the cascade superfusion technique. Tissues were selected from spirally cut strips of rabbit aorta, pulmonary artery, mesenteric artery, coeliac artery and vena cava, as well as rat stomach strip, rat colon, chick rectum, guinea pig ileum and guinea pig tracheal chain. […]

PGX (100 ng), whether extracted or not, did not contract strips of rabbit aorta, pulmonary artery or vena cava. PGX relaxed strips of rabbit mesenteric and coeliac arteries. PGX contracted rat stomach strip, chick rectum, guinea pig tracheal chain and guinea pig ileum, although its potency was less than that of $PGH_2$ or $PGG_2$. Rat colon was not contracted by endoperoxides or by PGX (100 ng), except after spontaneous decomposition of the prostaglandin endoperoxides, when there was a 25-40% conversion to PGE- or F-like substances.

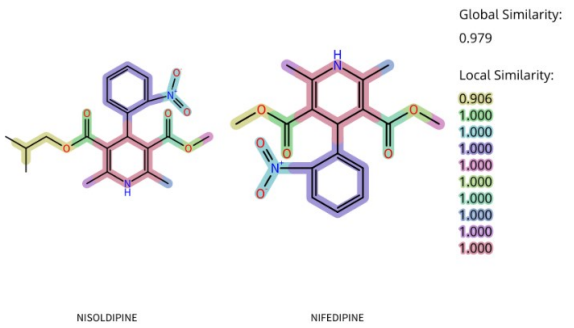
Aggregation of platelets in 1 ml fresh human platelet plasma (PRP) was monitored in a Born aggregometer […]

The lowest anti-aggregatory concentration was obtained at concentrations of 0.5-5 ng PGX $ml^{-1}$ PGX was about 30 times more potent than $PGE_1$ and 5-20 times more potent than $PGD_2$ as an anti-aggregatory agent (*423*)"

NISOLDIPINE

1995

Analogue of nifedipine(*21*)




RILUZOLE

1995

"The development of riluzole started in late 1980s as a free radical scavenger for stroke therapy. However, it has not been approved for treatment of stroke in the USA or Europe. Thereafter, it was repositioned for ALS therapy, but failed in many clinical trials prior to its final approval by the US Food and Drug Administration (FDA) in 1995."

"In the last decade, there has been much interest in the potential role of endogenous or exogenous excitotoxins in the etiology of ALS, either as a primary pathogenic mechanism, or, more likely, as an aggravating phenomenon hastening irreversible neurodegeneration. However, no direct evidence has yet been found for an excitotoxic mechanism in the etiology of ALS […]

The recent development of the excitotoxic hypothesis to explain the etiology of neurodegenerative diseases, such as ALS, has given rise to an extremely active research field aimed at developing neuroprotective drugs that would act by blocking the excitotoxic process. These agents have been developed on the basis that such compounds would break the glutamatergic loop that amplifies the neurodegenerative process, and thus slow down the progression, or limit the spread, of neuronal death. […]

The idea that the mechanism of action of riluzole may involve the blockade of glutamatergic transmission originally came from in vivo neuropharmacologic studies of the anticonvulsant profile of this drug. This hypothesis was supported by several studies, which showed that riluzole can block the effects of exogenous, excitatory amino acids(*424*)."

From the *in vivo* study cited in the previous quotation which is also the first report of this compound(*425*):

"2-Amino-6-trifluoromethoxy benzothiazole (PK 26124) prevented convulsions induced in rodents by maximal electroshock, inhibitors of the synthesis of γ-aminobutyric acid (GABA) and ouabain, but was inactive against seizures provoked by GABA antagonists, unlike diazepam, chlordiazepoxide, phenobarbital and valproic acid. 2-Amino-6-trifluoromethoxy benzothiazole prevented seizures induced by sound stimuli in DBA/2 mice, postural seizures in E1 mice and seizures induced by photic stimulation in the baboon, *Papio papio*, at 4 and 8 mg/kg. This spectrum of anticonvulsant activity closely resembles that reported previously for dicarboxylic amino acid antagonists. Indeed, PK 26124 prevented seizures induced by l-glutamate or by kainate and tremors induced by harmaline. In these tests diazepam was inactive (l-glutamate) or as potent as PK 26124 (kainate, harmaline), whereas it was 10–20 times more potent than PK 26124 against seizures induced by inhibitors of the synthesis of GABA(*426*)."

## MYCOPHENOLIC ACID

1995

"In any event, the discovery of mycophenolic acid can be more correctly dated to 1893 rather than 1896.

Gosio's big step forward was to investigate pure fungal cultures growing on Raulin's solution, a simple, well-defined medium. The fungus, a green species of *Penicillium*, was said to be *penicillium* (sic) *glaucum*. […] the culture medium produced symptoms resembling phenol poisoning in various animals. Gosio lamented that he had insufficient material to determine whether the isolated+D394 and purified material also produced poisoning in animals. However, he provided evidence for an 'azione antisettica.' When 50 mg of his compound was dissolved in a little soda ('piccola quantit à di soda') and then added to 5 mL of Löffler's broth, there was an inhibition of the growth of the anthrax bacillus; as just indicated, the latter was very expressively named as 'bacilli del carbonchio' (carbuncle bacillus). […]

MPA has been found to affect many physiological processes, and it is convenient to describe early investigations prior to about 1970 at this time. […] When MPA was rediscovered as an antibiotic, detailed studies indicated that it was more active against Gram-positive than Gram-negative bacteria and that some resistance to the antibiotic developed with *Staphylococcus aureus*. In mice intravenous injection of 1 mg of sodium mycophenolate in water had no toxic effect, 5 mg gave 'prolonged sickness,' and about 10 mg was a lethal dose. MPA has sometimes been classified as a mycotoxin since it does have some animal toxicity. […]

In tests of MPA against saprophytic fungi, development of the organisms generally tended to be retarded; with fungi pathogenic to humans significant growth inhibitions were observed. Much later, in 1968, *Cryptococcus neoformans* and *Blastomyces dermatitidis* were shown to be inhibited by a low level of MPA, *Candida albicans* and *Coccidiodes immitis* being less susceptible, and *Histoplasma capsulatum* being least susceptible. Activity was also observed against several *Trichophyton* species, and the symptoms caused by *Tricophyton asteroides* infections in guinea pigs were suppressed by MPA.

Beginning in 1968, biological activities were discovered in addition to the antibacterial and antifungal actions. Broth from growth of a strain of *Penicillium stoloniferum* had antiviral and antitumor properties, and the responsible agent was identified as MPA. The antiviral properties were observed at low concentrations in a monkey kidney cell line against vaccinia, measles, Herpes simplex, and Newcastle disease viruses, but there was no significant in vivo activity against vaccinia, Herpes simplex, and influenza virus in mice. Oral administration of MPA to chickens inhibited development of the Rous sarcoma virus and to a lesser extent splenomegaly in Friend virus infected DBA 2 mice. Similarly, MPA from an unidentified *Penicillium* sp. also had significant antiviral activity. The in vitro antiviral activity was reversed by guanine, guanosine, GMP, and deoxy-GMP.

Moreover, MPA inhibited growth of several transplantable murine solid tumors. Of particular note was marked inhibition of the rapidly growing and metastasizing Mecca-lymphosarcoma tumor. The antitumor activity of MPA was confirmed in 1969; however, there was no in vivo activity against neurovaccinia, Semliki Forest, encephalomyocarditis, and mouse sarcoma viruses. More extensive animal testing and preclinical toxicology were carried out in 1972. At the same time clinical trials against various cancers with a small group of patients showed only a poor response.

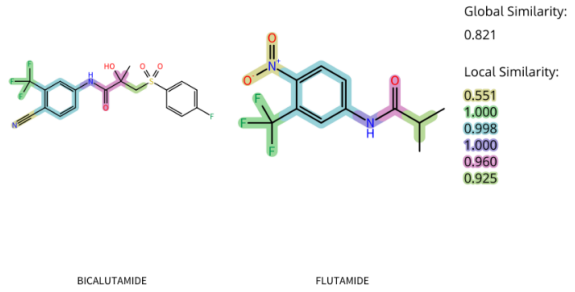
Planterose (1969) made the significant

observation that with mouse sarcoma virus, MPA appeared to act as an immunosuppressant. Thus, mean spleen weights in 2 week old TO mice when the drug dose was started for 2 days before infection with virus and continued for 2 weeks were as follows: controls, 119; MPA, 215; mercaptopurine, 200; methotrexate, 330. Similarly, in the same year, Mitsui and Suzuki reported that in mice, MPA depressed the immune response to sheep erythrocytes and suggested that it 'might be a useful immunosuppressive agent'(*427*)."

BICALUTAMIDE

1995

Analogue of flutamide(*21*)




SAQUINAVIR

1995

From the discoverer(s):

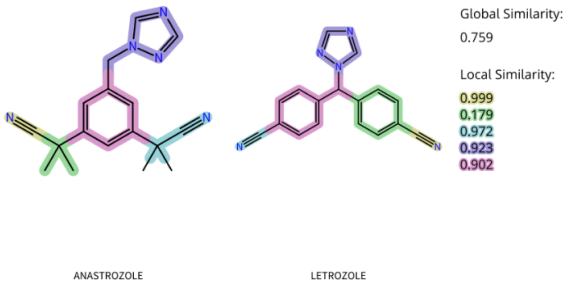
"It was against this background that we began our program to design inhibitors of HIV protease in the autumn of 1986. From the outset, we were particularly intrigued by the notion that HIV protease was able to cleave substrates N-terminal to proline residues. Since mammalian endopeptidases are unable to carry out such cleavages, it seemed likely that inhibitors based on this motif would be selective for the viral enzyme. Such inhibitors should not, therefore, cause side effects by inhibition of human aspartic proteases. […]

Roche molecular biologists in Nutley, USA and Basle, Switzerland set out to clone, express and purify the protease and its protein substrates. These materials were used to establish an assay, to test potential inhibitors and also for detailed mechanistic studies(*428*)."

ANASTROZOLE

1995

Analogue of letrozole(*21*)




ACARBOSE

1995

From the discoverer(s):

"It was our intention to achieve the retardation of carbohydrate digestion by inhibiting the intestinal α-glucosidases. Inhibitors of α-glucosidases effective against pancreatic e-amylase and against the sucrase and maltase activities of intestinal disaccharidases were discovered in culture broths of Actinomycetes, most frequently with strains of the genera Actinoplanes, Ampullariella and Streptosporangium. Various strains were found to affect one enzyme activity only; however, several strains were able to inhibit two or all three enzyme activities mentioned above. The inhibitory compounds were isolated from a large number of strains and found to be either peptides or oligosaccharides(*429*)."

The used bioassays for the discovery are not mentioned neither in this article nor in an article cited by it regarding their experiments.

AMIFOSTINE

1995

Secondary

CORTICORELIN OVINE

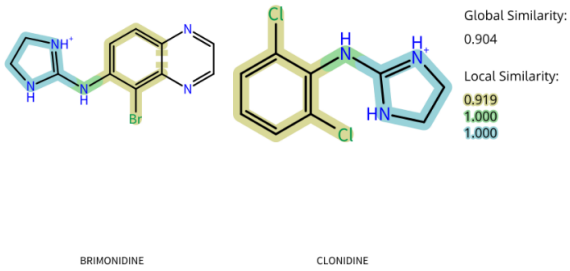
1996

Synthetic form of the peptide human cortico-tropin-releasing hormone (hCRH)(*2*)

## BRIMONIDINE

1996

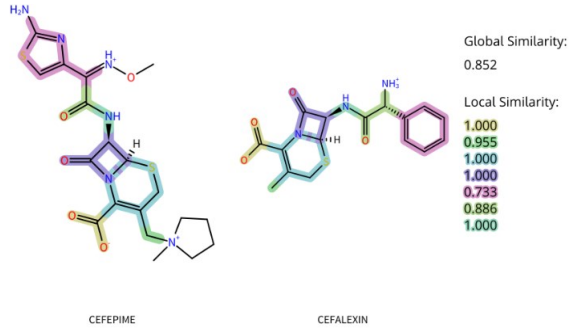
Analogue of clonidine(*21*)




## CEFEPIME

1996

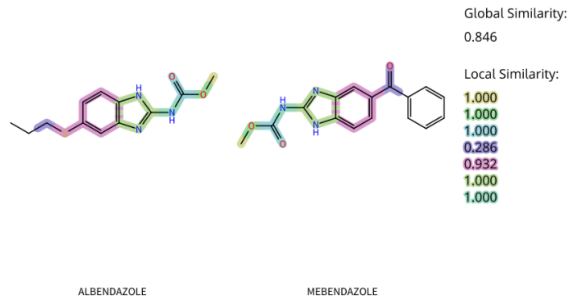
Analogue of cefalexin(*21*)




## ALBENDAZOLE

1996

Analogue of mebendazole




## PHENYLBUTYRIC ACID

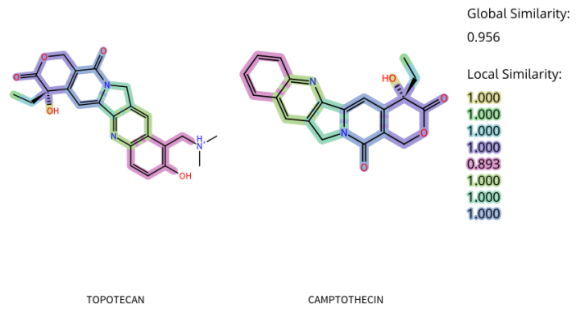
1996

Prodrug of phenylacetic acid(*2*)

## TOPOTECAN

1996

Analogue of camptothecin




"In addition to screening the plants collected for various chemical constituents, some extracts were tested for antibiotic, antitumor, and antiviral activity. In 1957, after a visit by the late Dr. Jonathan Hartwell from the Cancer Chemotherapy National Service Center, considered by most natural products scientists to be the pioneer worker in the field of plant antitumor constituents, it was agreed to send him 1000 ethanolic plant extracts for testing for antitumor activity. Almost a year later the astonishing result came back that the *Camptotheca* extracts were the only ones to have high activity in the CA-755 assay then used as one of the standard test systems(*430*)."

"20-(S)-Camptothecin was first discovered and isolated by Wall and Wani in 1966 from the bark of *Camptotheca acuminata* Decne., or Chinese Happy Tree, during a screening of various plant species with the aim to isolate novel steroids. They found that this extract showed substantial antitumor activity in standard in vitro test systems as well as in a mouse leukaemia model; this finding was in agreement with the use in Traditional Chinese Medicine as a natural remedy against cancer(*431*)."

## FOSPHENYTOIN

1996

Prodrug of phenytoin

ZAFIRLUKAST

1996

The first leukotriene antagonist to show acceptable efficacy and safety for FDA approval was zafirlukast, ICI 204219. According to the discoverer(s), it was an analogue of another antagonist that they had previously investigated, ICI 198615(*432*). I could not find any document elaborating the steps leading to the discovery of ICI 198615, yet, these are the bioassays whose results were reported in the earliest articles describing the action and pharmacology of this compound:

A. *In vitro* assays:

- ✓ "specific binding of [3H]5(S)hydroxy-6(R)-S-cysteinylglycyl -7(E), 9(E), 11(Z), 14(Z)-eicosatetraenoic acid ([3H]LTD4) to receptors on guinea pig lung parenchymal membranes and its inhibition by ICI 198,615(*433*)"
- ✓ Antagonism of LT-induced contractions of guinea pig trachea(*434*)
- ✓ Antagonism of $LTD_4$-induced contractions of guinea pig lung parenchymal strips(*434*)
- ✓ Antagonism of $LTC_4$- and $LTD_4$-induced contraction of human Isolated Intralobar airway smooth muscle(*434*)
- ✓ Evaluation of receptor selectivity in these isolated tissues: Guinea pig trachea, Rat aorta, Rat vas deferens, Guinea pig right atria, Guinea pig trachea, Rabbit aorta, and Guinea pig ileum(*434*)
- ✓ Inhibition of 5-, 12- or 15-Lipoxygenases partially purified from guinea-pig polymorphonuclear leukocytes, human platelets and soybeans, respectively(*435*)
- ✓ Inhibition of $LTD_4$-induced release of $TxB_2$ from chopped guinea pig lung

B. *In vivo assays*:

- ✓ Antagonism of Aerosol $LTD_4$-Induced Bronchopulmonary Effects in a Conscious Guinea Pig Model(*436*)
- ✓ Pulmonary Mechanics Studies in Anesthetized Guinea Pigs(*436*)
- ✓ Peptide leukotriene-induced increases in cutaneous vascular permeability in guinea pigs
- ✓ Inhibition of ovalbumin antigen-induced bronchoconstriction in guinea pigs
- ✓ Inhibition of ovalbumin antigen-induced mediator release from actively sensitized guinea pigs

TEMOZOLOMIDE

1996

From the discovery paper:

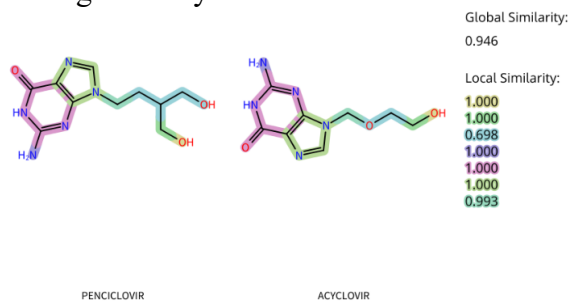
"In this paper, the first describing the activity of analogues of mitozolomide, we report on the chemical and antitumor properties of a series of 3-substituted derivatives in which the chloroethyl group of mitozolomide has been replaced by alkyl groupings, and in particular on the methyl analogue of mitozolomide, CCRG 81045. […]

The antitumor activity of 3-alkyl-substituted 8-carba-moylimidazo[5,1-d]-1,2,3,5-tetrazin-4(3H)-ones, was estimated in a primary screen in vivo using the TLX5 lymphoma, in a protocol which was identical to that which first identified the potent antitumor effect of mitozolomide(*437*)."

PENCICLOVIR

1996

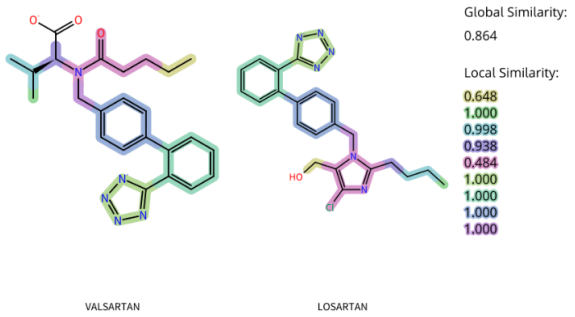
Analogue of acyclovir



## VALSARTAN

1996

Analogue of losartan(*21*)




## NEVIRAPINE

1996

From the discoverer(s):

"The decision to search for nonnucleoside inhibitors of HIV-1 RT required that we initiate a screening program to identify a structural lead. This was based not only on the preference to develop a novel structural class but also on the pragmatic basis that no suitable lead structures were known. […] Thus, it was fortuitous that after screening only approximately 600 random compounds from the company sample collection that a pyrido[2,3-b][1,4]benzodiazepinone was found that was weakly active (6 μM) in the HIV-1 RT enzyme assay. […]

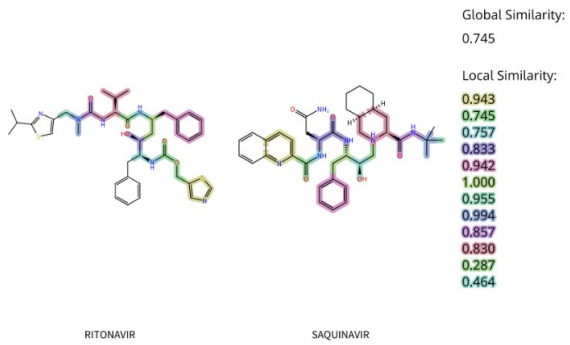
A focused screening of the available analogs from these four series of related compounds suggested that both the pyrido[2,3-b][1,5]benzodiazepinones and dipyrido[3,2-b:2',3'-e] [1,4]diazepinones showed the most promise as lead structures, and at this point there was no biological or physicochemical basis on which to choose one series over the other. […]

The lead optimization process requires that a set of criteria be established that are deemed essential for the selection of compounds (for preclinical and clinical development) with the characteristics necessary to achieve the therapeutic objective, desired route of administration, and so on. For this program the HIV-1 RT enzymatic assay was the primary screen. Active compounds (IC 50 < 1 μM) in this assay were then tested for their ability to block HIV-1 proliferation in cell culture, and a direct correlation was quickly found between the enzymatic and cellular potencies(*438*)."

## RITONAVIR

1996

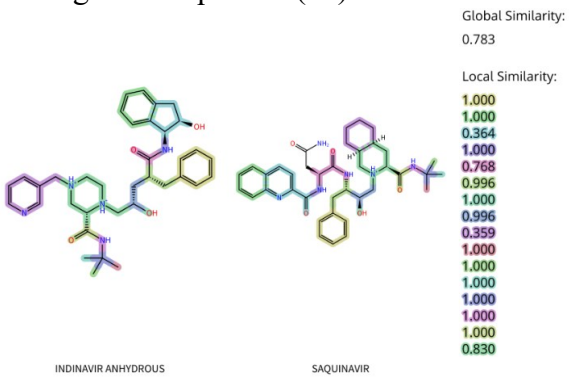
Analogue of saquinavir(*21*)




## INDINAVIR

1996

Analogue of saquinavir(*21*)




## BENTOQUATAM

1996

"Bentoquatam is a topical medication intended to act as a shield against exposure to the irritating substance urushiol, found in plants such as poison ivy or poison oak. Bentoquatam contains bentonite, a clay, and is only effective as long as the film is visible on the skin(*2*)."

## IVERMECTIN

1996

From the discovery paper:

"We have found a group of anthelmintic agents unrelated to any of the above compounds. They are produced by an actinomycete which was isolated at Kitasato Institute from a soil sample collected at Kawana, Ito City, Shizuoka Prefecture, Japan. It had been sent to Merck Sharp & Dohme Research Laboratories for testing in the various screening programs there. Early tests indicated that whole broth was active against *Nematospiroides dubius* in mice over at least an eightfold range without notable toxicity. Subsequently, the anthelmintic activity was isolated and identified as a family of closely related compounds. […]

Anthelmintic assays were performed in mice infected with *N. dubius*. […]

In early studies, avermectin was determined by its anthelmintic activity since it lacked detectable antimicrobial activity. The anthelmintic activity was associated with the mycelia and absent from the filtrate(*439*)."

From the discoverer(s):

"The biggest single factor leading to the discovery of ivermectin was steadfast reliance on empirical principles of drug discovery. The antiparasitic efficacy of the chemical class was revealed by a process that is part of a long tradition and that has many components. It represents an approach to drug discovery that is mostly, but not exclusively, concerned with the treatment of infectious disease. Its core element is the testing not only of substances that may reasonably be expected, on scientific grounds, to possess therapeutic activity, but also (and especially) of substances for which no such rationale exists.

**The Value of Casting a Wide Net**

The discovery of ivermectin resulted from screening microbial fermentation products for antiparasitic activity. The microbes themselves were gathered from a wide range of sources to enhance the diversification of assay input. Among those sources was the Kitasato Institute in Tokyo. A group of Kitasato scientists, led by Professor Satoshi Omura, routinely isolated microorganisms from soil by allowing them to grow in laboratory culture, after which they were tested for activity against a variety of other microorganisms. Under an agreement with Merck & Co., Inc., isolated microbes that were considered unusual in appearance or cultural characteristics were dispatched to Merck laboratories in the United States. When a batch was sent in 1974, it was understood by Merck microbiologists that those isolates had shown little antimicrobial activity in the Kitasato tests, and that was in accord with the results of routine antimicrobial tests done at Merck. In 1975, the isolates were transferred from the Merck Microbiology Department to the Parasitology Department, where they could be tested in a new assay that had been devised especially for testing microbiological fermentations for activity against parasites. One of those isolates, when regrown in the Merck laboratories and tested in the new antiparasitic assay, yielded a potent anthelmintic substance. That substance (a mixture of abamectin and several related structures known collectively as avermectins) would be the forerunner of ivermectin and, by extension, the macrocyclic lactone class of antiparasitic agents.

**The Value of Assay Innovation**

The discovery of ivermectin resulted from assay innovation. In the decades following the discovery of penicillin, many new antibiotics were found by screening fermentation products against microorganisms in vitro. Yet it would appear that not a single anthelmintic was found by the primary screening of fermentation products against parasitic worms. That was presumably because no suitable assay then existed. The breakthrough that yielded ivermectin was an in vivo assay.

Details of the assay have been published. In essence, fermentation products were fed to worm-infected mice, which were later examined for evidence that the infection still existed. The empirical nature of the system is abundantly evident: The mice were fed an arbitrary, though standard, amount of food containing an unknown amount of an unknown substance that might not be there(*440*)."

## DONEPEZIL

1996

From the discoverer(s)

"The research on donepezil started in 1983. Following research developments on tacrine, our group at Eisai Co., Ltd. started to develop tacrine derivatives. However, we failed to develop a non-toxic tacrine derivative. Through random screening, we encountered an N-benzylpiperazine derivative that was then originally being synthesized in a study on anti-arterial sclerosis. Our tests showed that the anti-AChE activity of the N-benzylpiperazine derivative had an $IC_{50}$ of 12.6 μM in rat brain homogenate. This was not very strong but the compound's novel structure was very promising. We decided to use the N-benzylpiperazine derivative as the seed compound and synthesized about 700 derivatives […]

The indanone derivatives were tested for in vitro inhibition of AChE. A rat brain homogenate was used as the AChE source(*441*)"

## FOSFOMYCIN

1996

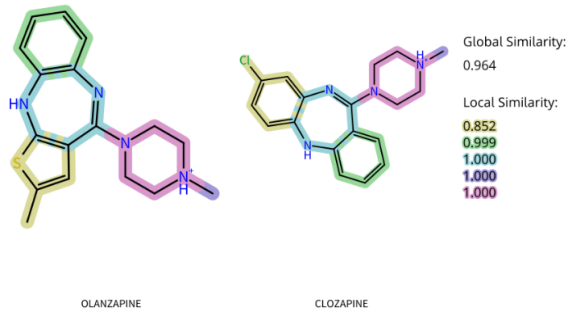
It was discovered by using spheroplasting method as the primary screen(*442*).

"Lederberg observed that protoplasts (later called spheroplasts in gram negatives) were formed upon treatment of *S. typhimurium* and *E. coli* with penicillin in the presence of sucrose and Mg++ under conditions which supported growth. At Merck, samples, generally clarified natural product broths or extracts, were added to bacteria in osmotically stabilized medium and cell morphology was observed by direct microscopy after a period of several hours. Spheroplasts appear as large round refractile bodies(*442*)."

## OLANZAPINE

1996

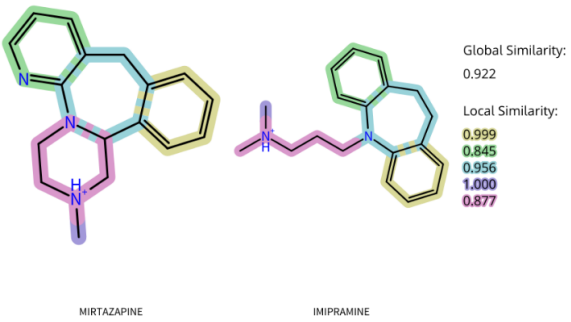
Analogue of clozapine(*21*)




## MIRTAZAPINE

1996

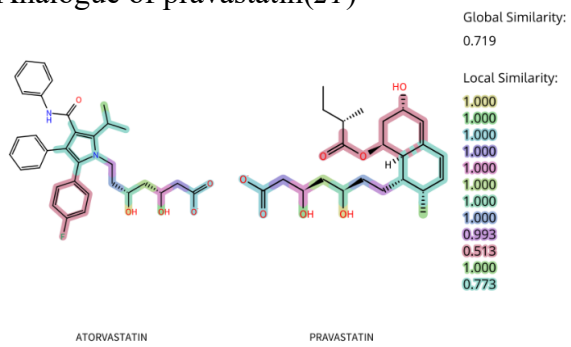
Analogue of imipramine




## ATORVASTATIN

1996

Analogue of pravastatin(*21*)



## TOPIRAMATE

1996

From the discoverer(s):

"Pharmacologist Joe Gardocki and I discovered topiramate (McN-4853) by using standard in vivo models that are highly predictive of clinical efficacy in humans. In fact, compounds with demonstrable activity in the Maximal Electroshock Seizure (MES) test in mice and rats have been considered to present a 95% chance of effectiveness in treating at least a sizable subgroup of epileptic patients. Since epilepsy is a multifactorial disorder with limited understanding about its etiology (i.e., the origin of seizures is idiopathic), drug discovery in this field has often taken a phenotypic route. […]

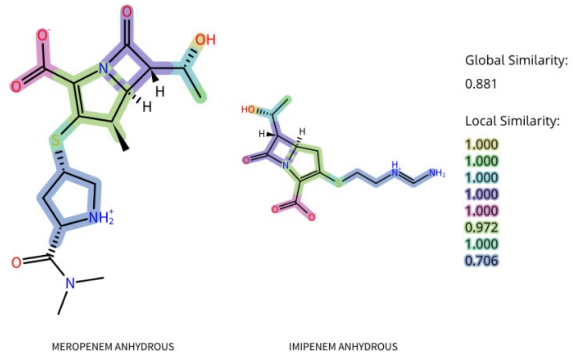
Topiramate was first synthesized as a chemical intermediate for another purpose, in 1979. Several grams were submitted to the corporate compound library, and it was assayed in whole animal tests for different potential therapies. The MES test was not part of the standard stable of animal assays because the company had little commercial interest in developing a medicine for epilepsy. However, after reviewing the compound submission sheet, Joe became intrigued with the chemical structure, especially the SO2NH2 moiety, and selected topiramate for testing in the MES test in mice. The anticonvulsant activity became apparent right away(*443*)."

"While the discovery of this drug was blessed by serendipity, its development was powered by determination, hard work, and heavy capital investment. Topiramate (McN-4853) actually emanated from a project directed to finding an inhibitor of the enzyme fructose-1,6-bisphosphatase (FBPase) as an antidiabetic agent. Several grams of synthetic intermediate topiramate were submitted to our compound library for pharmacological evaluation in animal models. This compound was selected on a hunch for anticonvulsant testing in the maximal electroshock seizure (MES) test in mice and found to be effective(*444*)."

## MEROPENEM

1996

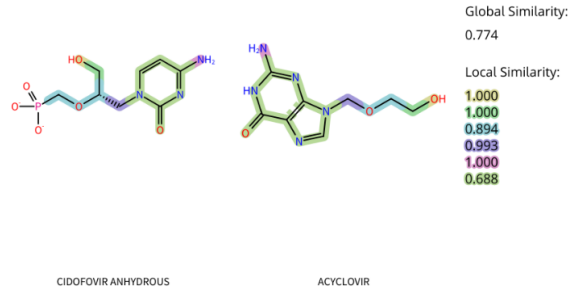
Analogue of imipenem(*21*)




## CIDOFOVIR

1996

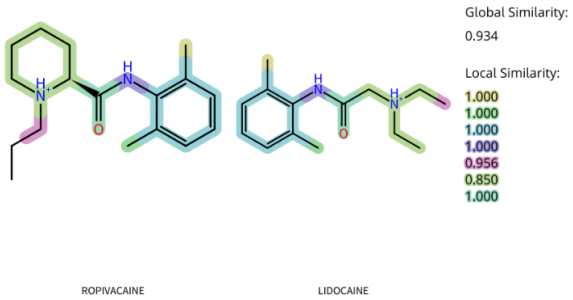
Analogue of acyclovir




## ROPIVACAINE

1996

Analogue of lidocaine




## INSULIN LISPRO

1996

Endogenous-based biopharmaceutical

## GLATIRAMER ACETATE

1996

"GA (also known as Copolymer-1 or Cop-1) was discovered serendipitously in the late 1960s/early 1970s during basic research on the immunological properties of synthetic polymers/copolymers of amino acids conducted by Teitelbaum et al. of the Weizman Institute in an attempt to produce a synthetic antigen capable of inducing experimental autoimmune encephalomyelitis (EAE), an animal model of autoimmune inflammatory CNS disorders, including MS. Teitelbaum et al. hypothesized that synthetic copolymers comprising amino acids analogous to those of myelin basic protein (found in the CNS and thought to act as an autoantigen in MS and in EAE) will induce EAE. Contrary to this hypothesis, copolymer mixtures produced were not encephalitogenic, but were observed to be protective against EAE. In particular, Cop-1 (heterogeneous mixture comprising L-alanine, L-lysine, L-glutamic acid, and L-tyrosine) had the greatest activity against EAE, reducing the incidence of EAE, as well as the prevalence and severity of histological lesions(*445*)."

From the discovery paper:

"**Induction of EAE**

Guinea pigs were injected with 10 µg of the purified BE in complete Freund's adjuvant into the footpads of the two hind legs. They were then observed daily for loss in weight, and for the appearance of clinical symptoms of the disease, as reflected by paralysis of the hind legs.

**Delayed hypersensitivity reactions**

The skin test reactions were carried out on the 10th or the 11th day after the challenge injection. […]

**Determination of lactic dehydrogenase (LDH) activity**

The level of LDH in the sera of the guinea pigs was assayed spectrophotometrically […]

**Histological tests**

The animals were sacrificed after 4 weeks by means of nembutal. The brain was taken out in its entirety after the skull had been sawn. […]

**Prevention of EAE**

Each animal received 8 repeated intradermal injections of 100 µg of the respective polymer in incomplete Freund's adjuvant (ICFA). The material was injected over the back and sternum of the guinea pigs twice a week for four weeks. Three days after the last injection the animals were challenged with 10 µg of BE in CFA into the two hind footpads.

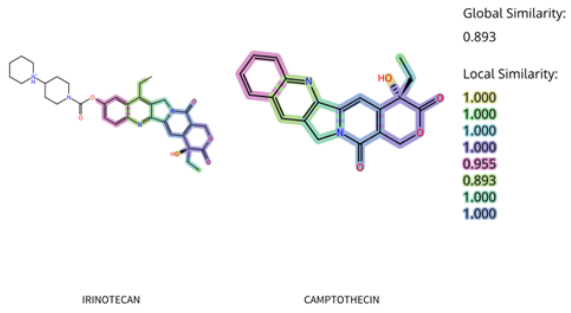
**Suppression of EAE**

After the initial challenge with 10 µg of BE, two methods of suppression were tried: (1) each guinea pig received 6 intradermal injections of 100 µg each of the respective polymer in incomplete Freund's adjuvant. The injections were given over the back and sternum of the guinea pig, twice a week for three weeks starting two days after the initial challenge. (2) Each guinea pig received three intravenous injections of 1 mg each of the respective polymer or protein in saline. The injections were given according to schedules mentioned in the text, which differed in the various experiments(*446*)."

## IRINOTECAN

1996

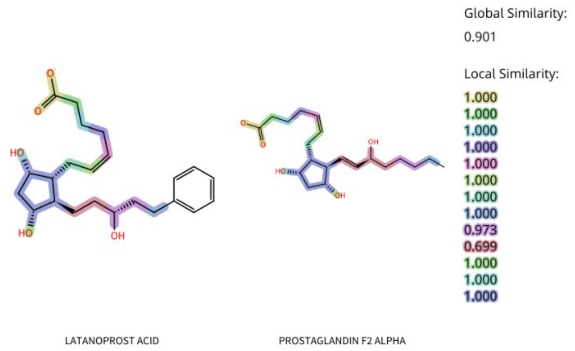
Analogue of camptothecin



## LATANOPROST

1996

Analogue of prostaglandin $F_2$ alpha(*2*)




"The potential of PGs as therapeutic agents for glaucoma was suggested by the discovery of the ocular hypotensive effects of topically applied endogenous PGs, especially $PGF_{2\alpha}$ and $PGE_2$, in cats and monkeys. This was followed by several reports of significant IOP-lowering effects of PGs in humans, using both topical and systemic administration(*447*)."

I could not find a relevant article cited in the previous quotation: Zajacz M, Torok M, Mocsary P (1976). Effect on human eye of prostaglandin and a prostaglandin analog used to induce abortion. IRCS Medical Science: Clinical Medicine: Library Compendium 4: 316 Chemical Abstracts Accession Number 85:72796.

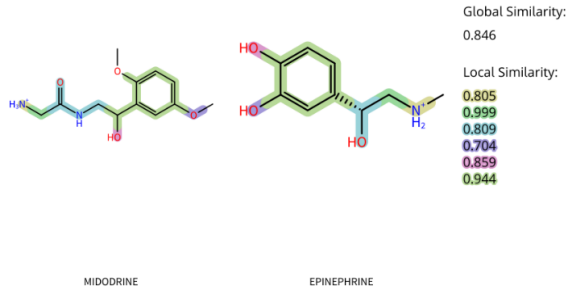
From a discovery paper cited in the previous quotation:

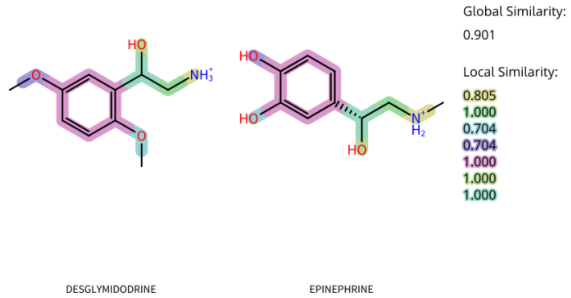
"It is generally accepted that exogenous or endogenous prostaglandins (PGs) can give rise to acute increases in intraocular pressure (IOP) and to the development of flare and other signs of uveitis. It was recently shown, however, that low doses of $PGE_2$ and/or $PGF_{2a}$ topically applied to rabbit or owl monkey eyes significantly reduce IOP. The present experiments show that topical application of 10 to 500 µg of $PGE_2$ also causes a highly significant IOP reduction in cat eyes lasting up to 48 hr with little or no development of flare or miosis, whereas similar application of $PGF_{2a}$ causes, in addition to an IOP reduction, the development of profound pupillary constriction. Topical application of either $PGF_{2a}$ or $PGE_2$ to the eyes of rhesus monkeys also causes significant dose-dependent reduction in IOP(*448*)."

## MIDODRINE

1996

Midodrine is a prodrug. Desglymidodrine, its major bioactive metabolite(*2*), is a close analogue of the endogenous epinephrine.

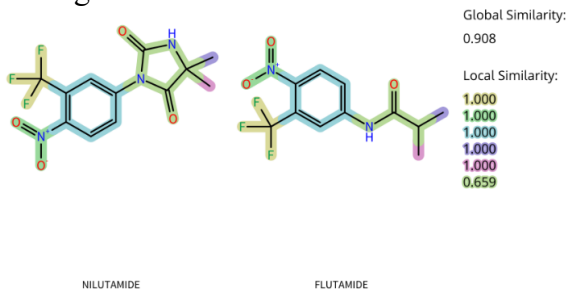



## NILUTAMIDE

1996

Analogue of flutamide




## LEVOFLOXACIN

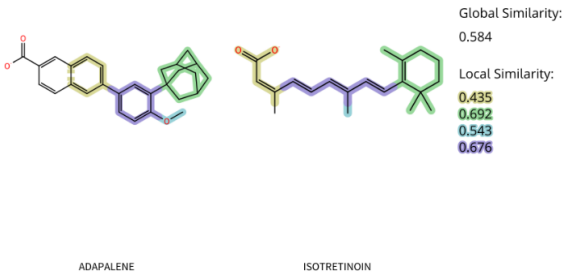
1996

Levo isomer of the racemic ofloxacin

## ADAPALENE

1996

Analogue of isotretinoin(*449*)




From the discovery paper of adapalene:

"Retinoids, natural and synthetic analogues of vitamin A, play a major role in controlling cell proliferation and differentiation. […]

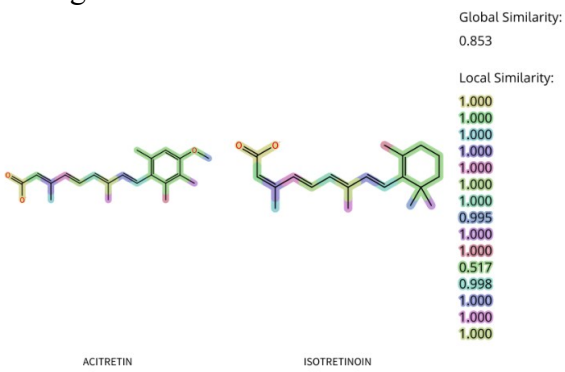
In this paper, we report the synthesis of naphthoic and propenylbenzoic acid derivatives of series I and II, respectively and their RARS binding affinities and F9 cell-differentiating activities. […]

In the absence of three-dimensional structural data on the binding sites of RARs, we designed new target compounds reasoning by analogy with arotinoid and the established leads, CD 367 and TTNN(*449*)."

## ACITRETIN

1996

Analogue of isotretinoin




## CAPROMAB PENDETIDE

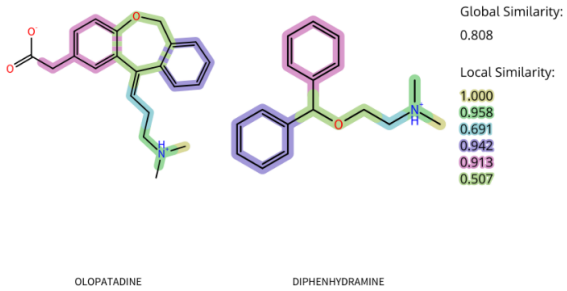
1996

Monoclonal Antibody

## OLOPATADINE

1996

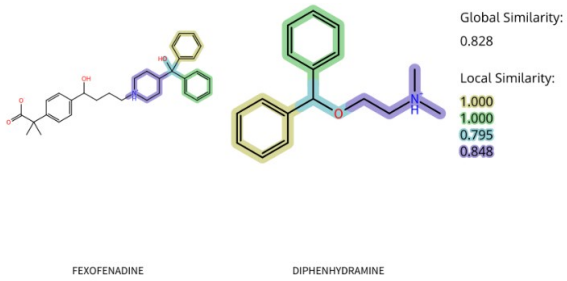
Analogue of diphenhydramine(*21*)




## FEXOFENADINE

1996

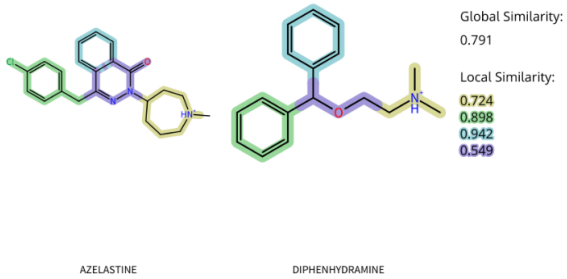
Analogue of diphenhydramine




## AZELASTINE

1996

Analogue of diphenhydramine(*21*)




## PENTOSAN POLYSULFATE

1996

Low molecular weight heparin(*2*)

## IODIXANOL

1996

Contrast agent

## ZILEUTON

1996

"The third step in developing clinically useful agents was to discover orally active inhibitors. In order to test the oral effectiveness of the hydroxamate inhibitors, an assay that measured the inhibition of leukotriene formation *in vivo* was established in our laboratories. The assay used was an adaptation of a model described by Orange *et al*. (1968) and utilizes rats passively sensitized with rabbit antisera to bovine serum albumin. Antigen challenge to the peritoneal cavity 3h after sensitization triggers the production of large amounts of peptidoleukotrienes (predominantly $LTC_4$ which is rapidly metabolized to $LTE_4$) as well as smaller quantities of $LTB_4$. This rat peritoneal analphylaxis assay provided a simple and rapid procedure to measure the ability of compounds to prevent leukotriene formation *in vivo* following oral administration. Initial studies with a large number of hydroxamates were disappointing. Even compounds as potent as A-61442 were ineffective in the rat at relatively high doses, although they were active when injected directly into the peritoneal cavity. Metabolism studies indicated that the hydroxamate moiety was being rapidly converted to the inactive carboxylic acid. The first breakthrough for the development of orally active compounds occurred when the relative position of the hydroxamate to the hydrophobic template was inverted. These retro or type B hydroxamates showed excellent oral activity in the rat. One of the best of these inhibitors was A-63162 which was found to be a relatively potent leukotriene inhibitor *in vitro* as well as *in vivo*. […]

**THE DISCOVERY OF ZILEUTON**: The next major advance in the development of orally active 5-lipoxygenase inhibitors at Abbott came from modifying the hydroxamate moiety. This was done by replacing the alkyl group of the hydroxamate with an amine group thus forming N-hydroxyureas. This modification provided compounds that had excellent pharmacokinetics in the rat and superior potency in inhibiting the production of $LTE_4$ in the peritoneal cavity. […] the N-hydroxy urea A-64077 (zileuton) was more potent in inhibiting the production of leukotrienes in the rat than both BW 755c and A-63162. […]

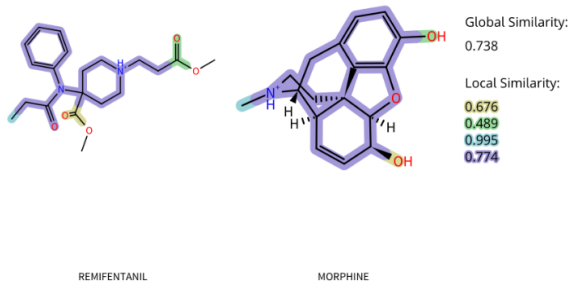
This compound also inhibits bronchospasm in the guinea-pig induced by arachidonic acid or antigen challenge, neutrophil influx into the pleural cavity of rats in an Arthus reaction, and arachidonic acid-induced ear edema in the mouse, all via the oral route(*450*)."

## REMIFENTANIL

1996

Analogue of morphine and fentanyl

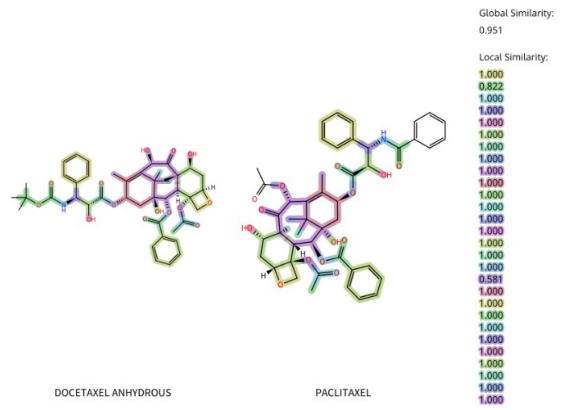
Also see the fentanyl entry and refer to Paul Janssen's article cited there.




## DOCETAXEL

1996

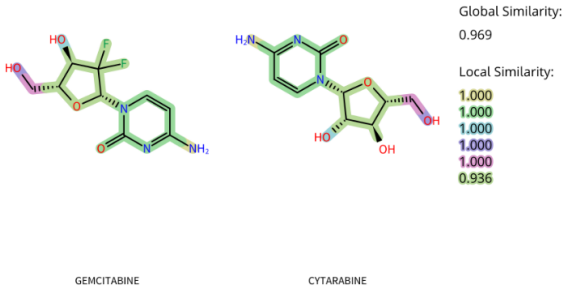
Analogue of paclitaxel(*21*)



## GEMCITABINE

1996

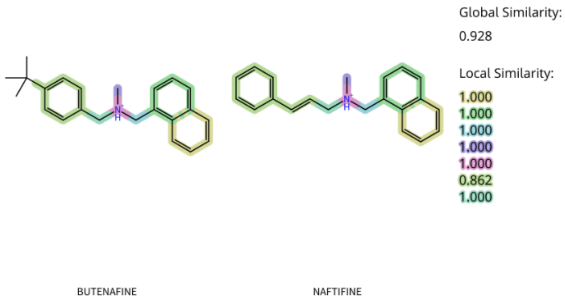
Analogue of cytarabine(*21*)




## BUTENAFINE

1996

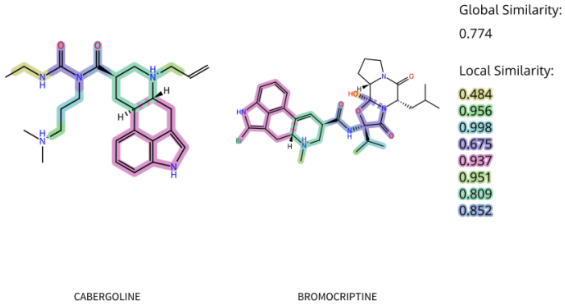
Analogue of naftifine




## CABERGOLINE

1996

Analogue of bromocriptine(*21*)




## ANAGRELIDE

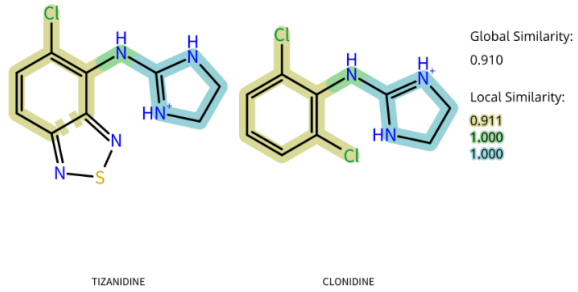
1997

"Initially, on the basis of *in vitro* investigations, an anti-aggregating activity on platelets was attributed to anagrelide. Thereafter, experiments on humans showed, however, that anagrelide under *in vivo* conditions, had only little influence on platelet function but rapidly lowered platelet counts. This caused the initiation of a series of clinical studies which led to the approval(*451*)"

## TIZANIDINE

1996

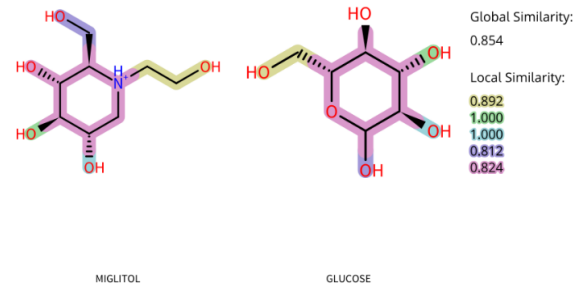
Analogue of clonidine(*21*)




## MIGLITOL

1996

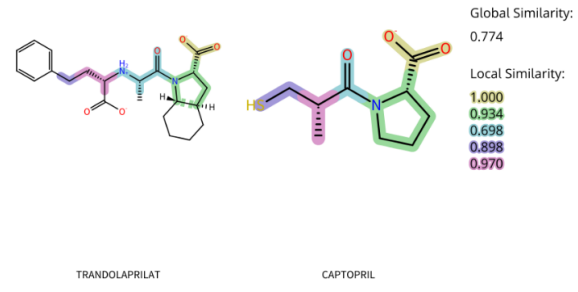
Analogue of glucose




## TRANDOLAPRILAT

1996

Analogue of captopril(*21*)




## PERFLUTREN

1997

Diagnostic

## PRAMIPEXOLE

1997

It was originally synthesized as an analogue of apomorphine as a potential antipsychotic with agonistic effect on dopamine autoreceptors:

From the discoverer(s):

"Dopamine (DA) receptor agonists that stimulate the DA autoreceptor in the brain represent a novel therapeutic approach in the treatment of schizophrenia by reducing the release of DA presynaptically. Those selective DA agonists should be devoid of the untoward dyskinetic side effects of the classical neuroleptics. Apomorphine exerts presynaptic DA receptor activity. […]

In order to study the influence of the exchange of the catechol subunit of DA agonists for the aminothiazole moiety on presynaptic DA receptor activity, we prepared the enantiomers of aminothiazolo analogues 4 and 5 of apomorphine and aminotetralin, respectively. […]

Agonistic activity on the presynaptic DA receptor was determined as previously described, by measuring the inhibition of y-butyrolactone (GBL) induced acceleration of DA synthesis in rat corpus striatum (i.e., DOPA accumulation in DOPA decarboxylase inhibited rats) and by measuring the utilization of DA in the whole brain of rats following inhibition of tyrosine hydroxylase with a-methyltyrosine methyl ester (a-MT)(*452*)"

From a later paper of the discoverer(s):

"It is generally accepted that schizophrenia is associated with hyperfunctioning of dopaminergic neurons in the mesolimbic system. Based on this hypothesis, all compounds being developed for antipsychotic treatment are aimed at directly or indirectly reducing the hyperactivity of these cells. Almost all drugs currently available for the treatment of schizophrenia are dopamine (DA) receptor antagonists, although the severe side-effects of most of these compounds limit their therapeutic use. Because of this disadvantage, which is attributable to the antagonistic mode of action of conventional neuroleptic treatments, novel mechanisms have been investigated, e.g. compounds that stimulate DA autoreceptors.

One of the first of these compounds was talipexole (B-HT 920), a substance formerly characterized as a central $\alpha_2$-adrenoceptor agonist. The DA autoreceptor agonistic properties had been revealed by Andén et al., who claimed that B-HT 920 was a selective presynaptic DA receptor agonist. Later studies on B-HT 920 revealed additional postsynaptic agonistic effects; however, these effects became evident only in models with presynaptic denervation or degeneration. […]

We now present the profile of a compound which was selected from a number of 2,6-diaminotetrahydro-benzothiazoles of which the (-)-(S) enantiomers proved the most active. Pramipexole (SND 919; 2-amino-4,5,6,7-tetrahydro-6-propylamino-benzthiazole-dihydrochloride) was tested in a number of in vivo and ex vivo models to provide evidence of presynaptic and postsynaptic effects on DA neurons(*453*)."

Among these models were animal models with relevance to parkinsonism. When investigating the postsynaptic activity of pramipexole, it was observed that it is effectivity is good enough in these models to indicate its potential also as a drug for Parkinson's Disease.

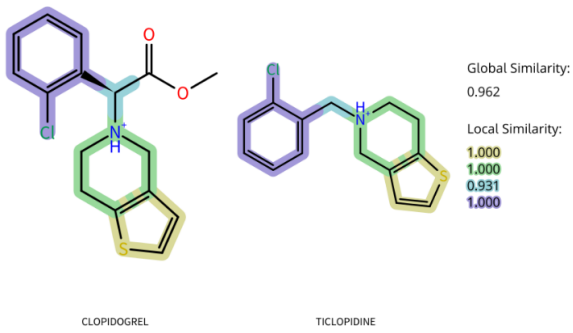
In this regard, from a later paper of the discoverer(s):

"It exerts its agonistic activity at DA autoreceptors and postsynaptic DA receptors. Pramipexole is presently being evaluated for clinical efficacy in Parkinson's disease(*454*)."

## CLOPIDOGREL

1997

Analogue of ticlopidine(*391*)




Also see the ticlopidine entry.

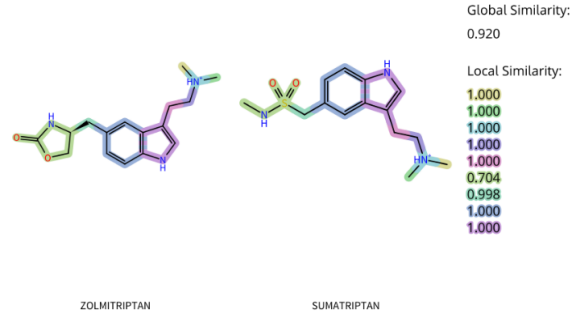
From the discoverer(s):

"In total, more than a thousand ticlopidine analogues were synthesized and tested in animals for their antiplatelet and antithrombotic effects. Eight of them were developed up to phase 1 studies in healthy volunteers and only the last one, PCR4099, proved to be clearly more active and better tolerated than ticlopidine(*391*)."

## ZOLMITRIPTAN

1997

Analogue of sumatriptan(*21*)




## FOMEPIZOLE

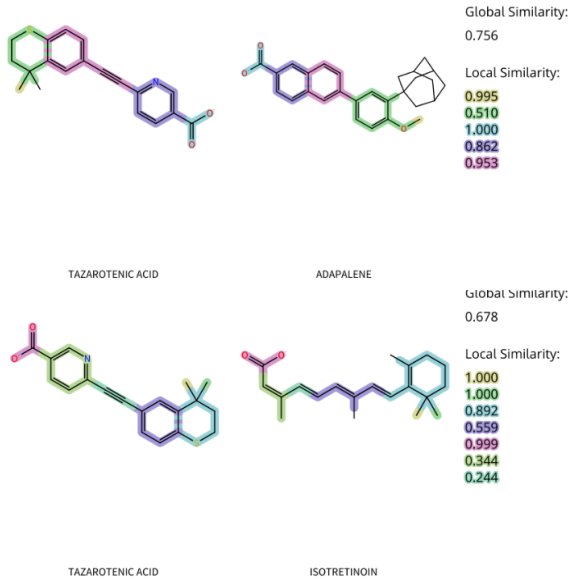
1997

"IN INVESTIGATIONS on the interaction *in vitro* between liver alcohol dehydrogenase (LADH) prepared from horse liver, and a large number of heterocyclic compounds, Theorell and Yonetani found pyrazole (m = 68) to be a most potent inhibitor of LADH. […] Tentative experiments in dogs showed pyrazole to be active as an inhibitor of ethanol metabolism in vivo(*455*)."

## TAZAROTENIC ACID

1997

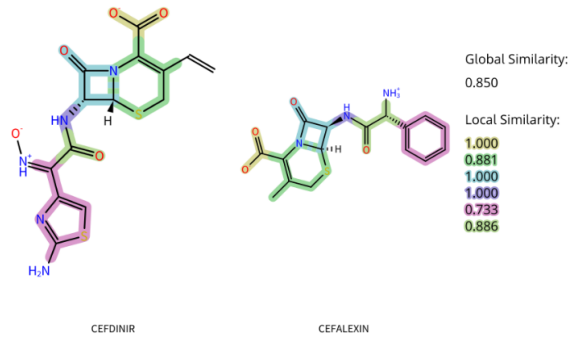
Analogue of isotretinoin




## CEFDINIR

1997

Analogue of cefalexin(*21*)




## BECAPLERMIN

1997

Endogenous-based biopharmaceutical

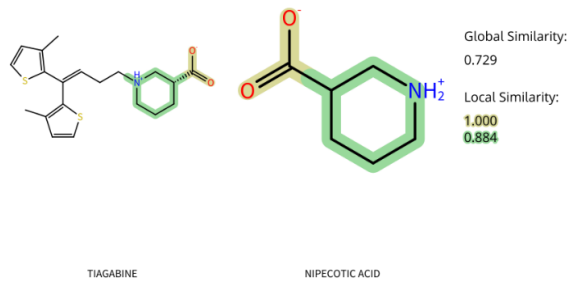
## SAMARIUM CATION SM-153

1997

## TIAGABINE

1997

A lipophilic analogue of nipecotic acid to enable CNS penetration(*21*)




"The antiepileptic drug tiagabine is a lipophilic derivative of nipecotic acid. Nipecotic acid inhibits GABA reuptake, but does not cross the blood brain barrier and is effective against seizures in animal models only when injected in the cerebral ventricles. Tiagabine's lipophilic anchor permits the passage of nipecotic acid from the systemic circulation across the blood brain barrier to the central nervous system(*456*)."

Discovery of nipecotic acid:

"This review describes the development of a new class of heterocyclic GABA uptake inhibitor using muscimol as a lead structure. Muscimol, which is a centrally active constituent of *Amanita muscaria*, is a GABA analogue, since the 3-isoxazolol nucleus can be regarded as a masked carboxyl group. Muscimol is a potent GABA receptor agonist and a substrate for the GABA transport carrier(s) in rat brain slices. As an attempt to 'separate' these effects, muscimol has been subjected to extensive molecular manipulations. As part of these studies the amino group of muscimol has been incorporated into additional ring structures. This approach led to the development of THIP (4,5,6,7-tetrahydroisox-azolo[5,4-c]pyridin-3-ol), which is a very potent and specific GABA receptor agonist. The related compounds isoguvacine, isonipecotic acid, and piperidine-4-sulphonic acid (P4S), obtained by replacement of the 3-isoxazolol moiety of THIP by carboxyl and sulphonic acid groups, are also very potent and specific GABA receptor agonists.

The compounds THPO (4,5,6,7- tetrahydroisoxazolo[4,5-c]pyridin- 3-ol) and THAO (5,6,7,8-tetrahydro-4H-isoxazolo[4,5-c]azepin-3-ol), on the other hand, are GABA uptake inhibitors with little or no affinity for the GABA receptors. […]

The cyclic amino acids nipecotic acid and guvacine, derived from THPO, are potent GABA uptake inhibitors, but in contrast to THPO these amino acids interact with both glial and neuronal GABA uptake(*457*)."

Bioassays in the study of the previous quotation(*457*):

- ✓ "Inhibition of GABA uptake in cultured glia cells"
- ✓ "Inhibition of GABA uptake in mouse brain 'mini-slices'"
- ✓ "Inhibition of GABA uptake in rat brain 'mini-slices'"
- ✓ "Inhibition of GABA uptake in rat brain synaptosomes"
- ✓ Inhibition of GABA receptor binding in preparations of cerebral cortex membranes from adult rats

"**SEPARATION OF GABA RECEPTOR AND UPTAKE AFFINITIES: DESIGN OF NIPECOTIC ACID AND GUVACINE**

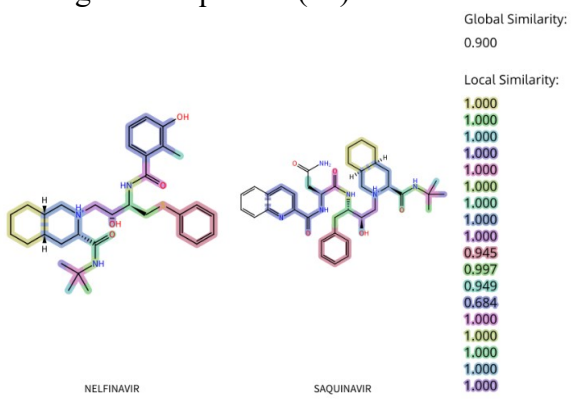
Muscimol (7), a constituent of the mushroom *Amanita muscaria*, is a very potent $GABA_A$ agonist, but 7 also is an inhibitor of neuronal and glial GABA uptake and a substrate for the GABA-metabolizing enzyme GABA transaminase. Thiomuscimol (8) shows a pharmacological profile similar to that of 7. Systematic variation of the structures of 7 and 8, notably transformation of these 3-isoxazolol and 3-isothiazolol bioisosteres of GABA into bicyclic analogues in order to separate

the multiple affinities of these compounds, has provided a number of specific $GABA_A$ receptor agonists and GABA uptake inhibitors. An important step in this drug design programme was the synthesis of the enantiomers of 4,5-dihydromuscimol (DHM), (S)-DHM (9) being a selective and highly potent $GABA_A$ agonist, whereas (R)-DHM (22) showed moderately potent inhibitory effect on GABA uptake. The key step was, however, the transformation of 7 into the isomeric bicyclic analogues 4,5,6,7-tetrahydro-isoxazolo[5,4-c]pyridin-3-ol (THIP, 14) and 4,5,6,7-tetrahydroisoxazolo[4,5-c]pyridin-3-ol (THPO,19), 14 being a potent and specific $GABA_A$ agonist and 19 a specific GABA uptake inhibitor showing some selectivity for the glial transport system. The 3-isothiazolol THIP analogue, Thio-THIP (15), on the other hand, is a weak $GABA_A$ agonist at spinal $GABA_A$ receptors but an antagonist at brain $GABA_A$ receptors(*458*)."

NELFINAVIR

1997

Analogue of saquinavir(*21*)




ALBUMIN HUMAN

1997

Endogenous-based biopharmaceutical

RITUXIMAB

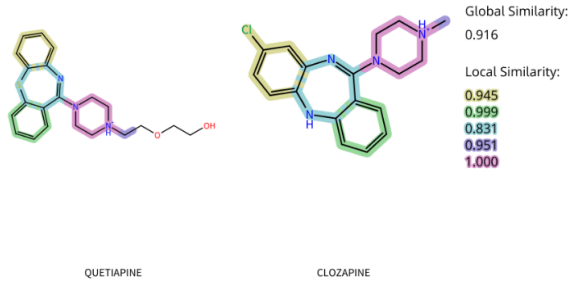
1997

Monoclonal Antibody

QUETIAPINE

1997

Analogue of clozapine(*21*)




IMIQUIMOD

1997

"The imidazoquinoline class of TLR-7 agonists was discovered somewhat fortuitously at 3M Pharmaceuticals. The original program was directed toward finding inhibitors of herpes virus replication that were based on the known anti-herpes adenine derivative. A series of adenine analogs based on the imidazoquinoline structures 6 and 7 were synthesized and found to inhibit replication of herpes virus in a mouse model of infection, but had no direct antiviral activity *in vitro*. The antiviral activity of these compounds in vivo was determined to result from induction of IFN-α by a specific mechanism that was unknown at the time. The *in vitro* assay used for subsequent compound optimization was based on IFN-α induction in human PBMCs. Ultimately this class of compounds was validated to act as agonists of TLR-7, which is consistent with their IFN-induction property(*459*)."

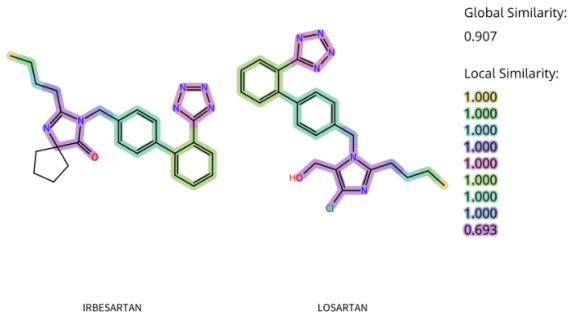
"Imiquimod was first noted in a programme screening for antiherpes virus activity in the 1980s. The slight toxicity of the drug series produced a slight reduction in herpes cytopathology in Vero cell cultures sufficient for compounds to be tested further in a guinea-pig model. Here, complete protection against herpetic lesions was observed. In fact all the antiviral effects of imiquimod were subsequently shown to be a consequence of its

ability to induce pro-inflammatory cytokines driving Th1 immune responses(*460*)"

IRBESARTAN

1997

Analogue of losartan(*21*)




TAMSULOSIN

1997

"R&D toward tamsulosin was not originally designed to create a dysuria drug. Instead, the original project was a new application of an already-known compound, which was explored and developed as an antihypertensive drug. After the potential of the compound to act as a drug for dysuria was recognized, improvement and commercialization in that direction were made […]

Takenaka played a key role in these studies wherein he focused on the effects of suspected sympatholytic drugs in dogs and rats. […] In brief, the compound was administered to the animal and vasoconstriction was monitored in the search for new antihypertensive drugs. It was through these studies that Yamanouchi developed the β-blocker indenolol (Prusan) in 1968 and formoterol (Atock) for bronchial asthma in 1972(*461*)"

From the discovery paper:

"More recently, we have synthesized the optical isomers of amosulalol and found the (+)-isomer to be one log unit order more potent and less potent than the (-)-isomer in blocking $\alpha_1$- and $\beta_1$-adrenoceptors, respectively. The finding stimulated us to synthesize the desoxy derivatives of amosulalol and its analogues to obtain more potent $\alpha_1$-adrenoceptor antagonists devoid of $\beta_1$-adrenoceptor blocking activity, since prazosin, a selective $\alpha_1$-adrenoceptor antagonist, is useful for the treatment of congestive heart failure in which 6-adrenoceptor blockade is considered to be contraindicated. This paper describes $\alpha_1$- and $\beta_1$-adrenoceptor blocking activities of the optical isomers of amosulalol and nine newly synthesized desoxy compounds derived from amosulalol and its analogues. The sulfamoylphenethylamines reported here were found to be a structurally new type of extremely potent $\alpha_1$-adrenoceptor antagonists(*462*)."

The bioassays used in the discovery paper for investigating the synthesized series(*462*):

- ✓ "$\alpha_1$-Adrenoceptor blocking activity was assessed by antagonism of the increase in mean blood pressure induced by (-)-phenylephrine in pentolinium-treated rats anaesthetized with urethane"
- ✓ "$\beta_1$-Adrenoceptor blocking activity was assessed by antagonism of the increase in heart rate induced by (-)-isoprenaline in reserpinized rats anaesthetized with pentobarbitone sodium"
- ✓ The cardiovascular effects were examined in anaesthetized dogs

Regarding testing tamsulosin for BPH, from the discoverer(s):

"**Classical pharmacology in drug discovery** *The discovery of tamsulosin*

The discovery of tamsulosin: In about 1975, in their small-scale clinical study, Caine et al. reported that phenoxybenzamine, an α-adrenoceptor (αAR) antagonist, was effective in treating symptomatic BPH. At that time αARs were pharmacologically classified into two subtypes, $\alpha_1$ and $\alpha_2$. At about the same time it was discovered that the αAR that controls the contraction of the human prostatic smooth muscles was the $\alpha_1$-subtype. […]

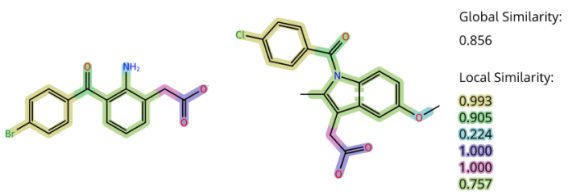
[I]chloroisoproterenol, the first β-adrenoceptor antagonist, was synthesized by chemically modifying the b-receptor agonist, isoproterenol. To obtain a new $\alpha_1$-antagonist, we used a similar approach in drug design by synthesizing and screening many derivatives of noradrenaline, an $\alpha_1$-agonist. From among these derivatives a potent and selective $\alpha_1$-antagonist, tamsulosin, was discovered. […]

Tamsulosin was investigated to discern the mechanism of its therapeutic action. An anaesthetized-dog model was used to investigate the $\alpha_1$-blocking activity of tamsulosin in the lower urinary tract and blood vessels. Phenylephrine, an $\alpha_1$-agonist, was used to increase intraurethral pressure and blood pressure, and the inhibitory effect of tamsulosin measured. Tamsulosin shifted the dose–response curve for phenylephrine to the right in both the urethra and blood vessels. However, the inhibition of phenylephrine-induced pressure elevation by tamsulosin was more pronounced in the urethra than in blood vessels. This suggested that the $\alpha_1$-blocking activity of tamsulosin is more selective for the urethra than for vascular endothelium(*463*)."

## BROMFENAC SODIUM

1997

Analogue of indomethacin




BROMFENAC SODIUM INDOMETHACIN

## REPAGLINIDE

1997

"Treatment of type 2 diabetes with SUs is associated with a number of problems. These include hypoglycemic episodes, secondary failure, and possible cardiovascular side effects. In attempts to overcome these problems, several novel antidiabetic compounds are currently in development, among them repaglinide, (S)-(+)-2-ethoxy-4[2-[[3-methyl-1-[2-(1-piperidinyl)-phenyl]-butyl]amino]-2-oxo-ethyl] benzoic acid (AG-EE 623 ZW), which is structurally distinct from the traditional SUs but shows some chemical resemblance to the nonsulfonylurea moiety of the glibenclamide molecule(*464*)"

"One such approach involved the study of a series of benzoic acid derivatives. However, meglitinide (HB699), as the lead compound, displayed only weak hypoglycaemic activity when compared to the most potent sulphonylureas exemplified by glibenclamide or glipizide. Within another series of benzoic acid derivatives, the racemic AG-EE 388 ZW and moreover its S-enantiomer AG-EE 623 ZW (=repaglinide) were found to be potent hypoglycaemic compounds when tested in vivo or in isolated pancreatic islets. Repaglinide, currently undergoing phase III clinical trials, represents one of the most potent antidiabetic compounds of this series described so far.

Like the sulphonylureas, repaglinide is an insulinotropic agent, as evidenced by in vitro studies with mouse and rat pancreatic islets. Similar to the sulphonylureas, repaglinide also inhibits adenosine 5'-triphosphate (ATP)-sensitive potassium channels thus leading to an increase in intracellular Ca 2+ concentration(*465*)."

## FENOLDOPAM

1997

"The first significant D-1 selective agonist identified in our laboratories was SK&F 38393, which was orally active and was both a dopaminergic renal vasodilator and a central dopamine agonist. It was the first example of a D-1 agonist that does not have D-2 agonist activity(*466*)."

"Benzazepines - A novel series of

dopaminergic agonists has been developed. The parent compound 17 (SKF 38393) is about one-tenth dopamine as a renal vasodilator in the anesthetized dog. When administered ip, causes diuresis and natriuresis in rats. Although it is long acting and has minimal adrenergic effects, 17 produces sub-maximal decreases in renal vascular resistance (RVR) and increases in RBF compared to dopamine. The renal depressor effects of 11 and dopamine are additive(*467*)."

From the discoverer(s), regarding the discovery of fenoldopam itself:

"Previous studies from our laboratories have described the central and peripheral activity of a novel dopaminergic agonist, SK&F 38393. For example, SK&F 38393 increases RBF and decreases RVR in anesthetized dogs and in anesthetized normotensive and hypertensive rats. However, the decreases in RVR and increases in RBF produced by SK&F 38393 are submaximal, relative to dopamine. The renal hemodynamic activity of SK&F 38393 in the dog is inhibited by bulbocapnine and in a competitive manner by metoclopramide, indicating involvement of a dopaminergic mechanism. SK&F 38393 also stimulates dopamine-sensitive adenylate cyclase in homogenates of rat caudate, as a partial agonist, and causes contralateral rotation in rats with unilateral 6-hydroxydopamine-induced lesions of the substantia nigra. However, in contrast to other dopamine agonists, SK&F 38393 does not inhibit prolactin release.

Several new 3-benzazepines were synthesized with the objective of obtaining enhanced selectivity and potency for activating renal vascular dopamine receptors, but with no central dopaminergic activity after systemic administration. Of these compounds, SK&F 82526, was chosen for further study, since it is several times more potent than dopamine as a renal vasodilator, is relatively selective for the kidney and apparently does not cross the blood-brain barrier(*468*)."

From the discoverer(s), regarding the discovery of the lead compound, SKF 38393:

"In addition to its vasodilator properties, dopamine is a potent α-receptor agonist and also stimulates β-receptors ($\beta_1$) in the heart, partially via an indirect action to release endogenous norepinephrine. Because of this multiplicity of actions, other stimulants of peripheral vascular dopamine receptors, particularly of a new chemical class, may be useful in order to better define and explore the physiological events associated with activation of these receptor sites. This paper describes initial studies with such a new dopamine receptor agonist, SK& F 38393 (2,3,4,5-tetrahydro-7,8-dihydroxy-l-phenyl-lH-3-benzazepine)(*469*)."

Bioassays reported in this discovery paper(*469*):

- ✓ Cardiovascular profile in anesthetized mongrel dogs of either sex surgically prepared for direct measurement of aortic blood flow (cardiac output), left renal blood flow, mean arterial blood pressure and heart rate
- ✓ Receptor specificity studies in dogs:

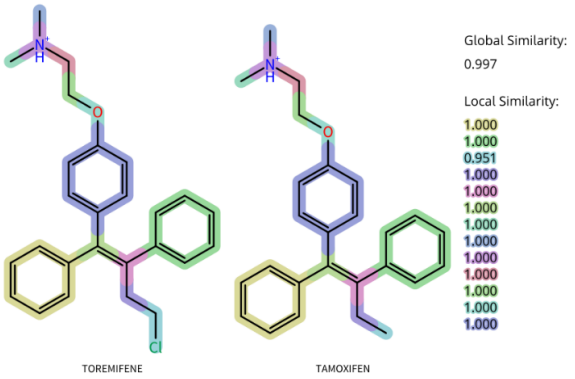
  "In a control study, 4 dogs received 100 µg/kg of SK & F 38393 in each of 3 rapid i.v. injections, spaced approximately 1h apart. This dose of SK & F 38393 was selected from a dose response curve (1-1000 µg/kg) obtained in 6 other dogs where it produced a near maximal renal dilator response for this drug. Saline was infused for 10 min prior to the second and third SK & F 38393 injections to simulate drug (antagonist) infusion periods in subsequent testing(*469*)."
- ✓ Rat diuretic studies:

"Male Charles River rats weighing 175-200g were fasted for 24 h and deprived of drinking water for the last 30 min. They were then dosed i.p. with SK & F 38393, 1.6-25 mg/kg in saline and placed in metabolism cages for a 30-min urine collection(*469*)."

TOREMIFENE

1997

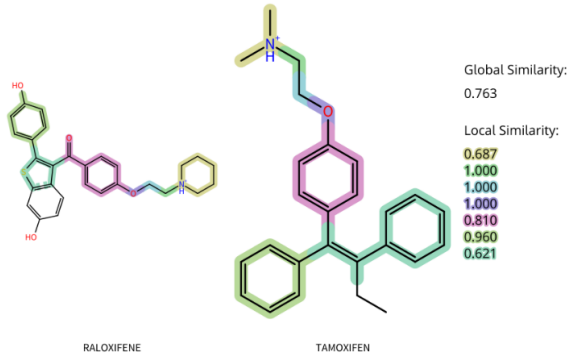
Analogue of tamoxifen




RALOXIFENE

1997

Analogue of tamoxifen




LETROZOLE

1997

"To improve on fadrozole, Novartis synthesized a series of new compounds. Structure-activity relationship studies were then performed to identify the most potent AI [Aromatase Inhibitor] from a series of benzylazole derivatives of fadrozole. The third-generation AI letrozole (Femara®) was the result of this structure-activity approach to drug design and achieved the research goal of creating a highly potent and totally selective Aromatase Inhibitor. These compounds were also used to design pioneering molecular modeling techniques used to map the active site of aromatase. Other third-generation Aromatase Inhibitors developed during this period were the nonsteroidal agents vorozole (since discontinued) and anastrozole(*470*)."

In discovery of letrozole, both *in vitro* and *in vivo* bioassays were used to guide towards the optimal activity:

From the discovery paper of letrozole:

- ✓ "*Inhibition of human placental aromatase in vitro*

  The microsomal fraction of fresh human term placenta was obtained using the method described by Thompson and Siiteri. The assay procedure for the determination of $IC_{50}$ values was carried out as described previously. Briefly, incubations contained [4-$^{14}$C]androstenedione, excess NADPH, microsomal protein and varying concentrations of inhibitor in phosphate buffer in a final volume of 1 ml. The incubation was carried out at 37°C. The reaction was started by the addition of enzyme and stopped after 20 min by addition of diethyl ethyl. […]

- ✓ *Inhibition of aromatase in vivo*

  The assay is based on the inhibition of the androstenedione-induced uterine hypertrophy in immature female rats(*471*)."

Discovery of fadrozole:

It was discovered via SAR studies in both *in vitro* enzyme-based and *in vivo* animal assays.

From the discovery paper of fadrazole:

"A new class of potent, selective, nonsteroidal inhibitors of aromatase have been discovered. The most potent member of this series is fadrozole hydrochloride, CGS 16949 A […]

**Structure-Activity Relationships**

**1. Effect of the Aromatic Side Chain and Substituents.** The original activity of *N*-(4-cyanobenzyl)imidazole (**9**) suggested that a lipophilic substituent on the aromatic ring was important for potent inhibition of placental aromatase. […]

Furthermore the choice of the aromatic substituent influenced both the in vitro enzyme inhibition […]

The 4-cyano and 4-bromo derivatives 26a and 26b proved to be the most potent inhibitors of the enzyme and more importantly their in vitro enzyme inhibitory activity was a reliable predictor of their in vivo potency. Other electron-withdrawing groups in the aromatic ring led to compounds with inhibitory activity in the 10 nM range in vitro. However, their in vivo potency tended to be significantly weaker. In general, it appears that hydrophilic electron-withdrawing para substituents are less effective in vivo. The more hydrophilic acid derivative **26e** was effective neither in vitro nor in vivo.

**2. Effect of Ring A Size and Flexibility.** […] Both tetrahydroimidazo[l,5-a] pyridine and 6,7-dihydropyrrolo[1,2-*c*]imidazole proved to be approximately 1 order of magnitude more potent than their uncyclized progenitor **9**. This in vitro superiority correlated to an improved in vivo potency(*472*)."

Used bioassays(*472*):

- ✓ In Vitro: Aromatase Tritiated Water Assay (Method 1)
- ✓ In Vitro: Product Isolation Assay For Aromatase Activity (Method 2)
- ✓ **"In Vivo: Ovarian Estrogen Assay.** Twenty-one-day-old female rats were injected (sc) with 10 IU of pregnant mare serum gonadotropin (PMSG). Two days later, the same rats were injected (sc) with 30 IU of hCG and, 24 h later, treated with either propylene glycol or the aromatase inhibitor in propylene glycol. One hour later, all of the rats were treated subcutaneously with 2.25 mg of androstenedione (A) in 0.1 mL of sesame oil. Four hours after the injection of A, the rats were killed. Their ovaries were freed of adhering tissue and stored at -40 ºC prior to measuring their estrogen content(*472*)."

ROPINIROLE

1997

From the first paper reporting the synthesis and dopamine-agonist activity of ropinirole (1c):

"4-[2-(Di-n-propylamino)ethyl]-2(3H)-indolone (SK&F 101468) is a potent and selective prejunctional dopamine receptor agonist. It caused a dose-related inhibition of the constrictor response to electrical stimulation in the isolated perfused rabbit ear artery ($EC_{50}$ = 100 nM), and this response was antagonized by (S)-sulpiride ($K_B$ = 7 nM). Compound 1c did not stimulate or block dopamine-sensitive adenylate cyclase and did not produce stimulation of the central nervous system in rats. It was prepared from (2-methyl-3-nitropheny1)acetic acid in a multistep sequence based on the Reissert indole synthesis. […]

We recently described2 two phenolic indolone derivatives, 1a and 1b that exhibited potent prejunctional dopamine agonist activity as determined in the isolated perfused rabbit ear artery (REA) assay. Compound 1b was unusually potent in this assay with an $EC_{50}$ of 1.8 h 0.3 nM (N = 10) compared to an $EC_{50}$ of 110 f 20 nM for *N,N*-di-*n*-propyldopamine. We have continued our investigations of the indolones with the objective of identifying active and selective nonphenolic prejunctional agonists for use in the treatment of cardiovascular disorders. In this paper, we

report the synthesis and initial biological evaluation of 1c, the des-OH derivative of lb. […]

**Biology.** Surprisingly, 1c ($EC_{50}$ = 100 nM) and *N,N*-di-*n*-propyldopamine were essentially equipotent in inhibiting the constrictor response to electrical stimulation in the REA preparation. […]

Compound 1c did not stimulate or block the dopamine-sensitive adenylate cyclase in homogenates from the rat caudate at concentrations up to $l0^{-4}$ M. Unlike apomorphine it did not increase confinement motor activity (CMA) upon intraperitoneal administration to conscious rats but actually produced some depression of CMA at high doses (>1 mg/kg). At doses up to 1 mg/kg (ip) 1c also did not potentiate hexobarbital-induced sleep time in the rat. These results indicate that 1c does not produce the central behavioral effects often seen with dopamine agonists.

Compound 1c has been selected for further characterization, and a full account of its pharmacology and the SAR of a series of indolones related to it will be published at a later date(*473*)."

## MODAFINIL

1998

"The history of modafinil dates back to 1974 in France. While they were screening molecules in search of analgesics two chemists, Gombert and Assous, from L. Lafon Ltd, a pharmaceutical company, identified a new molecule [benzhydryl sulfinyl-2 acetohydroxemic acid], called adrafinil. This molecule was later passed on to two pharmacologists, Duteil and Rambert, also from L. Lafon, Ltd. The intraperitoneal injection of adrafinil in male mice of the NMRI strain caused a significant dose-dependent increase in motor activity without exhibiting peripheral sympathomimetic effects.

As early as 1977-78, Michel Jouvet, working in the Clinical Neurophysiology Unit of the Neurological Hospital in Lyon, prescribed adrafinil to narcoleptic patients(*474*)."

## ARMODAFINIL

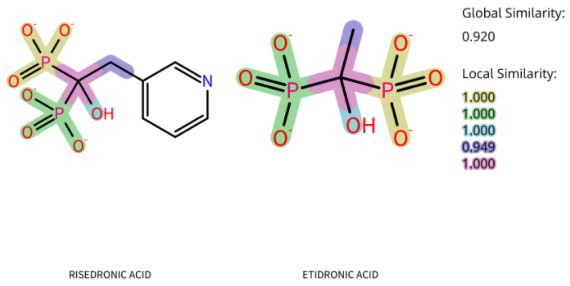
1998

Enantiopure modafinil

## RISEDRONIC ACID

1998

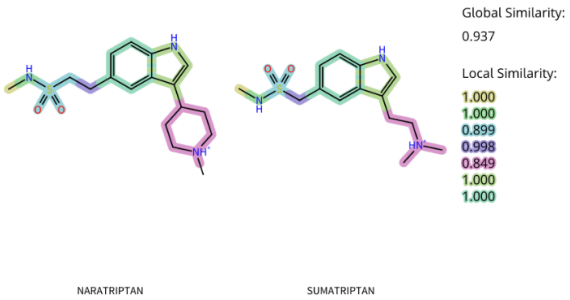
Analogue of etidronic acid(*21*)




## NARATRIPTAN

1998

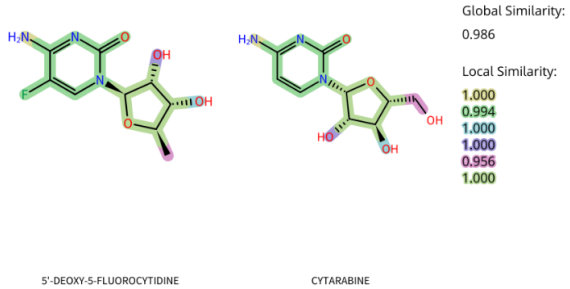
Analogue of sumatriptan




## 5'-DEOXY-5-FLUOROCYTIDINE

1998

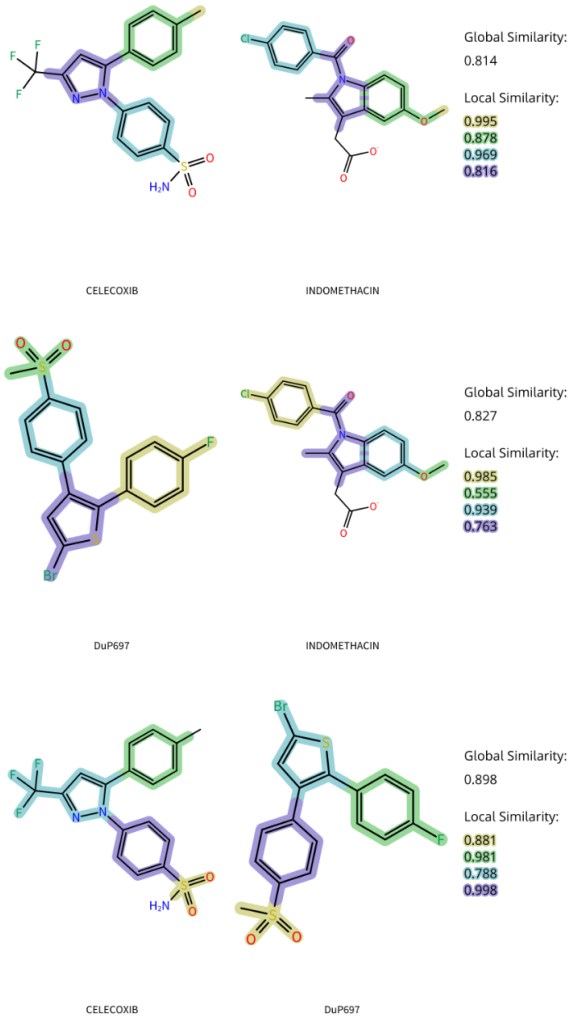
Analogue of cytarabine



## CELECOXIB

1998

Analogue of indomethacin




"Cyclooxygenase 2 (COX-2) was discovered in 1991 and the first lead inhibitors were described in 1992. A mere seven years later, the first examples of selective inhibitors are on the market. This remarkably fast drug discovery and development effort did not happen in a vacuum but took advantage of a solid base of medicinal chemistry and clinincal experience related to non-steroidal anti-inflammatory drugs (NSAIDs). […]

Enormous effort was expended in the development of NSAIDs between the 1960s and 1980s so there were numerous pharmacophores to test when COX-2 was discovered. The first breakthrough came with reports that the diarylheterocycle DuP697 and the acidic sulfonanilide NS398 were anti-inflammatory but non-ulcerogenic; once it was demonstrated that they were COX-2-selective inhibitors, the race was on to convert them into structurally related clinical candidates. The COX-2 inhibitors currently on the market, Celebrex and Vioxx, are descendants in the diarylheterocycle lineage(*475*)."

From the article cited in the previous quotation as the discovery report of DuP697, the first lead of COX-2 inhibitors:

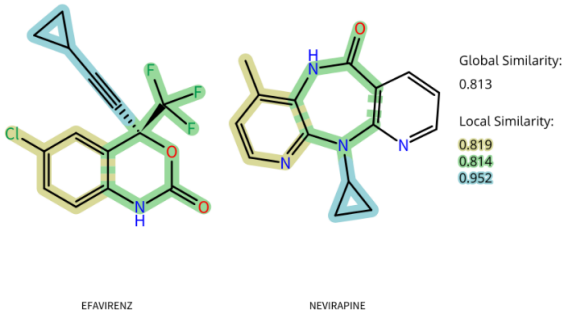
"DuP 697 (5-bromo-2[4-fluorophenyl]-3-[4-methylsulfonylphenyl]-thiophene) is a potent inhibitor of paw swelling in nonestablished and established adjuvant arthritis in rats. DuP 697 had no effect on phenylquinone writhing in rats, but was analgetic against inflammation-related pain in the Randall-Selitto assay and was a very potent antipyretic agent. The drug was not ulcerogenic in rats at single doses up to 400 mg/kg. DuP 697 did not alter renal blood flow or the renal vascular response to angiotensin II in furosemide-pretreated, volume-depleted rats. In contrast, indomethacin decreased renal blood flow and potentiated the renal vascular response to angiotensin II in these animals. DuP 697 was a moderate inhibitor of bull seminal vesicle prostaglandin (PG) synthesis and a potent inhibitor of rat brain PG synthesis but was ineffective against rat kidney PG synthesis. These differential effects of DuP 697 on PG synthesis by various tissues may account for its high potency as an anti-inflammatory and antipyretic agent and its minimal toxicity profile. DuP 697 (5-bromo-2-[4-fluorophenyl]-3-[4-methylsulfonylphenyl]-thiophene, is an anti-inflammatory drug with exceptional gastrointestinal safety in rats. In addition, DuP 697 may prove to be renal sparing inasmuch as it does not inhibit rat kidney PG synthesis or does it alter RBF in furosemide-pretreated, volume-depleted rats. In

this paper, an overview of the in vivo anti-inflammatory and safety profile of the drug will be presented and compared to piroxicam which is given once per day (anticipated clinical schedule for DuP 697) and indomethacin and sulindac, NSAID reported to be nephrotoxic and renal sparing, respectively. Most of the studies were performed in rats or their tissues to help define tissue selectivity for cyclooxygenase in one species. The mechanism of action of DuP 697 appears to be inhibition of PG synthesis in selected tissues including the brain(*476*)."

## EFAVIRENZ

1998

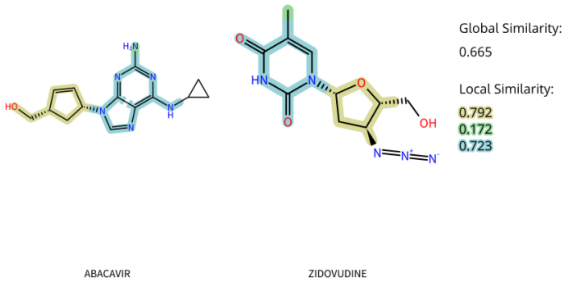
Analogue of nevirapine




## ABACAVIR

1998

Analogue of zidovudine(*21*)




## ETANERCEPT

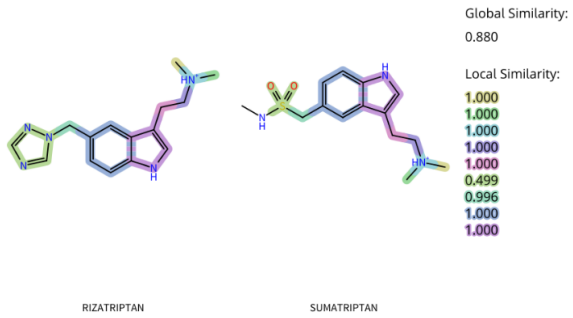
1998

"Dimeric fusion protein consisting of the extracellular ligand-binding portion of the human 75 kilodalton (p75) tumor necrosis factor receptor (TNFR) linked to the Fc portion of human IgG1(*2*)."

## RIZATRIPTAN

1998

Analogue of sumatriptan(*21*)




## THALIDOMIDE

1998

"Thalidomide was originally synthesised by Ciba in 1952: it was found to have no effect on animals and was discarded. In 1957 it was acquired by Chemie-Grunenthal in Germany. Further tests were carried out in animals, and in 1958 it was marketed as an anticonvulsant for the treatment of epilepsy in humans. It was of limited value for this purpose, but it was found to be effective at inducing sleep(*477*)."

"Thalidomide was synthesised in 1954 by the CIBA pharmaceutical company, and prescribed as a sedative, tranquiliser, and antiemetic for morning sickness. Chemically similar to barbiturates, the drug became a popular sedative, marketed under at least 37 names worldwide […]

Interest in thalidomide resurfaced in 1965 after, by chance discovery, it was found to be beneficial in erythema nodosum leprosum, a vasculitic complication of leprosy characterised by painful subcutaneous nodules, fever, and other constitutional symptoms(*478*)."

"Thalidomide's resurgence came about from the serendipitous discovery in 1964 of its surprising activity against a cutaneous

complication of leprosy called type 2 reaction or erythema leprosum nodosum (ENL)(*479*)."

SILDENAFIL

1998

From the discoverer(s)(*480*):

"In early clinical studies performed in 1991 and 1992, sildenafil was found to have simple linear pharmacokinetics, and also some vasodilatory activity, and was shown to modestly lower the blood pressure in healthy volunteers. The magnitude of the vasodilatory effect was rather modest compared with that of nitrates alone. Moreover, sildenafil was found to interact with nitrates, with the combination leading to exaggerated decreases in blood pressure in some individuals. Because nitrates are frequently prescribed to men with angina, further development of sildenafil for the lead indication of angina would have significant hurdles to overcome(*481*)."

From the discoverer(s)(*480*):

"In 1992, several multiple-dose, healthy volunteer studies were undertaken to investigate the pharmaco-kinetics, pharmacodynamics and tolerance of UK-92,480. When administered at doses of up to 75 mg three times per day for 10 consecutive days, some volunteers reported headaches, flushing, indigestion and muscle aches. Some volunteers also reported penile erections as a side effect. Initially this was not considered to be of major significance, because the volunteers were reporting these effects after a mere several days of UK-92,480 administration. Therefore, cardiovascular indications remained the primary focus of ongoing clinical investigations during 1992 and 1993. However, by mid-1993, UK-92,480 was looking less promising as a new treatment for angina pectoris. The relatively short half-life indicated that treatment would have to be administered at least three times per day for the chronic treatment of angina. The demonstrated interaction with nitrates was also a factor complicating future drug development for cardiovascular indications.

**Thoughts turn to erectile dysfunction**

During the 1980s, advances were made in the recognition and treatment of erectile dysfunction (ED). Prior to then, many clinicians considered ED to be either a relatively trivial issue and/or a condition that was predominantly attributable to psychological causes. However, urologists interested in ED had started treating their patients with intracavernosal injections of vasodilating drugs (for example, papaverine and prostaglandin E1) that functioned by modulating levels of cAMP. This pharmacological approach worked for many patients, but drawbacks included the invasive nature of the treatment, the induction of an 'artificial' erection that would often last long after intercourse had finished, with the added risks of local bleeding, bruising and priapism (a prolonged painful erection lasting longer than 6 hours). There was no doubt that an effective oral agent would be a major breakthrough in the treatment of this distressing condition, although at the time few researchers and clinicians in the field thought this was possible.

The decision to undertake pilot studies with sildenafil in ED was supported by the observation that penile erections were a common side effect in the multiple-dose sildenafil Phase I study. Furthermore, emerging data implicated NO as a key mediator of the neural and haemodynamic effects that lead to penile erection in men. In particular, in the early 1990s, Ignarro and others reported that NO is the neurotransmitter that is released from cavernous nerves during sexual stimulation. The NO diffuses into vascular smooth muscle cells of the penis, stimulating the production of cGMP and leading to corpus cavernosum smooth muscle relaxation, vasocongestion, veno-occlusion (by constriction of the venous outflow from the penis against the tunica albuginea) and, ultimately, erection. Local

neural production of high quantities of NO in the presence of sexual stimulation enables selective vasodilatation of the penile vasculature. The Pfizer team postulated that the administration of an inhibitor of cGMP breakdown would enhance and prolong the vasodilatory response, but only during sexual stimulation. The prospect of an oral agent that could work naturally with sexual stimulation to facilitate and maintain erections, without causing excessive vasodilatation in the systemic vasculature, was indeed an exciting prospect(*482*)."

## TIROFIBAN

1998

See also the eptifibatide entry.

The first antiplatelet drug derived from a snake venom protein was Tirofiban. Tirofiban is a non-peptide molecule that was developed based on the RGD motif present in the parent disintegrin molecule, Echistatin.

Echistatin was first isolated in 1988 from the venom of the saw-scaled viper and found as an effective antagonist of fibrinogen-induced platelet aggregation(*483*)."

## SACROSIDASE

1998

"Sacrosidase is a liquid enzyme preparation from S.cerevisiae used for the treatment of congenital sucrose-isomaltase deficiency (CSID). People with CSID have variable amounts of sucrose-isomaltase enzyme activity and therefore have issues metabolizing dietary disaccharide sucrose causing chronic or intermittent watery diarrhea in infants and children(*2*)."

## CALFACTANT

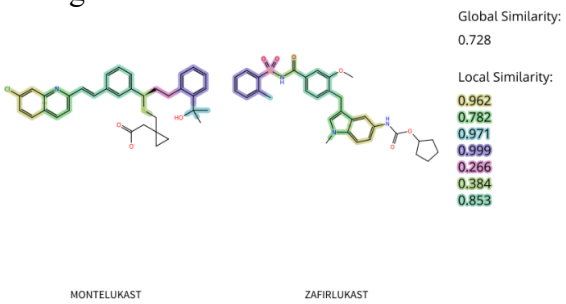
1998

"Calfactant is a sterile, non-pyrogenic lung surfactant intended for intratracheal instillation. It is an off-white suspension of an extract of natural surfactant from calf lungs suspended in 0.9% saline(*2*)."

## MONTELUKAST

1998

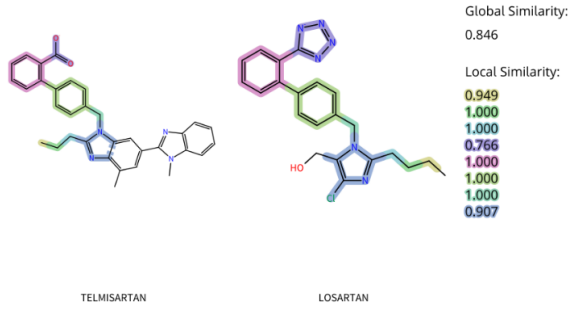
Analogue of zafirlukast




## TELMISARTAN

1998

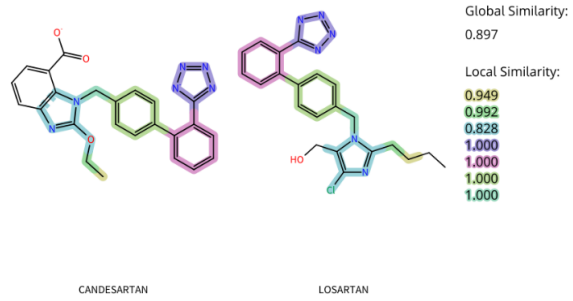
Analogue of losartan(*21, 474*)




## CANDESARTAN

1998

Analogue of losartan(*17*)




## RETEPLASE

1998

"Human tissue plasminogen activator, purified, glycosylated, 355 residues purified from CHO cells(*2*)."

## LEFLUNOMIDE

1998

From the first article reporting the antirheumatic effects of leflunomide, HWA 486:

"An often used method to determine the effectiveness of drugs on the developing adjuvant disease is to treat the animals from day 0-19 and read the results on day 19. Both non-steroidal anti-inflammatory drugs (NSAID) and immunosuppressive substances are effective in this test model. Perper et al. have suggested that it is possible to differentiate between anti-inflammatory and immunosuppressive agents by using a 'standardized arthritic assay.' In this assay twelve daily doses of immunosuppressive agents, started on the day of adjuvant injection, prevent the disease in the non-injected extremity. Standard anti-inflammatory substances are ineffective in this test when examined on day 21 (non-established arthritis). Thus, this immunopathological animal model was used to determine the disease modifying potential of antirheumatic agents including the novel isoxazole derivative HWA 486. This compound, which has the chemical name N-(4-Trifluoromethylphenyl)-5-methylisoxazol-4-carboxamide, is a non-steroidal agent and has been developed for use as an antirheumatic drug at our research laboratories. The present experiments compare the effects of HWA 486 with an immunosuppressive agent, cyclophosphamide, and the non-steroidal anti-inflammatory drugs indomethacin, phenylbutazone, and naproxen, on disease development as well as lymphocyte responsiveness in rats with adjuvant arthritis(*386*)."

## TOLCAPONE

1998

Secondary

## SEVELAMER HYDROCHLORIDE

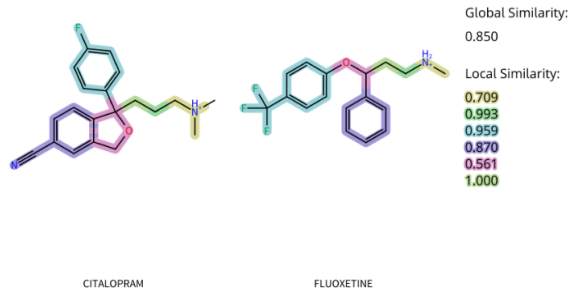
1998

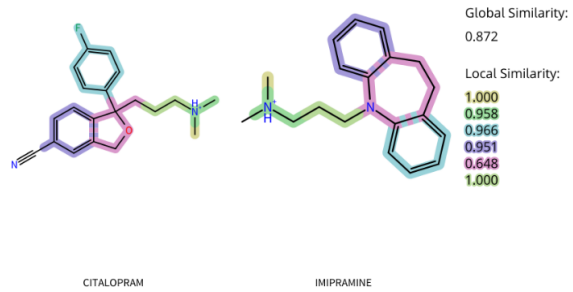
Phosphate binder and chelating agent

## CITALOPRAM

1998

Analogue of fluoxetine

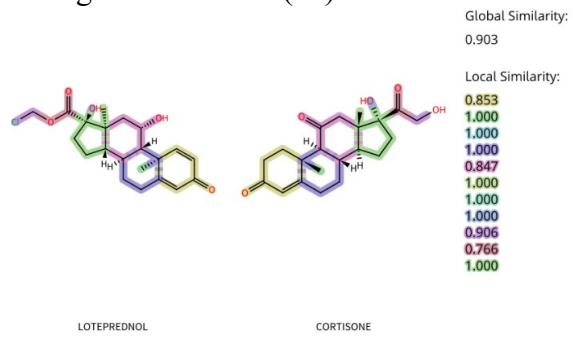



## LOTEPREDNOL

1998

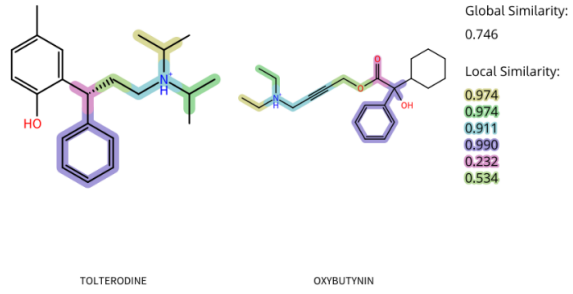
Analogue of cortisone(*21*)




## TOLTERODINE

1998

Analogue of oxybutynin



## EPTIFIBATIDE

1998

"Tirofiban and Eptifibatide are small, synthetic molecules developed from the snake venom RGD-disintegrins, which have high affinity and relative selectivity for the αIIbβ3 integrin. These compounds compete with fibrinogen for the αIIbβ3 integrin receptor in a dose-dependent manner and prevent platelet aggregation. The clinical therapeutic goal of using these drugs is to achieve 80% inhibition of platelet aggregation with minimal bleeding adverse effects(*483*)."

"In order to discover a selective disintegrin for αIIbβ3, several dozens of venoms were screened, leading to the discovery of Barbourin, purified from the venom of the snake *Sistrurus miliarius barbouri*. The disintegrin, Barbourin, isolated from this Southeastern pigmy rattlesnake, contains an amino acid substitution of Lys (K) for Arg (R) in the RGD sequence resulting with a KGD motif highly specific for αIIbβ3 (GP IIb-IIIa). Using this information, a series of conformational constrained, disulfide-bridged peptides were synthesized, containing the KGD amino acid sequence. Incorporation of the KGD sequence into a cyclic peptide template, followed by systematic optimization of the cyclic ring size, hydrophobicity, and the derivatization of the lysine side chain of the KGD sequence yielded peptide analogs which displayed αIIbβ3 integrin inhibitory potency and selectivity, comparable to that of Barbourin. Eptifibatide (Integrilin), one of the derivatives of Barbourin, is a cyclic heptapeptide, competitive antagonist for the activated, platelet αIIbβ3 integrin using the KGD integrin recognition sequence. Its mechanism of action is the prevention of the binding and cross-linking of fibrinogen to the platelet surface, causing inhibition of platelet aggregation and preventing thrombus formation(*483*)."

From the discoverer(s):

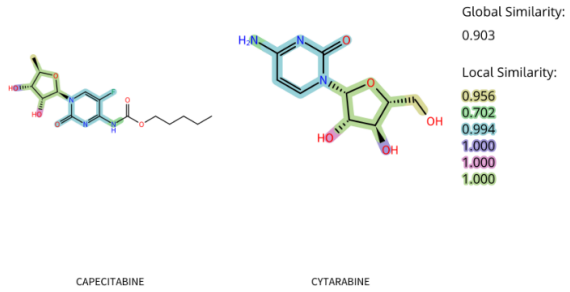
"During the past decade, a wide range of snake viper venoms have been shown to contain a family of compounds called disintegrins, small proteins that act as powerful antithrombotics and strongly inhibit platelet aggregation. Almost all these small proteins contain the amino acid sequence RGD (Arg-Gly-Asp), which is believed to play a role in the binding of fibrinogen to GP IIb/IIIa. However, RGD-containing venom disintegrins also bind to a number of other integrins, such as $\alpha_5\beta_1$ (fibronectin receptor) and $\alpha_v\beta_3$ (vitronectin receptor) and therefore lack the specificity for GP IIb/IIIa.

In an effort to find a disintegrin specific for GP IIb/IIIa, we screened 62 different snake venoms, 52 of which exhibited some type of integrin-binding activity. Only barbourin, a 73-amino acid disintegrin from the venom of the southeastern pigmy rattlesnake *Sistrurus barbouri*, selectively inhibited fibrinogen binding to GP IIb/IIIa and did not interfere with binding of RGD-containing ligands to other integrins, including $\alpha_5\beta_1$ and $\alpha_v\beta_3$(*484*)."

## CAPECITABINE

1998

Analogue of cytarabine(*21*)




## THYROTROPIN ALFA

1998

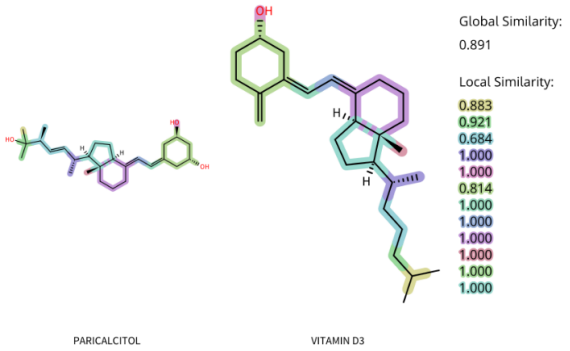
"Thyrotropin alfa is a recombinant form of thyroid stimulating hormone used in performing certain tests in patients who have or have had thyroid cancer. It is also used along

with a radioactive agent to destroy remaining thyroid tissue in certain patients who have had their thyroid gland removed because of thyroid cancer(*2*).”

PARICALCITOL

1998

Analogue of vitamin D




From an early paper on using vitamin D in hyperparathyroidism patients:

“IN patients with primary hyperparathyroidism the raised serum-alkaline-phosphatase I and the circulating immunoassayable parathyroid-hormone levels correlate well with the radiological extent of the bone disease. It is generally thought that the raised alkaline phosphatase reflects an increase in bone formation, secondary to the increase in bone resorption induced by parathyroid hormone. In theory the presence of vitamin-D deficiency in such patients might be expected to elevate the serum-alkaline-phosphatase further still, with worsening of the bone disease.

We have investigated two patients with primary hyperparathyroidism who had radiological evidence of bone disease and raised serum-alkaline-phosphatase levels. During treatment with small doses of vitamin D the radiological picture improved notably, and the serum-alkaline-phosphatase fell to normal(*485*).”

INFLIXIMAB

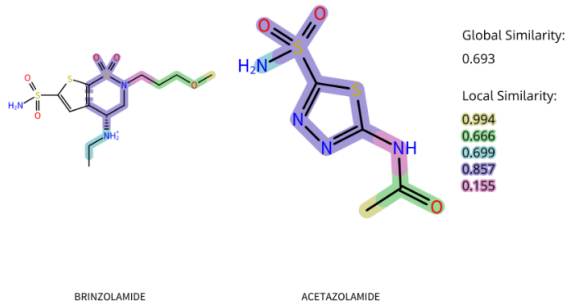
1998

Monoclonal Antibody

BRINZOLAMIDE

1998

Analogue of acetazolamide




RIFAPENTINE

1998

Analogue of rifampin

Error in similarity calculation by FTrees because of the unsupported macrocycle

PALIVIZUMAB

1998

Monoclonal Antibody

TRASTUZUMAB

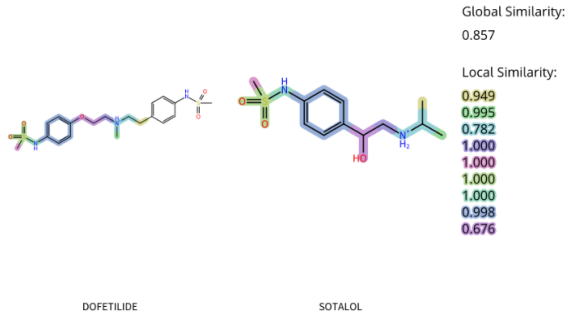
1998

Monoclonal Antibody

DOFETILIDE

1999

Analogue(*486*) of sotalol




AMINOLEVULINIC ACID

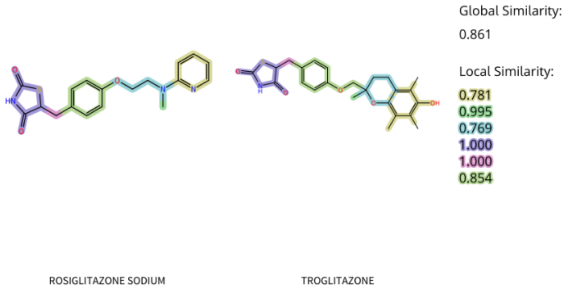
1999

Photochemotherapeutic

ROSIGLITAZONE SODIUM

1999

Analogue of troglitazone(*21*)




"Troglitazone and the other glitazones belong to a chemical class known as thiazolidinedione The antihyperglycemic potential of this class of compounds became apparent when ciglitazone (ADD-3878) was identified in the course of efforts at Takeda to synthesize triglyceride-lowering agents based on clofibrate. Ciglitazone proved to have anti-diabetic effects in diabetic rodents enhancing insulin action without directly stimulating insulin secretion

Troglitazone (CS-045) was first described by researchers at Sankyo in 1988 and increasing interest and activity in the area led to the identification of a number of other novel glitazones in the years that followed These agents shared a substituted thiazolidinedione structure, with modifications selected to improve their pharmacological efficacy.

Troglitazone was designed to combine the insulin-sensitizing activity of the thiazolidinedione class with lipid peroxide-lowering activity. Lipid peroxides are frequently elevated in diabetic patients and have been implicated in the development of atherosclerosis The structure of troglitazone incorporates the pharmacophore for a- tocopherol, an antioxidant that has been shown to confer resistance to oxidation on low-density lipoprotein cholesterol It was hoped that this design element would make troglitazone a particularly effective therapeutic agent.

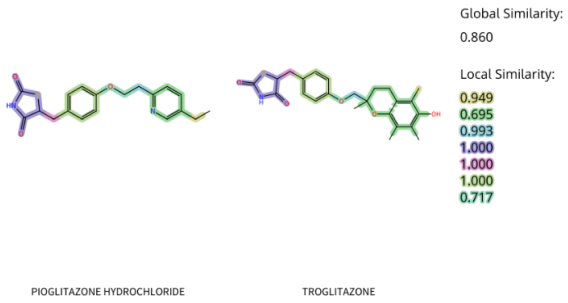
**4. Pre-clinical studies with glitazones**

In the late 1980s and early 1990s when the earliest thiazolidinedione anti-diabetic agents were synthesized, their molecular site of action had not been identified. The initial serendipitous observation that these agents were capable of reducing plasma glucose levels in hyperglycemic, hyperlipidemic mice were followed by more extensive characterization studies in rodent models of diabetes. These agents were found to decrease plasma glucose, insulin and triglyceride levels significantly in a number of genetically diabetic animals, including the *ob/ob* mouse, the *db/db* mouse, the KK mouse and the Zucker fatty rat. The anti-hyperglycemic activity of troglitazone was also demonstrated in non-genetic, diet-induced models of insulin resistance such as the fructose-fed rat and the fat-fed rat. Together these studies demonstrated the ability of thiazolidinediones to improve insulin action in a wide variety of insulin-resistant states, regardless of the underlying causative mechanism(s)(*487*)."

PIOGLITAZONE HYDROCHLORIDE

1999

Analogue of troglitazone(*21*)




FOSAMPRENAVIR

1999

Prodrug of amprenavir

INTERFERON GAMMA-1B

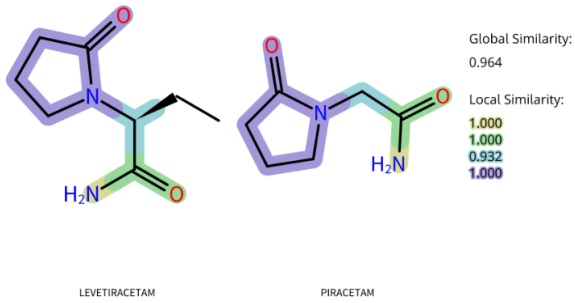
1999

Endogenous-based biopharmaceutical

## LEVETIRACETAM

1999

Analogue of piracetam(*488*)




Discovery of piracetam:

From the discoverer(s):

"It all started with a wrong hypothesis, namely, that by working with cyclic GABA derivatives we should find new sedative hypnotics because, we thought, we would provide an 'extra amount' of inhibition to the brain. During 1963-1964, Strubbe and Cyprysiak [1967], on the ground of this idea, synthesized several compounds, including piracetam (UCB 6215: Nootropyl), which is a cyclic, disubstituted GABA derivative. Piracetam never induced any sedation but, for reasons described elsewhere, we have tested and found it active to inhibit the central nystagmus in the rabbit, and also a vestibular nystagmus. Despite all our extensive studies, and with the exception of a particular anticonvulsant potency, piracetam was found to be nontoxic and devoid of any common psychopharmacological, cardiovascular, respiratory, or other activities. As for the GABA-related hypothesis to explain nystagmus inhibition, and particularly antiepileptic activities, we soon found out that it was also wrong. Indeed, piracetam, which is almost entirely eliminated as such, nonmetabolized, does not interfere with GABA metabolism or receptors(*489*)."

## ENTACAPONE

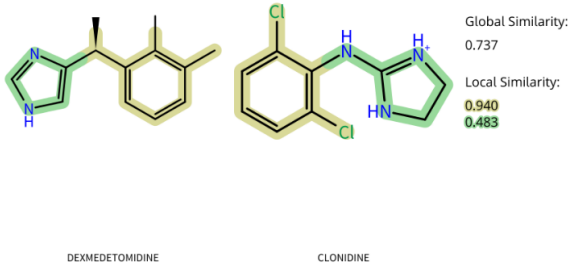
1999

Secondary

## DEXMEDETOMIDINE

1999

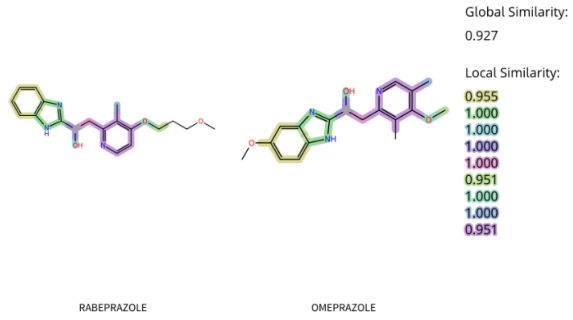
Analogue of clonidine(*21*)




## RABEPRAZOLE

1999

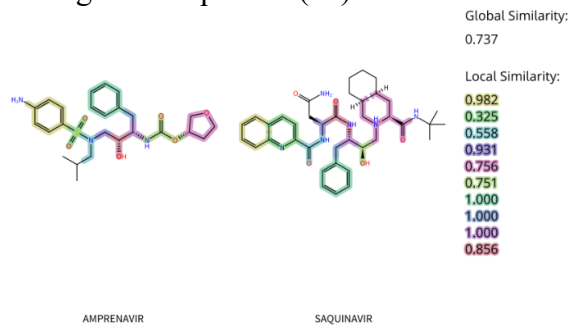
Analogue of omeprazole(*21*)




## AMPRENAVIR

1999

Analogue of saquinavir(*21*)




## PORACTANT ALFA

1999

"Poractant alfa is an extract of natural porcine lung surfactant consisting of 99% polar lipids

and 1% hydrophobic low molecular weight proteins(*2*)."

SIROLIMUS

1999

From the discoverer(s):

"Although sirolimus was isolated as an antifungal agent with potent anticandida activity, subsequent studies have revealed impressive antitumor/antiproliferative and immunosuppressive properties(*490*)."

From the discovery paper(*490*):

"**Identification of the Rapamycin-Producing Streptomycete**: Streptomycete strain AY B-994 was isolated from a soil sample collected in Easter Island (Rapa Nui): the soil was diluted in distilled water and the resulting suspensions were plated on yeast-starch agar according to the double-layer technique of PORTER et al. After one week of incubation at 28°C the streptomycete colonies were purified by repeated streaking and the pure strains grown separately on yeast-starch agar plates to yield confluent growth. After 4 to 10 days of incubation, discs were cut and transferred onto the surface of plates of Bacto-Blood Agar Base inoculated with test bacteria and SABOURAUD dextrose agar inoculated with test yeast and dermatophytes. […] When tested under the above conditions strain AY B-994 showed the following antimicrobial activity (diameter of inhibition zone in mm): *Sarcina lutea*, 24; *Staphylococcus aureus*, 20; *Escherichia coli*, *Enterobacter aerogenes*, *Proteus mirabilis* and *Pseudomonas aeruginosa*, no zone of inhibition; *Candida albicans*, 24; *Microsporum gypseum*, 26; *Trichophyton granulosum*, 27(*491*)."

From the oldest article found reporting antitumor activity(*490*):

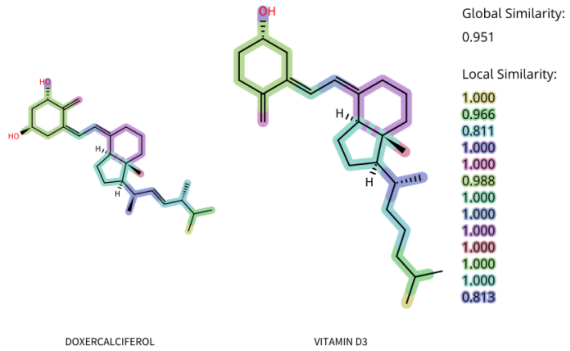
"Compounds are obtained by the Natural Products Branch through contracts, grants, and through an extensive worldwide surveillance program. Pure compounds are tested initially against tile P388 leukemia (*in vivo* pre-screen) at NCI unless there is biochemical data or antitumor data which indicates that other testing would be more desirable. […]
Rapamycin-NSC 226080 is a triene isolated by Ayerst Pharmaceuticals from Streptomyees fermentations. Originally this material was found to have good anti-Candida activity. Rapamycin was selected for further development at NCI based on its good activity against mammary and colon tumors and the brain tumor, ependymoblastoma(*492*)."

DOXERCALCIFEROL

1999

Analogue of vitamin D(*1*)

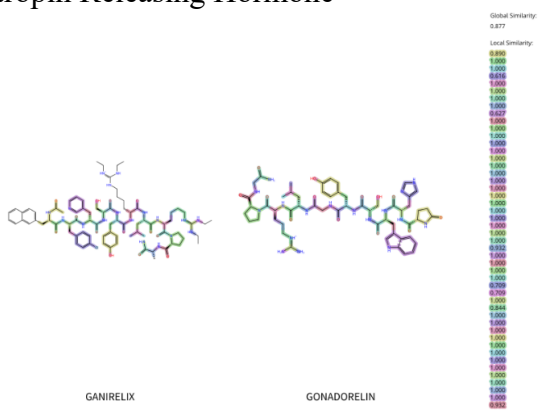
Also see the paricalcitol entry.




GANIRELIX

1999

Analogue(*486*) of the endogenous Gonadotropin Releasing Hormone



## DALFOPRISTIN - QUINUPRISTIN

1999

Analogue of streptogramin

Error in similarity calculation by FTrees because of the unsupported macrocycle

"Pristinamycin was identified in culture filtrates of *Streptomyces pristinaespiralis* in 1962, virginiamycin in *Streptomyces virginiae* in 1955, and mikamycin in *Streptomyces mitakaensis* in 1956. Natural mixtures of streptogramins have been available for clinical use in Europe since the mid-1950s. Streptogramins cannot cross the outer membrane of most Gram-negative bacteria and are primarily effective against Gram-positive bacteria. They have been used topically or orally in the treatment of skin, bone, and respiratory infections, mainly caused by staphylococci. The first semisynthetic injectable streptogramin compound, quinupristin–dalfopristin, was approved in 1999(*493*)."

"The antibiotic streptogramin was first obtained from culture filtrates of a species of Streptomyces, now classified as *Streptomyces graminofmiens* (Charney et al. 1953)(*494*)."

I could not find the article cited in the previous quotation as the discovery paper of streptogramin(*495*), yet, due to the trend at the time, 1953, it was probably discovered by screening different culture filtrates against bacteria cultures or infected animals.

## ORLISTAT

1999

From the discovery paper:

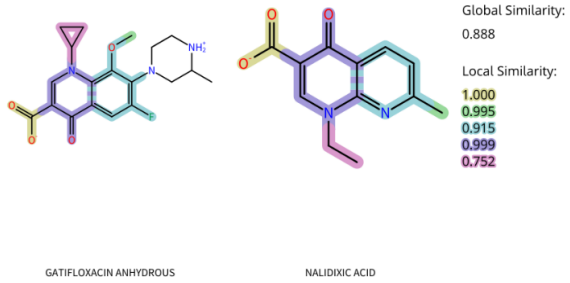
"The key enzyme of dietary triglyceride absorption is pancreatic lipase, exerting its activity at the water-lipid interphase, in conjunction with bile salts and co-lipase. A target directed screening of microbial broths from soil organisms resulted in the discovery of a very potent, selective and irreversible inhibitor of pancreatic lipase, which was named lipstatin. […]

Fermentation broths from actinomycetes and fungi, isolated from soil samples, were screened for inhibition of lipase activity. The most active broths were from the fermentation of two streptomyces strains, No. 85~13 found in a soil sample from Mallorca (Spain) and No. 72~21 in a soil sample from Gstaad (Switzerland)(*496*)."

## GATIFLOXACIN

1999

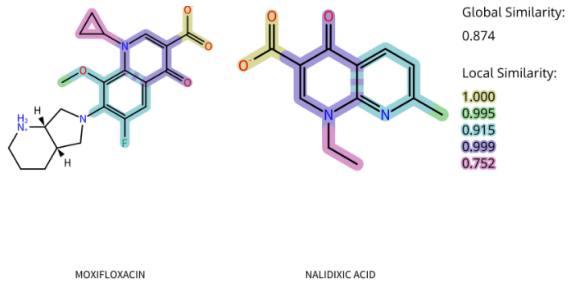
Analogue of nalidixic acid(*21*)




## MOXIFLOXACIN

1999

Analogue of nalidixic acid(*21*)




## QUINUPRISTIN

1999

Analogue of streptogramin(*493*)

Refer to the dalfopristin entry.

## ZANAMIVIR

1999

"Computer-assisted drug design, based on

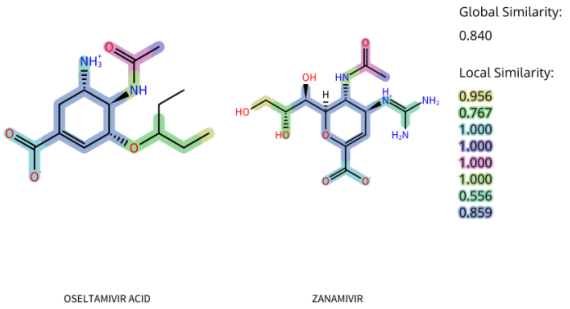
the crystal structure of the influenza viral neuraminidase, led to the identification of zanamivir (GG167) as a specific and potent inhibitor of the enzyme, and of the *in vitro* and *in vivo* replication of both influenza A and B virus(*497*)."

"Two potent inhibitors based on the crystal structure of influenza virus sialidase have been designed. These compounds are effective inhibitors not only of the enzyme, but also of the virus in cell culture and in animal models. The results provide an example of the power of rational, computer-assisted drug design, as well as indicating significant progress in the development of a new therapeutic or prophylactic treatment for influenza infection(*498*)."

## OSELTAMIVIR ACID

1999

Analogue of zanamivir(*497*)




## CILOSTAZOL

1999

"The mechanism of cilostazol on the symptoms of intermittent claudication is not fully understood. […] The predecessors of cilostazol were identified by screening new synthetic compounds in blood platelet aggregation assays(*486*)."

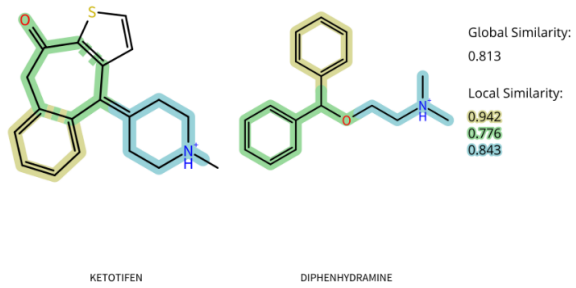
From the discovery paper cited in the previous quotation:

"The purpose of this work was to synthesize many alkyl 4-(2-oxo-1,2,3,4-tetrahydro-6-quinolyloxy) alkanoates and related compounds for testing for inhibitory activity *in vitro*. We describe here the synthesis of various 2-oxoquinoline derivates possessing high inhibitory activity towards blood platelet aggregation and we discuss their structure-activity relationship(*499*)."

## KETOTIFEN

1999

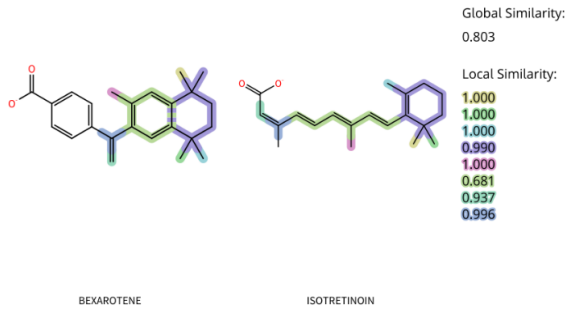
Analogue of diphenhydramine(*21*)




## BEXAROTENE

1999

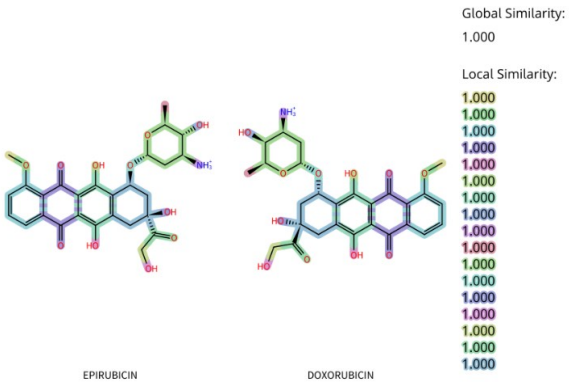
Analogue(*486*) of isotretinoin




## EPIRUBICIN

1999

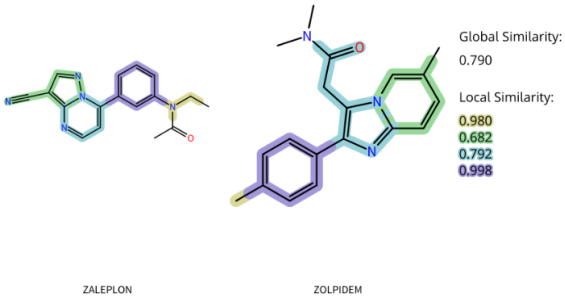
4'-epi-isomer of doxorubicin(*1*)



## ZALEPLON

1999

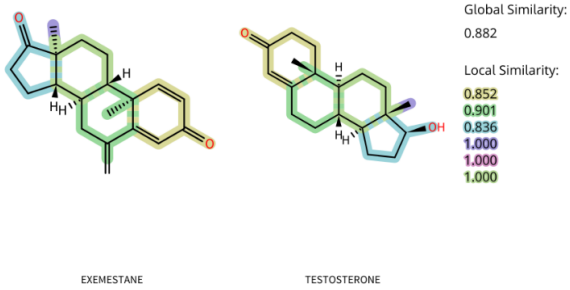
Analogue(*486*) of zolpidem




## EXEMESTANE

1999

Analogue(*486*) of testosterone




## DOCOSANOL

2000

"The antiviral activity of a long-chain, saturated fatty acid was initially reported 70 years ago by Stock and Francis. Their work was based on previous studies showing the anti-infective properties of soaps. Katz and coworkers reported in 1991 that 1-docosanol, a 22-carbon-long saturated alcohol inhibited viral replication. The precise MMOA of this fatty acid, which is approved to treat genital warts, is unknown(*486*)."

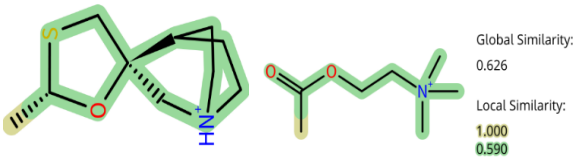
From a 1976 paper cited in the previous quotation:

"This report describes the inactivation of lipid-containing viruses by several long-chain alcohols. A striking peak in antiviral activity was found for saturated alcohols having chain lengths from 10 to 14 carbons. Viruses having different membrane structure showed different susceptibilities to alcohols having different chain lengths and structural features. Decanol, dodecanol, and tetradecanol readily inactivated herpes simplex virus and the enveloped bacterial virus. The lipid-containing virus PM2 was susceptible to decanol and dodecanol but comparatively unsusceptible to tetradecanol(*500*)."

## CEVIMELINE

2000

Analogue of acetylcholine(*488*)

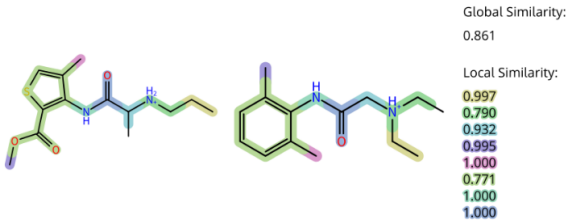



CEVEMELINE ACETYLCHOLINE

## ARTICAINE

2000

Analogue of lidocaine




ARTICAINE LIDOCAINE

## PIPERONYL BUTOXIDE

2000

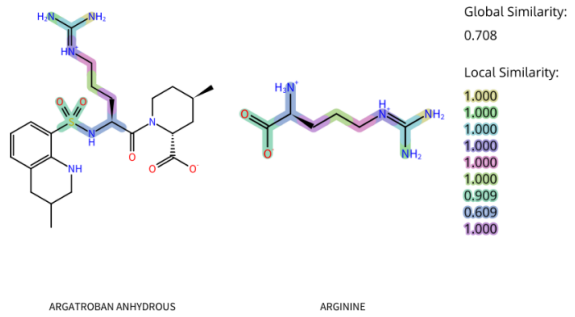
"Piperonyl butoxide (PBO) is an organic compound used as a component of pesticide formulations. It is a waxy white solid. It is a semisynthetic derivative of safrole. It is used for the treatment of head, pubic (crab), and body lice. Piperonyl butoxide is a synergist.

It has no pesticidal activity of its own(*1*)"

ARGATROBAN

2000

Analogue of arginine(*1, 501, 502*)




From the discovery paper:

"**A** series of $N^2$-substituted L-arginine ester and amide derivatives has been examined for inhibitory effects on thrombin. Potent inhibition of thrombin has been found with arginine derivatives having two hydrophobic moieties […]

In this paper, the inhibitory effect of (2*R*,4*R*)-MQPA on thrombin is compared with that on trypsin, plasmin, plasma kallikrein, and factor Xa to examine the specificity of inhibition."

"The active sites of fIIa and fXa are structured for specific catalytic cleavage of physiological substrates. FIIa cleaves, among others, the sequences GlyGlyGlyValArg-GlyPro and PhePheSerAlaArg-GlyHis in fibrinopeptides A and B, respectively. FXa cleaves PhePheAsnProArg-ThrPhe and TyrIleAspGlyArg-IleVal in prothrombin. Both enzymes strongly prefer arginine as the residue preceding the scissile peptide bond (P1 in the nomenclature of Schechter and Berger)(*502*)."

RACEPINEPHRINE

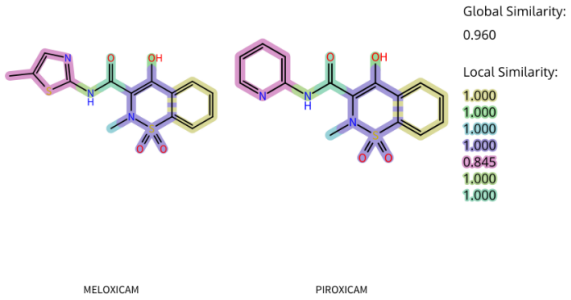
2000

"Racepinephrine or racemic epinephrine is a mixture of levo and dextro isomers of epinephrine act as a nonselective agonist at adrenergic receptors(*1*)."

MELOXICAM

2000

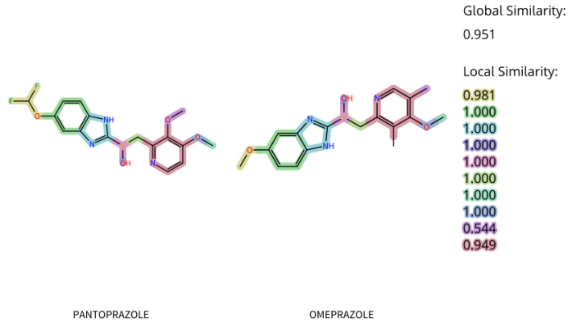
Analogue of piroxicam(*21*)




PANTOPRAZOLE

2000

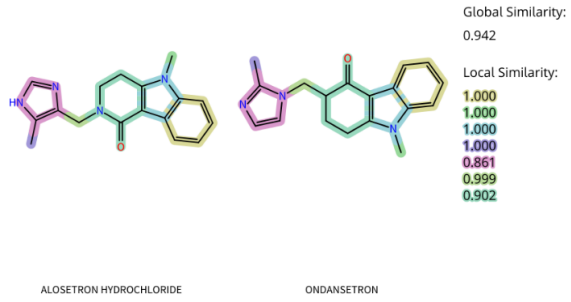
Analogue of omeprazole(*21*)




ALOSETRON HYDROCHLORIDE

2000

Analogue of ondansetron(*21*)




INSULIN GLARGINE

2000

Endogenous-based biopharmaceutical

## BIVALIRUDIN

2000

Analogue of the hirudin(*1, 486*)

Error in similarity calculation by FTrees because of the unsupported macrocycle

"Leeching is an art dating back at least to ancient Egypt. It reached its zenith in the late 18th and early 19th centuries. The antithrombotic quality of leech saliva was first noted by Haycraft in 1884 and the active anticoagulant ingredient isolated in 1904 by Jacoby. He gave this agent the name 'hirudin'. Hirudin was isolated in pure crystalline form by Markwardt in 1957 and first produced in quantity by genetic engineering in 1986(*503*)."

## R-LINEZOLID

2000

"The oxazolidinones are a novel class of totally-synthetic antibacterial agents. (S)-3-aryl-5-acetamidomethyl-2-oxazolidinones were discovered by researchers at EI Dupont de Nemours and Co., Inc. and were reported in 1987. An initial screening-derived lead was S-6123, a 5-hydroxymethyl-2-oxazolidinone(*504*)."

From the discovery paper of oxazolidinones, cited in the previous quotation:

"The antibacterial activity of compounds of the oxazolidinone series was initially identified in a screening program. The first members of this new synthetic class were primarily active against staphylococci and streptococci(*505*)."

## ZONISAMIDE

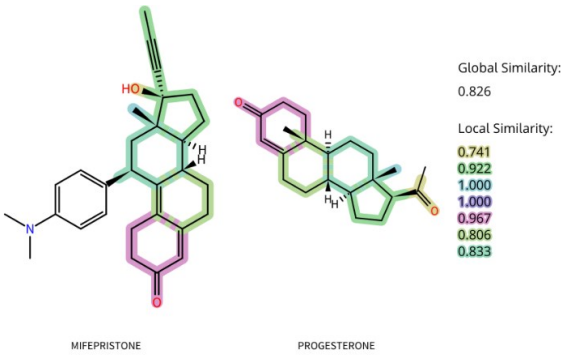
2000

"The anticonvulsant properties of zonisamide were discovered through the testing of numerous 3-substituted 1,2-benzisoxazole compounds in animal models. The exact MMOA is unknown(*486*)."

## MIFEPRISTONE

2000

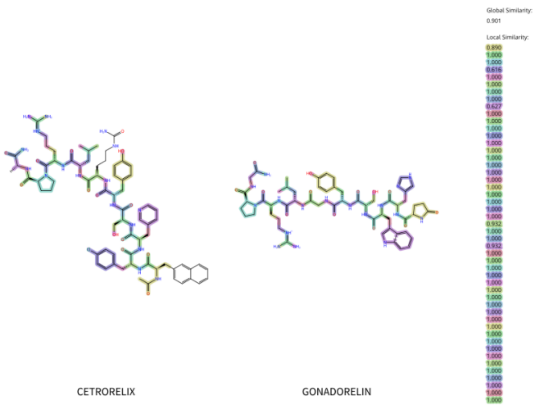
Analogue of progesterone




## CETRORELIX

2000

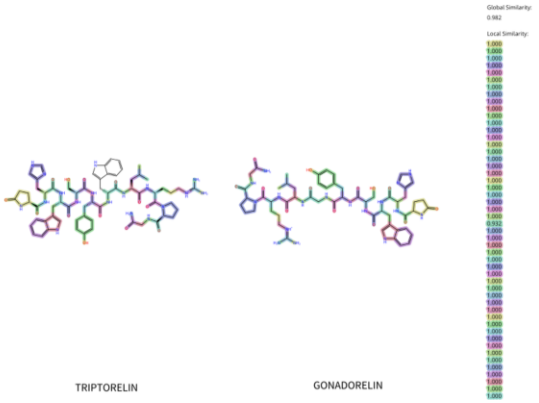
Analogue of the endogenous Gonadotropin Releasing Hormone




## TRIPTORELIN

2000

Analogue of GnRH(*1*)



## VERTEPORFIN

2000

Photochemotherapeutic

Analogue of the natural substrate, protoporphyrin IX(*486*)

“Verteporfin is a chemically modified version of protoporphrin IX. Verteporfin is activated by light in the presence of oxygen, generating highly reactive, short-lived singlet oxygen and reactive oxygen radicals. Light activation of verteporfin results in local damage to neovascular endothelium, resulting in vessel occlusion(*486*).”

“As far back as the mid 1980s, it was realised that although PDT with sensitisers based on haematoporphyrin heralded the introduction of a new therapeutic technology, there were many potential defects with these materials which could potentially be eliminated with new sensitisers. In particular, there was a need for new compounds which could be made chemically pure, which absorbed light at longer wavelengths to assist tissue penetration and which did not cause the prolonged skin photosensitivity seen with haematoporphyrin derivative. It was against this background that BPD was first synthesised(*506*)”

“Verteporfin is a chlorin, that is one of the five membered rings is reduced. Compared with the corresponding porphyrin molecules, chlorins have stronger absorption at longer wavelengths, enabling light of longer wavelengths to be used for therapy, allowing deeper tissue penetration(*506*).”

“Soon after its preparation, preliminary *in vitro* studies demonstrated that BPD was a powerful sensitiser and more effective than haematoporphyrin. After 1 h incubation, it was found that BPD was 10-70 times more photocytotoxic than haematoporphyrin towards various cells in culture. This work also emphasised the absorption maximum around 700 nm, which is in the range of wavelength that penetrates tissues best. Interestingly, this early work foresaw that BPD could be a drug of choice in cancer PDT, but non-cancer applications were not then envisaged(*506*).”

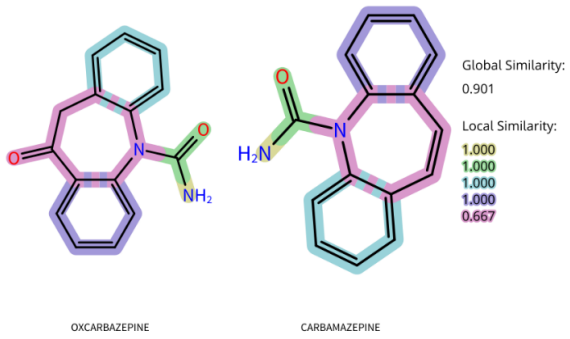
“Similar studies were then carried out in a mouse tumour model *in vivo*. Distribution and clearance studies showed that relative distribution in a variety of mouse tissues was similar for all BPD analogues. However, again, the monoacid forms of BPD were found to be much more photodynamically active than the diacid analogue.

By 1991, it was realised that verteporfin was a powerful new photosensitiser with strong potential for PDT application, although at that time it was still thought that this would be in the cancer field(*506*)”

## OXCARBAZEPINE

2000

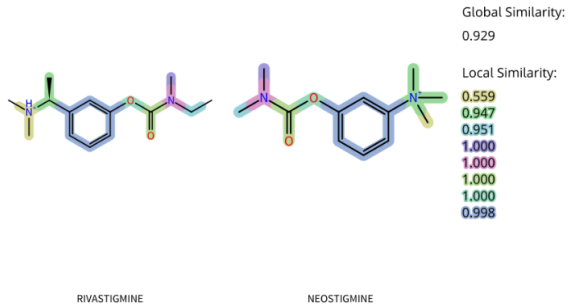
Analogue of carbamazepine(*21*)




## RIVASTIGMINE

2000

Analogue of neostigmine(*21*)




## CHORIOGONADOTROPIN ALFA

2000

Recombinant human chorionic gonadotropin(*2*)

NATEGLINIDE

2000

"In the course of screening in 18-hour-fasted normal mice for hypoglycemic effects, Shinkai and coworkers found that N-benzoyl-DL -phenylalanine exhibited a slight blood glucose lowering activity at an oral dose of 500 mg per kg. The component parts of the molecule were systematically varied leading to the identification of nateglinide(*486*)."

From the discovery papers cited above:

"To seek another type of antidiabetic drug, we screened numerous compounds in 18-h-fasted normal mice for hypoglycemic effects. In the course of this screening, we found that N-benzoyl-DL-phenylalanine exhibited a slight blood glucose lowering activity at a oral dose of 500 mg/kg(*507*)."

"In further studies on the relationships between the structure of the acyl moiety and activity, N-(cyclohexyl-carbonyl)-D-phenylalanine was found to be more potent than N-benzoyl-D-phenylalanine. This result suggested that the planar structure (benzene ring) of the acyl moiety of N-benzoyl-D-phenylalanine derivatives was not always necessary for activity. Various analogues of 5 with modified cyclohexylcarbonyl groups were synthesized and evaluated for blood glucose lowering activity. A highly active compound, N-[(trans-4-isopropylcyclohexyl)-carbonyl]-phenylalanine, which showed a 20% blood glucose decrease at an oral dose of 1.6 mg/kg in normal fasted mice was obtained. The three-dimensional structure of the acyl moiety was characterized by high-resolution $^{1}H$ NMR spectroscopy and semiempirical molecular orbital calculation (MNDO) in order to study the relationship between the three-dimensional structure of the acyl moiety and the activity(*508*)."

BOTULINUM TOXIN TYPE B

2000

"In 1822 Kerner published 155 case reports of patients with probable botulism and hypotheses on the 'sausage poison' in a second monograph 'Das Fettgift oder die Fettsäure und ihre Wirkungen auf den thierischen Organismus, ein Beytrag zur Untersuchung des in verdorbenen Würsten giftig wirkenden Stoffes' ['The fat poison or the fatty acid and its effects on the animal organism, a contribution to the examination of the substance which acts toxically in bad sausages']. The monograph contained the accurate description of all muscular symptoms and clinical details of all autonomic disturbances occurring in botulism such as mydriasis, decrease of lacrimation and secretion of the salivary glands, gastrointestinal and bladder paralysis. Kerner also experimented with various animals by feeding them with extracts from bad sausages and finally carried out heroic experiments on himself. […] In the eighth chapter of the monograph of 1822, Kerner developed the idea of using the toxin for therapeutic purposes. He concluded that small doses would be beneficial in conditions with pathologic hyperexcitability of the nervous system. Kerner favored various diseases in which he suspected an overexited nervous ganglia system (e.g., motoric hyperkinesias) as appropriate indications for the therapeutic use of the 'toxic fatty acid' botulinum toxin(*509*)."

BALSALAZIDE

2000

"a prodrug that is enzymatically cleaved by bacterial azoreduction to release equimolar quantities of mesalamine (5-aminosalicylic acid or 5-ASA) in the colon, an anti-inflammatory drug(*1*)."

INSULIN ASPART

2000

Analogue of human insulin (*1*)

TENECTEPLASE

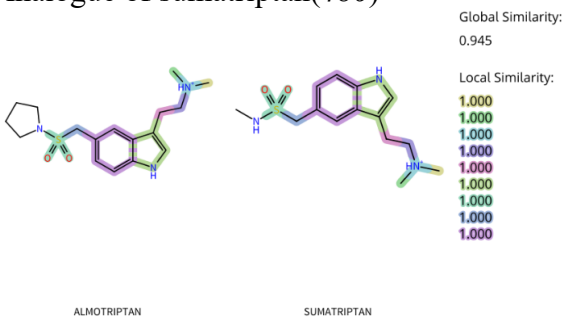
2000

“Tenecteplase is a tissue plasminogen activator (tPA) developed from modifications of natural human tPA complementary DNA (cDNA)(*2*).”

ALMOTRIPTAN

2001

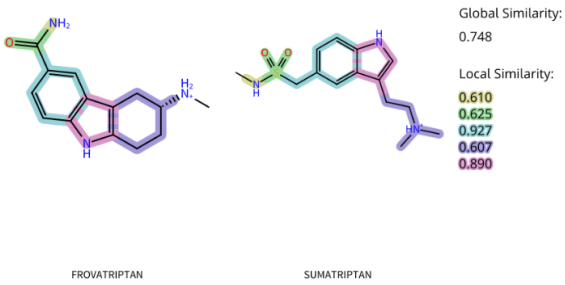
Analogue of sumatriptan(*486*)




FROVATRIPTAN

2001

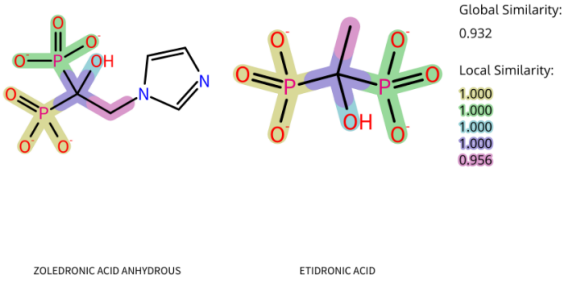
Analogue(*486*) of sumatriptan




ZOLEDRONIC ACID

2001

Analogue of etidronic acid




IMATINIB

2001

“The shortened version of chromosome 22, which is known as the Philadelphia chromosome, was discovered by Nowell and Hungerford, and provided the first evidence of a specific genetic change associated with human cancer. The molecular consequence of this inter-chromosomal exchange is the creation of the *BCR–ABL* gene, which encodes a protein with elevated tyrosine-kinase activity. The demonstration that *Bcr–Abl* as the sole oncogenic event could induce leukaemias in mice has established *BCR–ABL* as the molecular pathogenic event in CML.As the tyrosine-kinase activity of BCR–ABL is crucial for its transforming activity, the enzymatic activity of this deregulated gene could plausibly be defined as an attractive drug target for addressing BCR–ABL-positive leukaemias. For the first time, a drug target was identified that clearly differed in its activity between normal and leukaemic cells. […]

In the case of Glivec, a lead compound was identified in a screen for inhibitors of protein kinase C (PKC). This compound — a phenylaminopyrimidine derivative — had promising ‘lead-like’ properties and a high potential for diversity, allowing simple chemistry to be applied to produce compounds with more potent activity or selectivity. Strong PKC inhibition in cells was obtained with derivatives bearing a 3′-pyridyl group at the 3′-position of the pyrimidine. During the optimization of this structural class, it was observed that the presence of an amide group on the phenyl ring provided inhibitory activity against tyrosine kinases, such as the BCR–ABL kinase(*510*).”

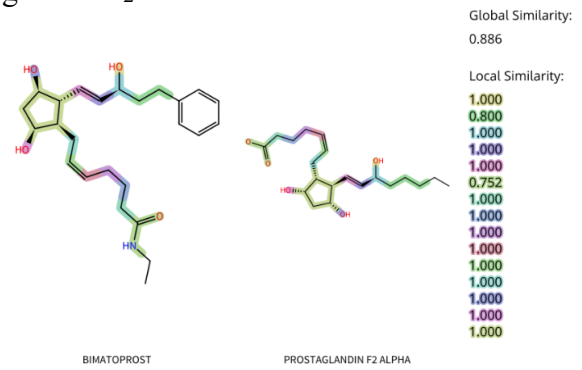
“Many of the medicines that were invented starting with a target specific assay required an additional empirical phenotypic assay to prioritize the actives and identify candidates with functional efficacy. The discovery of gleevec, a c-abl kinase inhibitor that works

through stabilizing the kinase inactive state, PARP inhibitors such as olaparib(*511*)"

BIMATOPROST

2001

Analogue of the endogenous(*486*) prostaglandin $F_2\alpha$




Eyelash hypertrichosis stimulating activity of latanoprost and bimatoprost was observed as a side effect in some of their users(*512*).

CASPOFUNGIN

2001

From the discovery team:

"Echinocandin B was one of the first cyclic lipopeptides of this class reported in 1974 by Sandoz. It was the lead for medicinal chemistry efforts at Sandoz (now Novartis) and subsequently at Eli Lilly. Merck's natural product screening efforts led to the discovery of the pneumocandin series which had two major structural differences compared to the echinocandins. The natural product pneumocandin $B_0$ eventually became the starting material for the synthesis of caspofungin acetate (CANCIDAS®). The discovery of pneumocandin $B_0$ began in 1985 at CIBE, a subsidiary of Merck located in Madrid, Spain when *Glarea lozoyensis* (originally named as *Zalerion arboricola*) was isolated, fermented, and extracted by an organic solvent and determined to produce a potential cell-wall active antifungal agent(*513*)."

From a paper cited in the previous quotation, regarding the discovery of pneumocandin $B_0$:

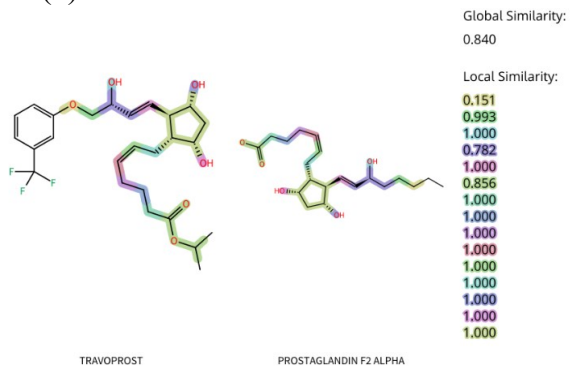
"In screening for new antifungal agents from fungi, a new lipopeptide antifungal agent, L-671,329, similar to echinocandin B, has been isolated from *Zalerion arboricola.* Studies indicate that L-671,329 is produced under both solid and liquid fermentation conditions. […]

The methods of detection utilized in the following studies and isolations were antifungal activity as measured via zones of inhibition in a disc diffusion assay on agar plates seeded with *Candida albicans*(*514*)."

TRAVOPROST

2001

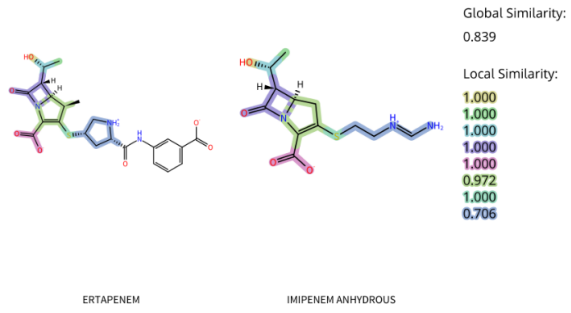
Analogue of the endogenous prostaglandin $F_2\alpha$(*1*)




ERTAPENEM

2001

Analogue of imipenem(*488*)




DARBEPOETIN ALFA

2001

Human erythropoietin with 2 aa substitutions to enhance glycosylation(*1*)

## GALANTAMINE

2001

"In 1947, a Soviet journal reported the presence of previously unknown alkaloids in the common snowdrop, *Galanthus nivalis*; the authors named the major (yet undefined) compound galanthamine. A few years later, the same team isolated and characterized it from the closely related *Galanthus woronowii*. Japanese researchers appear to have isolated the same alkaloid from the red spider lilly (*Lycoris radiata*), calling it lycoremine. It seems likely that ethnomedicine prompted these investigations […]

The discovery generated very limited international interest until 1960, when therapeutic usefulness was suggested based on the finding that the alkaloid is an inhibitor of cholinesterases, with stronger activity toward muscle acetylcholinesterase than pyridostigmine but somewhat less than neostigmine. Almost immediately, galanthamine (the 'h' was dropped only in the 1990s when the international nonproprietary name was defined) was added to the armamentarium provided by these older cholinesterase inhibitors to treat myopathies or postpolio paralytic conditions, and for reversal of neuromuscular blockade after anesthesia. It was also found useful for the treatment of peripheral neuropathies and radiculitis […]

While these are all peripheral actions, galantamine (a tertiary ammonium base) easily penetrates the blood–brain barrier and also inhibits brain cholinesterases, increasing central cholinergic tone. This certainly contributed to the drug's action in spinal poliomyelitis and awakening from anesthesia, and also to the positive effects reported in intracerebral hemorrhage from various causes. There is anecdotal evidence that some European neuropsychiatrists used Nivalin off-label to treat cognitive and emotional impairments after traumatic brain injury. However, no case reports or studies were published.

In 1977, Baraka and Harik, perhaps following up on earlier Soviet Union animal data, reported that galantamine reversed the acute anticholinergic syndrome (drowsiness and disorientation up to delirium) that the muscarinic receptor antagonist, scopolamine induces in cognitively normal volunteers but they made no attempt to quantify cognitive restitution in their subjects. […]

However, once the cholinergic hypothesis of Alzheimer's disease was accepted (which happened quickly because the lack of cholinergic tone in patients' brains was demonstrated only a year later), perspectives for an additional use of galantamine as an antidementive drug should have been immediately evident(*515*)."

"It is a natural product known from several members of the Amaryllidaceae and the idea for developing a natural product from these species seems to be based on ethnobotanical information. This alkaloid was first isolated from snowdrop (*Galanthus* spp., most notably *G. woronowii*), but today it is obtained from *Narcissus* spp. and *Leucojum* spp. (esp. *L.* aestivium) as well as synthetically. […]

After galanthamine (GAL) had been used for many years in Eastern Europe, in the 1980s researchers for AD treatment in Western Europe switched their attention to GAL due to its ability of penetrating the blood–brain barrier and specifically to augment central cholinergic function. This led to clinical trials of GAL in the treatment of AD. In 1996, Sanochemia Pharmazeutika in Austria first launched GAL as 'NIVALIN®' for AD treatment. […]

According to unconfirmed reports, in 1950s, a Bulgarian pharmacologist noticed the use of the common snowdrop growing in the wild by rubbing on their foreheads to ease nerve pain. Also, some of the earlier publications indicate extensive use of snowdrop in Eastern Europe, such as Romania, Ukraine, Balkan

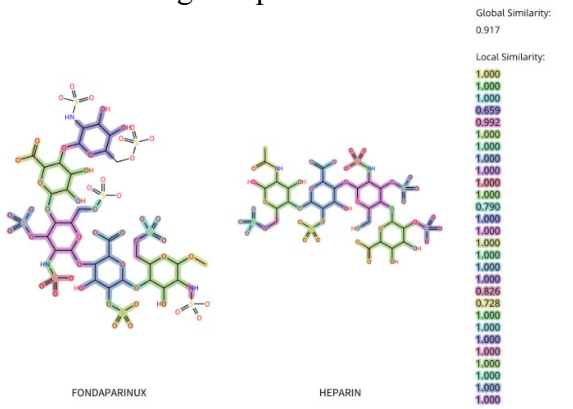
Peninsula and Eastern Mediterranean countries. […]

In the early 1950s, the Russian pharmacologist Mashkovsky worked with GAL isolated from the Galanthus woronowii. In 1951, Mashkovsky and Kruglikova-Lvova used an ex vivo system (striated muscles—frog straight abdominal and leech dorsal muscle) as well as smooth muscles (isolated rabbit small intestine and guinea pig uterus) to proof its AChE inhibiting properties and antagonising effects against curare-induced effects. Consequently, this is the first published work that demonstrates AChE-inhibiting properties of galanthamine(*516*).”

## FONDAPARINUX

2001

Analogue of the natural substrates(*486*), low molecular weight heparins




“The structure of fondaparinux is identical to the heparin pentasaccharide sequence, the smallest fragment required for antithrombin III function. The pentasaccharide sequence was discovered by Choay and coworkers in their search for minimal molecular weight heparin fractions still retaining high anti-factor Xa potency in plasma(*486*)”

## PIMECROLIMUS

2001

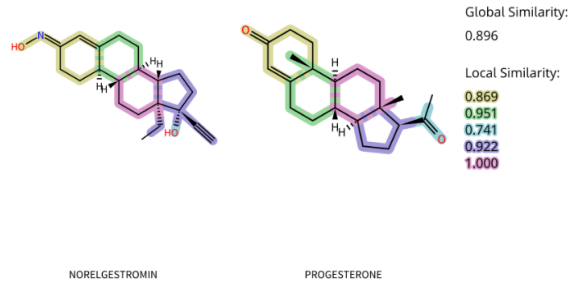
Analogue(*486*) of sirolimus

Error in similarity calculation by FTrees because of the unsupported macrocycle

## NORELGESTROMIN

2001

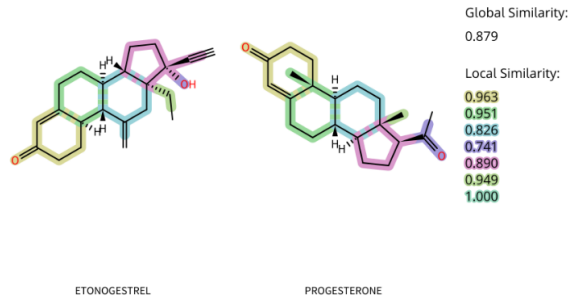
Analogue of progesterone(*488*)




## ETONOGESTREL

2001

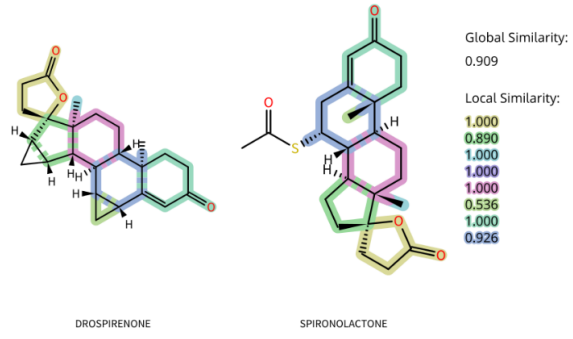
Analogue of progesterone(*21*)




## DROSPIRENONE

2001

Analogue of spironolactone(*21*)




## DESLORATADINE

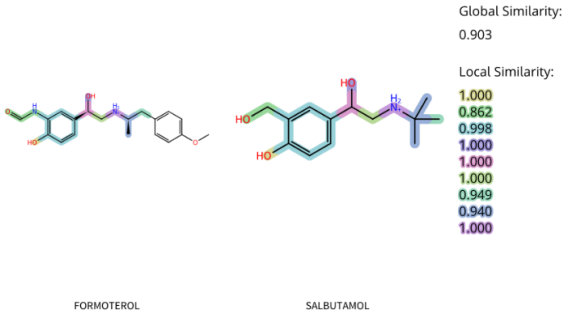
2001

Enantiopure loratadine

## FORMOTEROL

2001

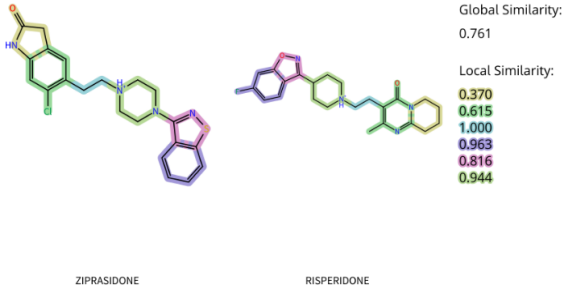
Analogue of salbutamol(*21*)




ZIPRASIDONE

2001

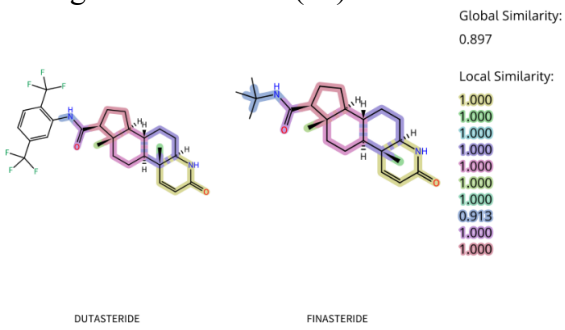
Analogue of risperidone




DUTASTERIDE

2001

Analogue of finasteride(*21*)




ANAKINRA

2001

"The difference between anakinra and the native human IL-1Ra is that anakinra has an extra methionine residue at the amino terminus(*1*)."

DEXMETHYLPHENIDATE

2001

Enantiopure methylphenidate

BOSENTAN

2001

"**Target-based screening(*486*)**"

From the earliest paper reporting bosentan:

"ET-1 might play a role in chronic and acute diseases that are associated with focal or systemic vasoconstriction and perhaps also cellular proliferation, bronchoconstriction or inflammation. The development of selective ET antagonists is essential to understand the pathophysiological roles of ET and could lead to new therapeutic approaches. We recently described the first orally active ET receptor antagonist, Ro 46-2005. In this study, we report the pharmacological properties of bosentan, also called Ro 47-0203 or 4-tert-butyl-N-[6-(2-hydroxy-ethoxy)-5-(2-ethoxy-phenoxy)-2,2'-bipyrimidin-4-yl]-benzeneulfonamide, which was obtained by structural optimization of Ro 46-2005. We describe the in vitro and in vivo effects of bosentan and its capacity to inhibit the biological consequences of stimulation of the three receptors: $ET_A$, $ET_{B1}$ and $ET_{B2}$. For this purpose, we developed specific test systems that allowed us to evaluate each one of the receptors separately. Overall, the results show that bosentan blocks all three $ET_A$, $ETB_1$ and $ET_{B2}$ receptors, is extremely specific for ET and is orally active(*517*)."

From the discovery paper of Ro 46-2005 cited in the previous quotation:

"Because ET was suspected to play a role in chronic diseases, the development of non-peptidic, small $M_r$ antagonists that could be orally administered was an important objective. For this purpose several thousands of compounds from a chemical library were screened for their capacity to inhibit specific I-ET-1 binding in a human placenta membrane preparation. This screening led to the

identification of a class of pyrimidinyl sulphonamides that had been synthesized as part of an antidiabetic project and were noted to be weak inhibitors of I-ET-1 binding. Structural modification of these compounds by chemical synthesis led to the discovery of Ro 46-2005 (4-tert-butyl-N-[6-(2-hydroxy-ethoxy)-5-(3-metoxy-phenoxy)-4-pyrimidinyl]-benzenesulphonamide), a potent inhibitor itself devoid of hypoglycaemic activity. […]

Before testing Ro 46-2005 *in vivo*, it was crucial to assess its binding and functional characteristics, and its selectivity. Ro 46-2005 completely inhibited the specific binding of 125 1-ET-1 to human vascular smooth muscle cells (ETA receptor) and rat aortic endothelial cells (ET 8 receptor), with half-maximal inhibition at concentrations of $2.2 \times 10^{-7}$ M and $1 \times 10^{-6}$ M, respectively. The *in vitro* functional activity of Ro 46-2005 was examined on vascular preparations carrying $ET_A$ and $ET_B$ receptors. In isolated rat aortic rings denuded of their endothelium ($ET_A$ receptors), Ro 46-2005 had no agonistic effect, but antagonized the contractions induced by ET-1 in a concentration dependent manner(*518*)"

NITAZOXANIDE

2002

"Originally developed and commercialized as an antiprotozoal agent, nitazoxanide was later identified as a first-in-class broad-spectrum antiviral drug and has been repurposed for the treatment of influenza(*486*)."

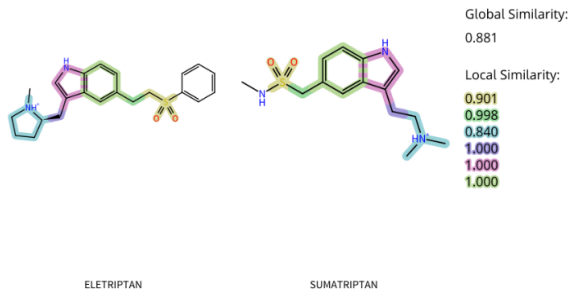
"**Phenotypic screening of compound-specific libraries based on significant prior knowledge of compound properties**(*486*)"

"Nitazoxanide or 2-(acetyloxy)-N-(5-nitro-2-thiazolyl) benzamide was first synthesized in the early 1970s on the scaffold of niclosamide in replacing one benzene ring, a 6-membered ring heterocycle, by a nitrothiazole, a 5-membered ring heterocycle. Initially, nitazoxanide was developed as an oral anti-parasitic agent and studied for activity against protozoan and helminthic infections *in vitro* and/or *in vivo* in mice, cats, dogs and sheep(*519*)."

ELETRIPTAN

2002

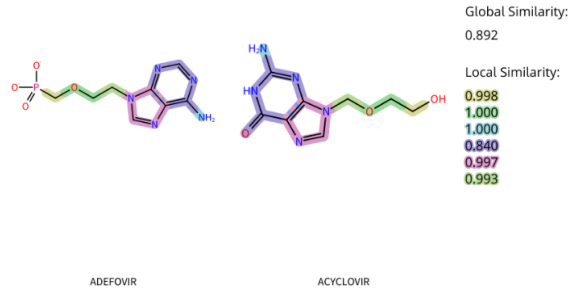
Analogue of sumatriptan(*21*)




ADEFOVIR

2002

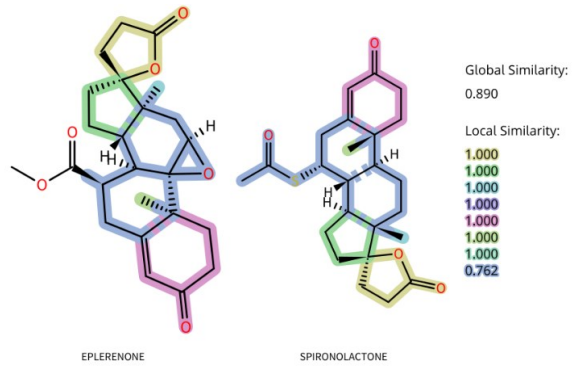
Analogue of acyclovir(*21*)




EPLERENONE

2002

Analogue of spironolactone(*21*)




PEGINTERFERON ALFA-2A

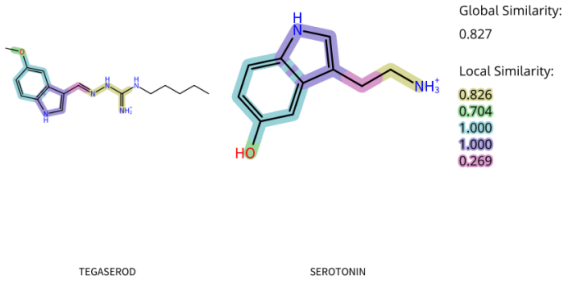
2002

Endogenous-based biopharmaceutical

TEGASEROD

2002

Analogue of the endogenous small molecule, serotonin(*488*)




From the discovery papers:

"Substantial biochemical, pharmacological, and histochemical evidence has been accumulated over the last 35 years in support for a role of serotonin (5-HT) as a neurotransmitter, neuromodulator, and hormone. The largest amount of 5-HT in the body is found in the gut and more precisely in the enterochromaffin (EC) cells of the gastrointestinal mucosa. Its role in the gut is complicated by the presence of multiple 5-HT receptor subtype. […]

We report here the design and the pharmacological evaluation of a new, selective 5-$HT_4$ receptor agonist as well as a receptor map of the 5-$HT_4$ agonist recognition site. This program was initiated, several years ago, by the observation that the activity of prokinetic agents of the benzamide class (cisapride, metoclopramide, zacopride, renzapride) can be attributed to agonism at the 5-$HT_4$ receptor. […]

Receptors of the 5-$HT_4$ type have been identified both peripherally and centrally. In the periphery, the pharmacology of the 5-$HT_4$ receptor has been characterized by using the electrically stimulated or nonstimulated guinea pig ileum longitudinal muscle preparation, the recently developed tunica muscularis mucosae preparation of rat esophagus, and the guinea pig ascending and distal colon longitudinal muscle-myenteric plexus preparations. Agonists at the 5-$HT_4$ receptors cause contractions of the guinea pig ileum and colon mediated by activation of the cholinergic system, enhancements of 'twitch' responses in electrically stimulated guinea pig ileum, and relaxation of the muscularis mucosae preparation. […]

Due to its potent agonism at the 5-$HT_4$ receptor (vide infra), serotonin appeared as a promising starting point for the design of new ligands for this receptor. […]

Serotonin 5-$HT_4$ receptor agonism was measured in the electrically stimulated longitudinal muscle preparations of the, guinea pig ileum. 5-HT causes an augmentation of contractions of the guinea pig ileum induced by field stimulation through activation of the 5-$HT_4$ receptor. 5-HT is a potent agonist in this assay, exhibiting a $pD_2$ value of 8.4 in the field-stimulated preparation.

**Biological Activities. 5-$HT_3$ Receptor Antagonism.** The guinea pig longitudinal muscle with adhering 'plexus myentericus' was prepared as described before. […] 5-$HT_3$ receptor-mediated contractions were measured isotonically […]

**Binding Experiments.** The radioligand-binding experiments have been performed as previously described. Radioligands used in the binding assays were 8-OH-DPAT (pig cortex), ketanserin (rat cortex), tropisetron (mouse N1E-1151, SCH 23390 (calf striatum), spiperone (calf striatum), and prazosin (calf cortex) for 5-$HT_{1A}$, 5-$HT_{2A}$, 5-$HT_3$, $D_1$, $D_2$, and $\alpha_1$ receptors, respectively(*520*)."

From the subsequent discovery paper:

"The activity of a number of known agonists and the new compounds at the 5-$HT_4$ receptor was measured using the field-stimulated guinea pig ileum longitudinal muscle preparation according to previously described methods. All compounds described in this

paper behaved as agonists in this assay, as well as in a variety of in vivo models (stimulation of myoelectric activity in dogs, gastric emptying in rats, small intestinal transit in guinea pigs), results of which will be reported separately(*521*)."

Regarding the discovery of serotonin gastrointestinal effects:

"When reading the various stories of how serotonin was discovered, it immediately becomes apparent how fortuitous it was that serotonin was discovered at all. It started out as an annoying artifact that had to be gotten rid of before the real work of finding the cause of hypertension could be gotten to. It ended as one of the most important discoveries in neuroscience. Indeed, in many ways, serotonin gave birth to the field of neuroscience. […]

In the 1930's, Dr. Erspamer was interested in the smooth muscle constricting or contracting properties of various amine substances found in the skins and intestinal tracts of a variety of species, including rabbits, mollusks, and frogs. One substance which interested him was found in enterochromaffin cells of the gut. An acetone isolate of the cells caused smooth muscle contraction, especially rat uterus. He deduced that the substance wasn't epinephrine and that on the basis of color tests, it was likely an indole. He named the substance enteramine and continued studies on smooth muscle for several more years. He also studied the mollusc heart and the occurrence of enteramine in the salivary glands of the octopus. […]

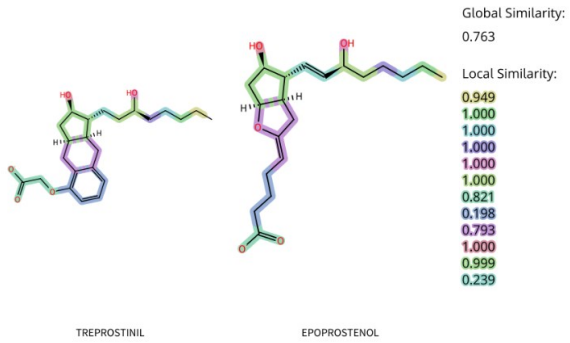
Dr. Page felt that hypertension could best be explained by the presence of endogenous constricting factors in blood. However, whenever blood was studied for such a factor, another substance was produced as soon as the blood coagulated. Dr. Page realized that this serum substance would have to be removed from the blood preparations before any progress could be made on the hypertension-producing factor. For this, Dr. Page had the foresight to recruit a highly skilled organic chemist, Maurice Rapport, and an equally skilled and distinguished biochemist, Arda Green. Page, Rapport, and Green succeeded in isolating and characterizing the serum substance and named it serotonin. […]

In order to test for such a substance, he would ask Arda Green to test it in the rabbit ear artery(*522*)."

TREPROSTINIL

2002

Analogue of the endogenous prostaglandin $I_2$, epoprostenol




PEGFILGRASTIM

2002

"Pegfilgrastim is a PEGylated form of the recombinant human granulocyte colony-stimulating factor (G-CSF) analogue, filgrastim(*2*)."

RASBURICASE

2002

"Rasburicase is a recombinant urate-oxidase enzyme produced by a genetically modified *Saccharomyces cerevisiae* strain. The cDNA coding for rasburicase was cloned from a strain of *Aspergillus flavus*(*2*)."

IBRITUMOMAB TIUXETAN

2002

Monoclonal Antibody

## 4-HYDROXYBUTANOIC ACID

2002

Analogue and an endogenous metabolite of GABA(*1*)

From one of the discoverers, Henri Laborit:

"THE importance of butyric acid in cell metabolism as well as its possible role in the functions of certain organs such as the nervous system had induced our research group to study the effects of its i.v. injection in the animal. A definite hypnotic action was observed, but urine analysis showed that most of the drug injected undergoes β-oxidation.

In an attempt to modify this metabolic fate, an OH-group was introduced on carbon of butyric acid in the hope that its electro-negative properties would alter the electronic configuration of the molecule enough to interfere with β-oxidation. This led to the preparation of sodium 4-hydroxybutyrate starting from butyrolactone. At the same time, as 7-aminobutyric acid does not cross the brain-blood barrier, it was hoped that 4-hydroxybutyrate in the brain might function like a GABA precursor facilitating its synthesis in the brain. Recently BESSMAN and FISHBEIN (1963) have detected the presence of 4-hydroxybutyric acid in physiological amounts in the brain under normal conditions. […]

RESUTLS:

Toxicity-Dosage:

*In the animal*. A 10 per cent solution of sodium 4-hydroxybutyrate was used. Sleep, as determined by the maintenance of the lateral decubitus, can be obtained in rat with 0-5 gm/kg by the i.p. route; in rabbit and dog, with 1 gm/kg by the i.v. route. In rat, the $LD_{50}$ is 1.70 gm/kg; the $LD_{100}$, 2 gm/kg. The cause of death is respiratory depression, and under artificial respiration, rabbits can tolerate up to 7 gm/kg. […]

*In man*. 50 mg/kg by the i.v. route induce sleep. 4 gm must be injected as an initial dose. In surgery, depending on the duration of the intervention, 1 or 2 gm should be injected again when needed. […]

*Quantitative determination of urinary excretion*

In a 12 kg dog, after the i.v. injection of 6 gm of 4-hydroxybutyrate, only 720 gm are excreted in 4 hours.

Professor OSTEUX kindly made an electrophoretic study of cerebral aminoacids in the rat following administration of the drug, and did not observe any increase of 7-aminobutyric acid. […]

*Anticonvulsant activity*

Table 2 compares the protective action of butyric acid and of sodium 4-hydroxybutyrate against convulsions induced by strychnine, cardiazol, izoniazide and ammonium chloride.

*Potentiation of anaesthetics and neuroplegics*

In rat paradoxically, 0.25 gm/kg of 4-hydroxybutyrate delays the onset and shortens the duration of pentothal narcosis, in dogs however it produces pentathol as well as chloralose. […]

*E.E.G. study […]*

*Stereotaxic study of evoked potentials […]*

*Action on monosynaptic reflexes*

*Pharmacological antagonists*

In the rabbit and the dog, tile injection of 4-hydroxybutyrate does not affect the cardiovascular effects of epinephrine, acetylcholine, atropine, serotonin and pendiomide. On the other hand, the *hypnotic effect* of the drug can be clearly antagonized […]

4-hydroxybutyrate antagonizes strongly this electro-encephalographic excitation produced by polyphenols at the level of the telencephalic centers in the 'isolated brain'. But the 'excitation-hypotonia' syndrome persists

even after high sectioning of the cord due to the direct action of the drug on the cord. […]

*Oxygen consumption*

Both in the animal and in man, the sleep induced by 4-hydroxybutyrate *is not accompanied by a decrease in $O_2$ consumption*.

*Action on ventilation […]*

The spirometric determination of ventilation per minute shows a maintenance of its initial value following anaesthetic doses both in the animal and in man.

*Action on temperature*

In the rat, rabbit and dog, 0.50 gm/kg of 4-hydroxybutyrate causes a slight drop in body temperature.

*Antagonistic action against oxygen under pressure and ionizing radiations*

*Action on the cardiovascular system*

No obvious action was observed on the isolated heart of rabbit, isolated atrium, ileum or aortic strip.

In the *rabbit*, 4-hydroxybutyrate causes a constant but short drop in blood pressure, which persists after section of the two vagi. In the dog, it has either no effect or causes a slight and progressive increase in blood pressure, which appears even under controlled ventilation and is not tied to an increase of the $pCO_2$.

In *man*, an injection of 2 to 4 gm has no effect on blood pressure. In surgery, however, in the case of insufficient inhibition of the reticular formation by a concomitant neuroplegia

*Antishock action*

In the animal, we have observed a strong hepatic and renal vasodilating action, which is particularly marked during hemorrhagic shock.

*Electrocardiogram*

Fifty patients were used in this study

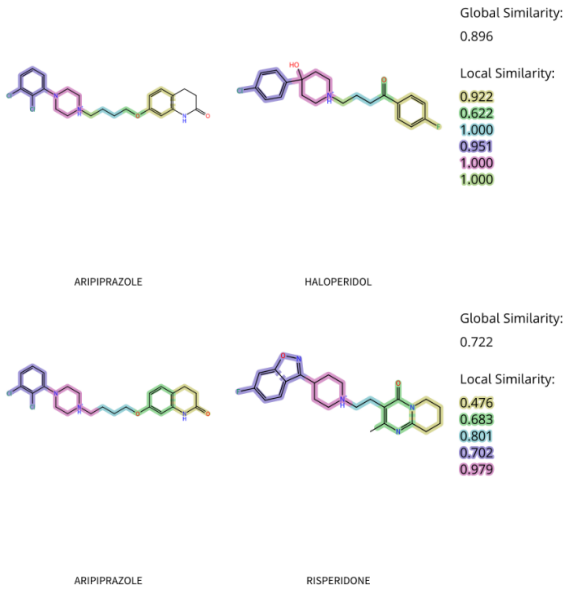
*Blood pressure effect and carotid reflexes*

*Effect on blood constituents*(*523*).”

ARIPIPRAZOLE

2002

Analogue of haloperidol




“Aripiprazole was discovered through investigating dopamine antagonist activity in animal models. The mechanism of partial agonism was demonstrated later(*486*)”

From a discovery-related article cited in the previous quotation:

“We have synthesized a series of new compounds with a variety of modifications of compound 1 and examined the postsynaptic DA receptor antagonist activity of all compounds synthesized by evaluation of their ability to antagonize the DA agonist apomorphine in the stereotypy test. Selected compounds which showed a potent postsynaptic DA receptor antagonist activity were evaluated for their DA autoreceptor agonist activity by testing their reversing effects on the γ-butyrolactone (GBL)-induced increase in L -dihydroxyphenylalanine (DOPA) synthesis in the mouse brain(*524*).”

ESCITALOPRAM

2002

"S-enantiomer of racemic citalopram"

HYDROQUINONE

2002

"In the 1930's, Edward Oliver and his coworkers studied a group of workers in a leather tanning factory who had experienced total loss of pigmentation from their hands and forearms. A few workers noted depigmentation also at distant sites of the body such as the trunk. The depigmented skin corresponded to skin covered by a rubber gauntlet gloves worn for protection during the tanning process. The palms and finger tips were spared. Some of the workers experienced itching while wearing the gloves although most did not develop a rash. Hair color on the arms and hands was not affected.

The investigators noted that 48 individuals in the factory wore the rubber gloves and 25 (52%) had leukoderma. The percentage of those with leukoderma seemed to vary with the duration of time the workers wore the gloves during their work shifts. The investigators learned that the manufacturer of the rubber gloves had changed its method of production and added the antioxidant agerite alba, an ingredient that improved the stability and aging properties of the rubber. Agerite alba chemically is monobenzyl ether of hydroquinone (monobenzone). Patch testing of 10 men with depigmentation by application of various chemicals including monobenzone (agerite alba) produced color loss at the site of the patch tests. Additional studies confirmed that agerite alba (monobenzone) was indeed the culprit. Many of the affected workers noted repigmentation of their hands and arms after discontinuing the use of the rubber gloves. There were no deleterious health effects noted in the affected workers. A decade later, investigators interested in finding treatments for hyperpigmentation undertook a series of studies on three chemicals, i.e., monobenzone, hydroquinone and para-hydroxypropiophenone. These three chemicals were chosen based on earlier publications reporting their hypopigmenting effects on skin and hair color. Prior investigators observed that hydroquinone mixed into food of cats lightened the color of their fur. Oliver had reported the depigmenting effects of monobenzone. French workers noted the beneficial effects of para-hydroxypropiophenone on the hyperpigmentation of five patients with Riehl's melanosis(*525*)."

EZETIMIBE

2002

"The predecessors to ezetimibe were discovered by using animal models for cholesterol lowering with no idea of the MMOA(*486*)"

From the discovery paper cited in the previous quotation:

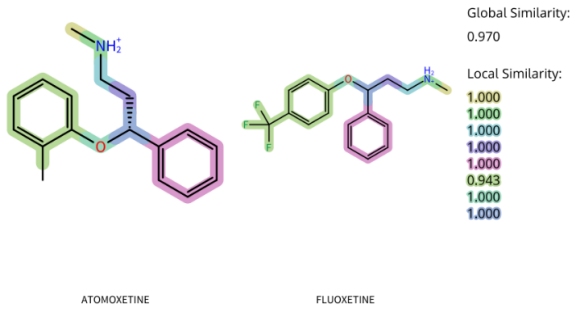
"In this report we describe the hypocholesterolemic activity of a newly-discovered compound, (3R,4S)- 1,4-bis- (4-methoxyphenyl)-3-(3-phenyl-propyl)-2-azetidinone (SCH 48461), which interferes with the intestinal absorption of cholesterol in a number of animal species. This activity is not mediated through a mechanism that is attributable to ACAT inhibition, cholesterol esterase inhibition, cholesterol precipitation or bile acid sequestration. Rather, this compound presumably inhibits cholesterol absorption via a novel and previously unknown mechanism. SCH 48461is a potent and effective hypocholesterolemic agent in cholesterol-fed animal models. […]

We utilized the measurement of cholesteryl ester accumulation in the livers of hamsters fed a cholesterol-supplemented diet to assess the activities of novel synthetic organic compounds on cholesterol absorption. This in vivo assay, with which SCH 48461 was identified initially, was found to constitute an indirect but reliable measurement of intestinal cholesterol absorption(*526*)."

## ATOMOXETINE

2002

Analogue of fluoxetine(*488, 527, 528*)




"The tricyclic antidepressants, desipramine and nortriptyline, have emerged as alternative therapies for the treatment of ADHD. Desipramine and nortriptyline have high affinity for NE transporters relative to DA and serotonin (5-HT) transporters and have been shown in clinical evaluations of adults and children to be effective in ADHD. However, tricyclic antidepressants have significant affinity for α1-adrenergic, cholinergic and histaminergic receptors potentially resulting in sedation, dry mouth, weight gain and cognitive impairment and also have cardiovascular concerns. Therefore, the tricyclic antidepressants are also limited in usefulness(*529*)."

"Tricyclic anti-depressants that inhibit the reuptake of norepinephrine, such as desipramine and nortriptyline, have efficacy in treating ADHD. The same side effect issues that impair utility of these medicines in treating depression limit their use in treating ADHD, including anticholinergic and antihistaminergic side effects. Moreover, effects of these drugs on cardiac conduction is of concern, particularly regarding use of these medicines in fairly healthy children. Because of some documented cases of sudden death in children treated with tricyclic antidepressants, their use in treating ADHD has fallen into disfavor.

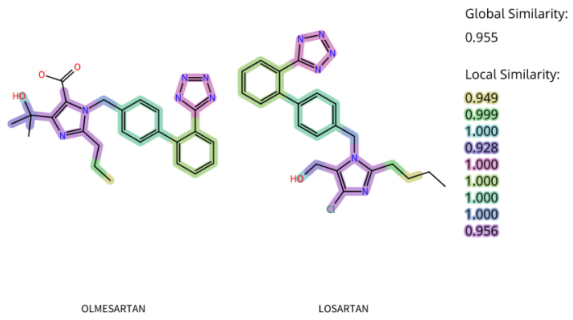
Atomoxetine, currently under development for treating ADHD in adults and children, was one of the earliest described selective norepinephrine reuptake inhibitors that does not interact with the postsynaptic receptor systems that produce side-effect liabilities of tricyclic anti-depressants. Interestingly, it is a close structural analog of fluoxetine, a prototypic selective serotonin reuptake inhibitor (SSRI). Like fluoxetine, atomoxetine has weak affinities for adrenergic, histaminergic and cholinergic receptors(*528*)."

"The implication of the dopaminergic and noradrenergic systems in ADHD has also provided the rationale for testing a range of other agents known to affect them, including various antidepressants. […] It was initially identified more than 20 years ago as part of a programme aimed at the discovery of antidepressants, but although it entered clinical trials, it was dropped from development for depression, as a related compound, fluoxetine (Prozac; Eli Lilly) looked more promising. However, initial trials in ADHD indicated that it had potential for this condition(*527*)."

## OLMESARTAN

2002

Analogue of losartan(*21*)




## OXALIPLATIN

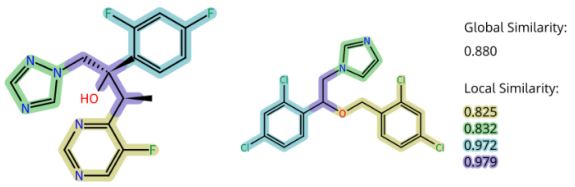
2002

Analogue of cisplatin(*21*)

## VORICONAZOLE

2002

Analogue of miconazole(*21*)




## NITISINONE

2002

"The discovery of both molecules originated with phenotypic assays, then using chemical biology the molecules were used to test hypothesis that led to the approved indication(*486*)."

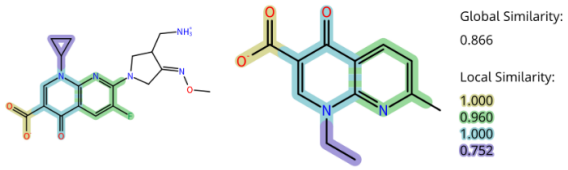
"With the advent of paediatric liver transplants in the late 1980s and early 1990s, transplant was widely offered as a treatment of tyrosinaemia type 1. However, the clinical development of nitisinone in the 1990s has dramatically changed this practice. Following the observation that plants do not grow well under the Australian bottle-brush plant (*Callistemon* spp.), Stauffer Agrochemical worked on leptospermone, a polyketide natural product from the bottle-brush plant. In 1982 they discovered the herbicidal activity of triketones: 2- benzoylcyclohexane-l,3-diones.

Imperial Chemical Industries (ICI) Plant Protection division acquired Stauffer Agrochemical in 1987 and started work on the triketone 2-(2-nitro-4-trifluoromethylbenzoyl) cyclohexane-l,3-dione, abbreviated as NTBC. This is a corn tolerant and grass and broad leaf weed killer which caused bleaching and subsequent death of the plants due to reduced synthesis of plastoquinone. Animal toxicity studies were carried out at ICI and subsequently Zeneca, which was established in 1993 by demerging of various business units of ICI. These studies demonstrated that rats treated with NTBC developed corneal lesions due to hypertyrosinaemia and high levels of tyrosine in the aqueous humour of the eyes, which disappeared on discontinuing of the herbicide. Although the herbicide programme was abandoned, it was established that the hypertyrosinaemia was due to inhibition of 4-hydroxyphenylpyruvate dioxygenase (HPPD), an enzyme in the tyrosine catabolism pathway HPPD that converts 4- hydroxyphenylpyruvate to homogentisic acid which is implicated in the pathogenesis of ochronosis seen in alkaptonuria. NTBC was shown to be a potent, time-dependent, tight binding yet reversible inhibitor of HPPD in rats. ICI/Zeneca's central toxicology laboratory collaborated with Professor Lindstedt to demonstrate that NTBC, in addition to being a rat HPPD inhibitor, was a potent inhibitor of human HPPD as well. Once this was demonstrated, Professor Lindstedt requested ICI/Zeneca to supply NTBC to treat children with tyrosinaemia type I(*530*)."

## GEMIFLOXACIN

2003

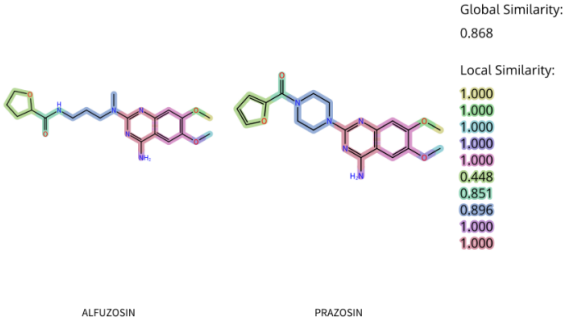
analogue of nalidixic acid




## ALFUZOSIN

2003

Analogue of prazosin(*21*)



APREPITANT

2003

"**Target-based screening** […]

The isolation of substance P (SP) in 1931, and the later discovery of its preferred neurokinin (NK)1 receptor, led to an intense research effort aimed at elucidating the biological role of SP, particularly within the central nervous system. Large investments were made by multiple pharmaceutical companies in discovering (using HTS assays) and developing NK1 receptor antagonists such as aprepitant for indications including depression and pain. Although these trials were not successful, the role of the NK1 receptor in emesis provided the basis for the approval of aprepitant as an anti-emetic agent in patients receiving chemotherapy(*486*)."

"Despite strong anatomical evidence supporting a potential role for substance P in pain and affective disorders, the SPAs were inactive as analgesics and as antidepressants. The hypothesis that substance P was involved in emesis was initially supported by three preclinical observations: substance P was localized in the emetic centers of the brain, substance P could cause emesis, and depletion of substance P using a toxin (resiniferatoxin) could prevent emesis in preclinical species with a vomiting reflex. The critical proof that the substance P/NK-1 receptor axis played a crucial role in mediating the vomiting response to a number of stimuli came with demonstration that highly selective SPAs had profound activity against emesis induced by broad range of central and peripherally acting emetogens. Moreover, these SPAs were active in multiple species with a vomiting reflex against a broad range of emetogens, giving high confidence that the mechanism would translate to clinically meaningful activity(*531*)."

ADALIMUMAB

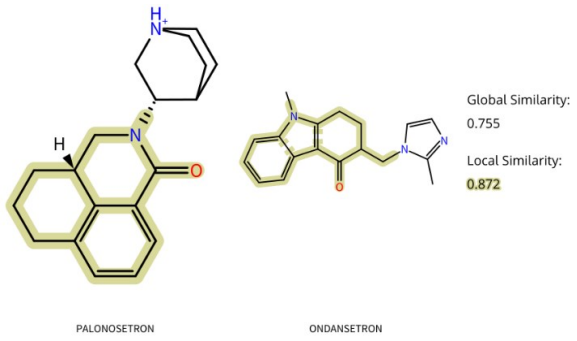
2003

Monoclonal Antibody

PALONOSETRON

2003

Analogue of ondansetron




GEFITINIB

2003

"**Target-based screening: optimized MMOA subsequently identified.** Gefitinib was discovered on the basis of assays for inhibition of the intracellular phosphorylation of the tyrosine kinase associated with the epidermal growth factor receptor (EGFR), which is overexpressed in non-small-cell lung cancer cells(*486*)."

From the discoverer(s):

"Chemical compounds were tested as potential inhibitors of EGFR-TK activity in a substrate phosphorylation assay with a synthetic peptide substrate and a plasma membrane preparation derived from human A431 cells, which overexpress the EGFR. This assay first identified the anilinoquinazoline class of EGFR-TK inhibitors, and subsequently the candidate drug EGFR-TK inhibitor, ZD1839 designated Iressa(*532*)."

"An important aspect of our drug discovery strategy required a test which would distinguish between specific EGFR-TKI-mediated effects on cell growth and non-target-specific cell growth inhibition or cytotoxicity. For this purpose we selected the human KB cell line derived from a vulval squamous tumour(*532*)."

## MEMANTINE

2003

“**Phenotypic screening: serendipitous discoveries**

Memantine was first synthesized by Eli Lilly in the early 1960s as a potential antidiabetic agent, but was ineffective at lowering elevated blood sugar. It was later found to have CNS activity, and entered clinical trials for dementia in Germany in 1986, but NMDA receptor antagonism was not identified as the mechanism of its therapeutic action until 1989(*486*)”

“As a chemotype, amantadine (19) was the progenitor of 4 and was originally introduced in the 1960s as an antiviral (influenza) medication. Serendipitously, a lone patient on 19 for her flu infection noted improvements in her PD symptoms. This observation led to additional studies and approval of 19 for the treatment of PD as Symmetrel, although its utility for influenza has languished. Thus, this chemotype and chemical class was recognized to have utility for neurodegenerative disorders in 1969. Memantine (4) was first synthesized in 1963 by researchers at Eli Lilly as a building block to prepare a series of N-arylsulfonyl-N′-adamantylureas as putative blood sugar lowering agents (antidiabetics). While proven to be ineffective, the data with 19 undoubtedly led researchers at Merz to evaluate functionalized variants of 19 for CNS activity, such as 4. Thus, in 1972, Merz and Co. filed patent applications for 4 with CNS activities relevant to PD and other cerebral disorders. The NMDA receptor pharmacology was not discovered until after clinical trials had initiated, but successful trials led to the approval of 4 in Germany in 1989 under the brand name Axura and the INN name memantine(*533*).”

Also see the amantadine entry.

## AGALSIDASE BETA

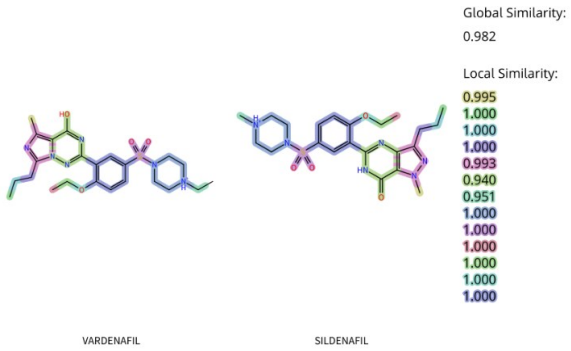
2003

“Agalsidase beta is a recombinant human α-galactosidase A similar to agalsidase alfa(*2*).”

## VARDENAFIL

2003

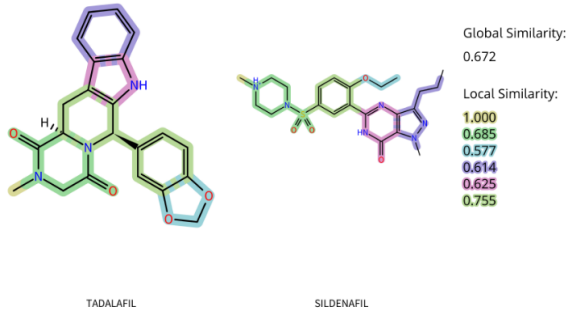
Analogue of sildenafil(*488*)




## TADALAFIL

2003

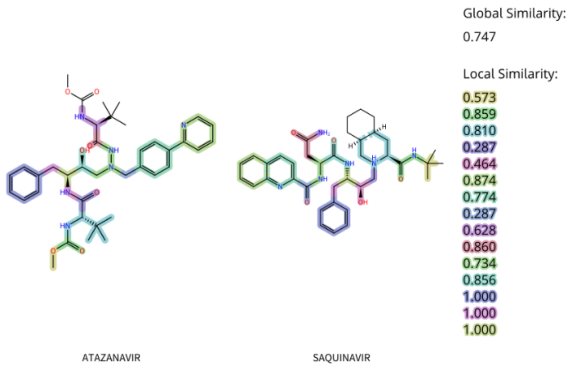
Analogue(*486*) of sildenafil




## ATAZANAVIR

2003

Analogue(*21*) of saquinavir



BORTEZOMIB

2003

"**Target-based screening** […]

Bortezomib was discovered as proteasome inhibitor, and an initial aim was to harness this activity to treat muscle-wasting disorders. However, based on growing understanding of its biological activity — in particular, its anticancer effects — bortezomib was first approved for multiple myeloma(*486*)."

From the discoverer(s):

"The development of proteasome inhibitors for treatment of cancers has had a curious history that reflects the multiple strands of my own research career. When we initiated this research, we were not aiming to find new cancer therapies. Instead, our goal was based upon my long-standing interest (spanning almost 50 yr) to clarify the mechanisms of muscle atrophy, as occurs upon disuse, aging, or disease (e.g., cancer). These early experiments demonstrated unexpectedly that the rapid loss of muscle protein after denervation or fasting was caused primarily by an acceleration of overall protein breakdown rather than a reduction in protein synthesis, thereby providing the first evidence that overall rates of protein breakdown in mammalian cells are precisely regulated and help determine muscle size. […]

Eventually, our two research interests in the physiological regulation of muscle protein breakdown and in the biochemical mechanism for proteolysis began to interconnect. In the late 1980s, we showed that the excessive proteolysis responsible for muscle wasting in many rodent disease models (e.g., cancers, renal failure, or denervation atrophy) was primarily caused by an activation of the ubiquitin–proteasome pathway. […]

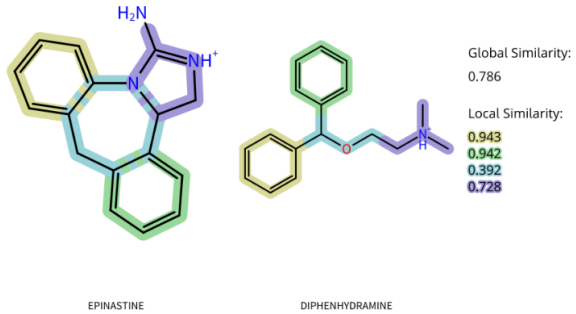
The first proteasome inhibitors synthesized were simple peptide aldehydes, which were analogues of the preferred substrates of the proteasome's chymotrypsin-like active site. These inhibitors were not obtained through random screening of huge chemical libraries but instead were initially synthesized based on our knowledge of the substrate specificity of the proteasome's active sites. Although the proteasome's architecture and enzymatic mechanisms were unknown at the time, it was clear that the chymotrypsin-like site is the most important one in protein breakdown, and we knew that small hydrophobic peptides could often penetrate cell membranes. Therefore, the C termini of hydrophobic peptide substrates were derivatized to form peptide aldehydes, which were known to be effective inhibitors of serine and cysteine proteases. (Thus, MG132 is, in fact, simply carbobenzyl-Leu-Leu-Leu-aldehyde). This compound was the lead molecule in medicinal chemistry efforts led by Julian Adams to enhance potency, selectivity, and stability. In place of the aldehyde, he introduced the critical boronate 'warhead,' which increased its potency 50–100-fold, and modifications in the peptide backbone then generated bortezomib within months. […]

The 20S proteasome was subsequently found to have a unique proteolytic mechanism, through the x-ray crystallographic studies of Huber and Baumeister(*534*)."

EPINASTINE

2003

Analogue of diphenhydramine(*21*)




LARONIDASE

2003

Human recombinant α-L-iduronidase(*2*)

ENFUVIRTIDE

2003

"Enfuvirtide is a synthetic peptide derived from gp41 of HIV1. Initially, synthetic peptides derived from gp41 were not targeted as inhibitors of HIV1 fusion, but were investigated as part of epitope-mapping experiments aimed at evaluating strategies in vaccine development. It was observed that when these were incubated with human T cells, an antiviral effect was seen(*486*)."

MIGLUSTAT

2003

"**Phenotypic screening of compound-specific libraries based on significant prior knowledge of compound properties** […]

"It was originally developed as an antiviral agent because most enveloped viruses use the same pathway for glycoprotein synthesis in infected cells(*486*)"

From the discovery paper cited in the previous quotation:

"We have investigated the effects of deoxynojirimycin and its alkylated derivatives on the biosynthesis of glycolipids in HL-60 cells. […]

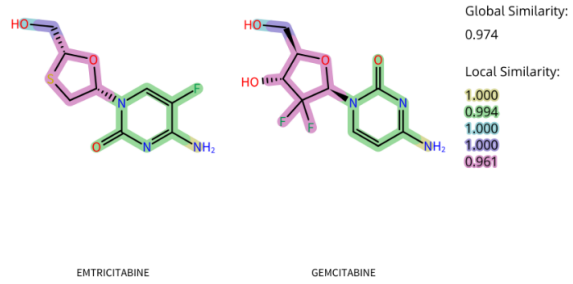
The imino sugar *N*-butyldeoxynojirimycin (*N*B-DNJ) is an inhibitor of the *N*-linked oligosaccharide processing enzymes a-glucosidase I and II and is an inhibitor of HIV replication *in vitro*. It is probable, although not proven, that these two activities are causally related. This compound is currently under clinical evaluation as a potential AIDS therapeutic and has been found to exhibit little cytotoxicity *in vitro*.

To understand more completely the range of activities exhibited by this glucose analogue we wished to determine whether or not *N*B-DNJ can also inhibit glucosyltransferases involved in glycoconjugate biosynthesis. We have focused on the glycolipid biosynthetic pathway which is initiated by the glucosyltransferase-catalyzed synthesis of glucosylceramide (Glc-Cer). We have established in this report that the imino sugar *N*B-DNJ is a potent inhibitor of the glycolipid biosynthetic pathway and offers a unique approach for selectively manipulating cellular glycolipid levels(*535*)."

EMTRICITABINE

2003

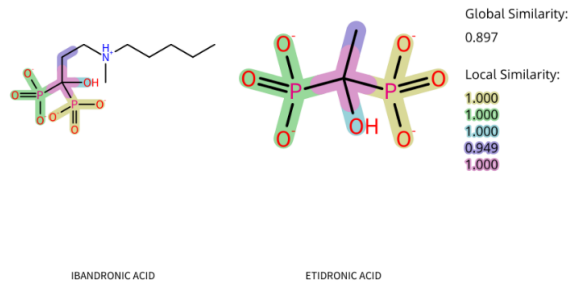
analogue of gemcitabine




IBANDRONIC ACID

2003

Analogue of etidronic acid




PEGVISOMANT

2003

From the discoverer(s):

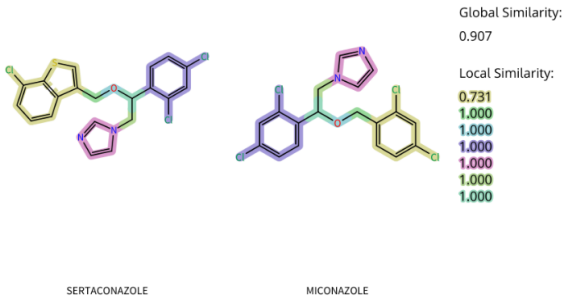
"Using a structure–function approach to the understanding of the molecular topology of the GH molecule, we discovered that glycine in the third a-helix of GH (G119 of bovine GH and G120 of human GH) was an

important amino acid required for GH action. Substitution of this glycine residue with a variety of amino acids results in molecules that lack growth-promoting activity. More importantly, these molecules inhibit the actions of GH both *in vitro* and *in vivo*. These results, obtained more than a decade ago, were the basis for the discovery of GH antagonists(*536*).”

SERTACONAZOLE

2003

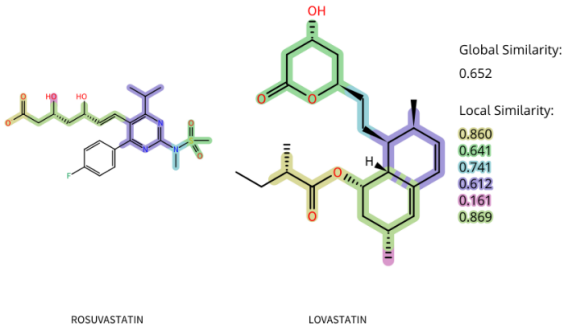
Analogue(*486*) of miconazole




ROSUVASTATIN

2003

Analogue of lovastatin(*21*)




DAPTOMYCIN

2003

“**Phenotypic screening of ‘random’ compound library**(*486*)”

From the discoverer(s):

“Daptomycin is a natural product of a soil actinomycete, as are most of the important antibiotics developed in the past 50 years. The producing microorganism, *Streptomyces roseosporus*, was isolated by scientists at Eli Lilly from a soil sample from Mount Ararat (Turkey). This sporulating actinomycete produced a family of lipopeptide antibiotics designated A21987C. Eli Lilly scientists also isolated a strain of *Actinoplanes utahensis* that produced a secreted deacylase that could cleave the natural long-chain lipid side chains from the A21978C factors. This enabled the production of the core cyclic peptide for reacylation with different lipid side chains. Daptomycin, which contains an n-decanoyl side chain, was chosen for clinical development because of its in vivo efficacy and low toxicity in animals(*537*).”

OMALIZUMAB

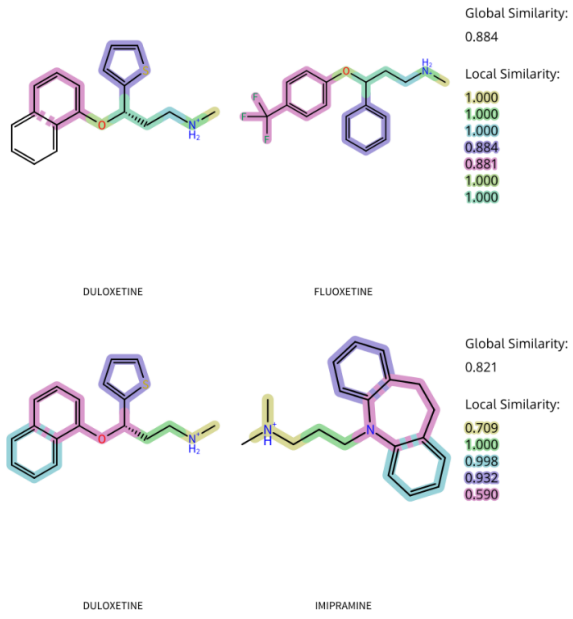
2003

Monoclonal Antibody

DULOXETINE

2004

Analogue of fluoxetine




GLUTAMINE

2004

Endogenous amino acid(*217*)

## CINACALCET

2004

"Nemeth and coworkers used a library of phenylalkylamines in a phenotypic assay to discover cinacalcet(*486*)."

From Nemeth:

"High-throughput screening was not used to discover calcimimetics. The approach that was used is no secret and is stated plainly in the first sentence of the Results section: 'To screen for agonist-like activity on the $Ca^{2+}$ receptor, we assessed the ability of test substances to evoke an increase in $[Ca^{2+}]_i$ in bovine parathyroid cells.' In the absence of a parathyroid cell line or a cDNA encoding the calcium receptor, this seemed to be the best, perhaps only, approach. Moreover, most of the evidence supporting the existence of the calcium receptor derived from studies in dissociated bovine parathyroid cells and we knew a lot about the characteristics of the (still putative) calcium receptor in these cells. It was, and remains a tedious and laborious assay and at best permits the screening of 20 to 40 compounds a week—truly ultra-low throughput. By today's standards, a technically unsophisticated assay bordering on the comical. But it was a functional assay, with a physiologically meaningful readout, and this, it turns out, was pivotal to the discovery of type II calcimimetics—the allosteric modulators. Despite all the hype about translational molecular medicine, calcimimetics were discovered in the old fashioned way, by testing compounds on live animal tissue in an assay configured to detect compounds having the desired therapeutic effect. In his Nobel Lecture, Sir James Black explains how this is done and how this approach yielded two (not just one) first-in-class drugs: propranolol and cimetidine. And he did it without a clue about the structure of the receptors these drugs target(*538*)."

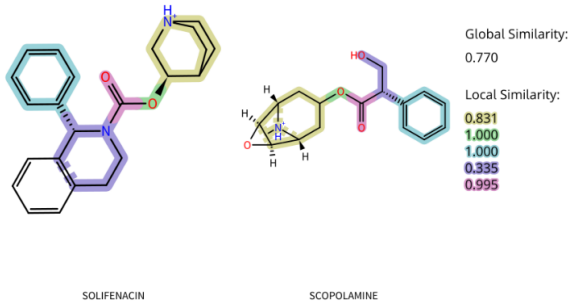
## LANTHANUM CATION (3+)

2004

## SOLIFENACIN

2004

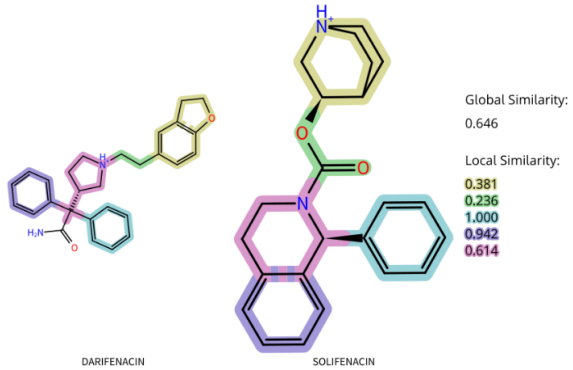
Analogue(*486*) of scopolamine

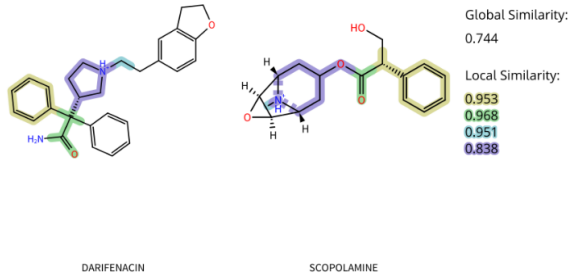


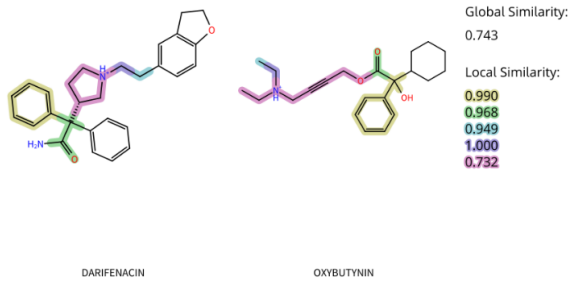

## DARIFENACIN

2004

Analogue(*486*) of solifenacin



ZICONOTIDE

2004

"**Phenotypic screening of compound-specific libraries based on significant prior knowledge of compound properties** […]

Ziconitide is derived from a toxin iolated from *Conus geogruphus*, a marine snail that captures fish by injecting a potent venom through a disposable harpoon-like tooth. During routine bioassays of chromatographic fractions, some fractions caused a persistent shaking in mice that had been injected intracerebrally(*486*)."

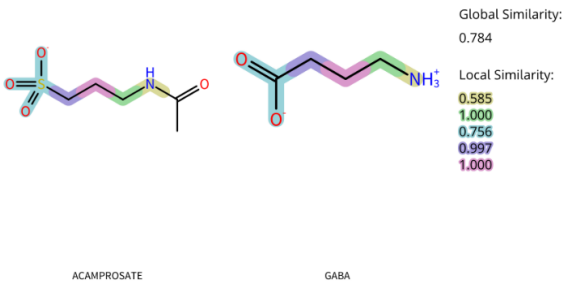
From the discovery paper(*486*):

"We have been investigating ω-conopeptides from several species of Conus and have characterized peptides with high affinity for N-type channels that bind in a reversible manner. We have synthesized relatively large quantities of peptides corresponding to nine naturally occurring ω-conopeptides derived from five different species of Conus and examined their biochemical, electrophysiological, and pharmacological properties. The synthetic peptide SNX-111, corresponding to the structure of the ω-conopeptide MVIIA from *Conus magus*, was found to be a highly effective neuroprotective agent in animal models of transient global ischemia(*539*)."

ACAMPROSATE

2004

"**Modified natural substance**

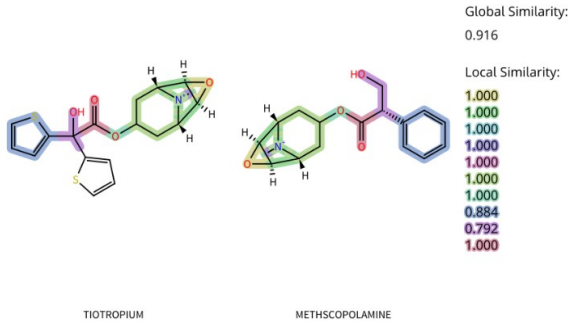



*Acamprosate*. Acamprosate was discovered based on evidence for a role of GABA in the action of ethanol. The evidence led Boismare and coworkers to study the effects of homotaurine, a potent and stable GABA receptor ligand in rats. The acetylated form of homotaurine, acamprosate, was used to increase brain penetration(*486*)."

TIOTROPIUM

2004

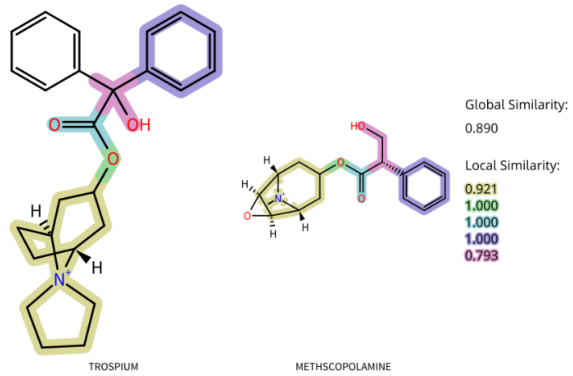
Analogue of methscopolamine




TROSPIUM

2004

Analogue of methscopolamine(*21*)




PEGAPTANIB

2004

Polynucleotide aptamer

BEVACIZUMAB

2004

Monoclonal Antibody

TRYPAN BLUE

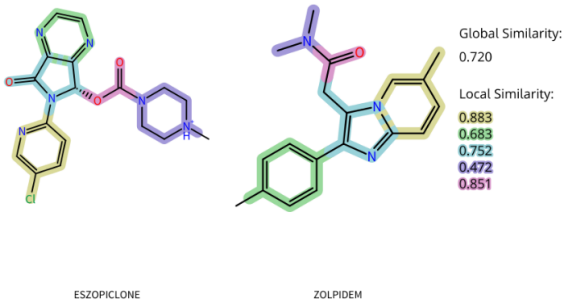
2004

Dye

## ESZOPICLONE

2004

Analogue of zolpidem




From the earliest reporting paper

"The pharmacological properties of 6-(5-chloropyrid-2-yl)-5-(4-methylpiperazin-l-yl) carbonyl-oxy-7-oxo-5,6 dihydropyrrolo [3,4-b] pyrazine (=Rr 27 267) were compared with those of chlordiazepoxide and nitrazepam in a variety of animal tests: pentylenetetrazole-induced convulsions and max. electroshock in mice and rats, footshock fighting behaviour, traction and rota-rod in mice, loss of righting reflex in normal and in chlorpromazine-pre-treated mice, inclined screen and intercollicular decerebrate rigidity in rats, muscle relaxation in unanesthetized cats and inhibition of spinal polysynaptic reflexes in anesthetized cats(*540*)."

## RIFAXIMIN

2004

Analogue of rifampin(*541*)

Error in similarity calculation by FTrees because of the unsupported macrocycle

## CETUXIMAB

2004

Monoclonal Antibody

## NATALIZUMAB

2004

Monoclonal Antibody

## INSULIN GLULISINE

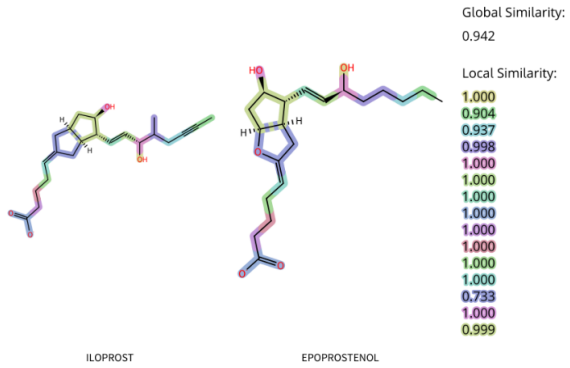
2004

Endogenous-based biopharmaceutical

## ILOPROST

2004

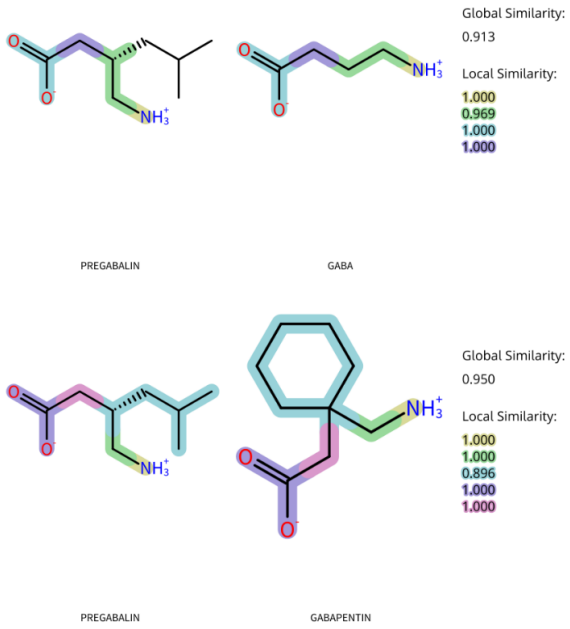
Analogue of prostaglandin $I_2$, epoprostenol




## PREGABALIN

2004

Analogue of gabapentin and the endogenous substance, GABA(*488*)




## PALIFERMIN

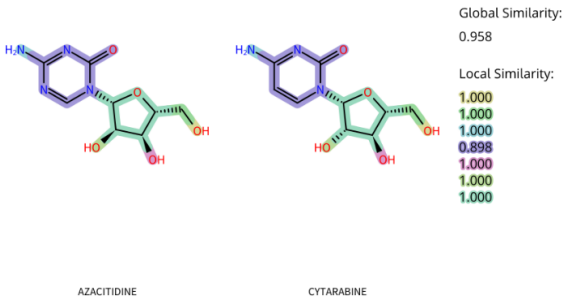
2004

Recombinant human keratinocyte growth factor(*2*)

AZACITIDINE

2004

Analogue of cytarabine



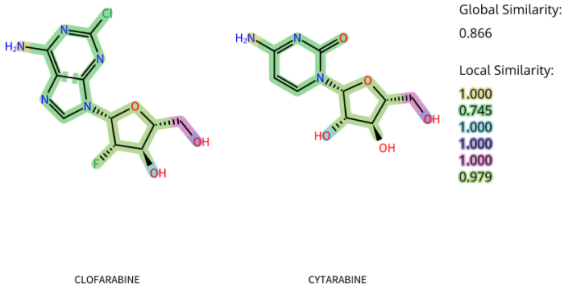

"**Phenotypic screening of compound-specific libraries based on significant prior knowledge of compound properties**

*Azacitidine*. Azacitidine is a nucleoside analogue of cytidine that specifically inhibits DNA methylation by trapping DNA methyltransferases. It was originally developed as a cytotoxic agent, and an application to the FDA requesting its approval as such was turned down more than 25 years ago. The discovery in the early 1980s that it was a hypomethylating agent, and the elucidation of the role of DNA hypermethylation in cancer, prompted its re-evaluation and eventually led to its approval(*486*)."

CLOFARABINE

2004

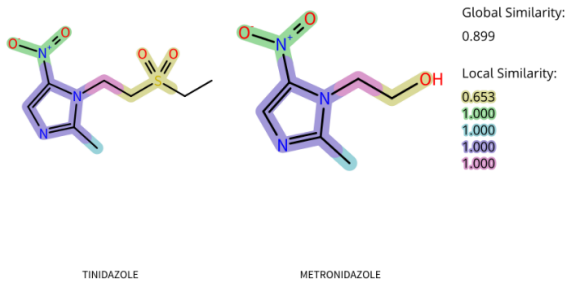
Analogue of cytarabine




TINIDAZOLE

2004

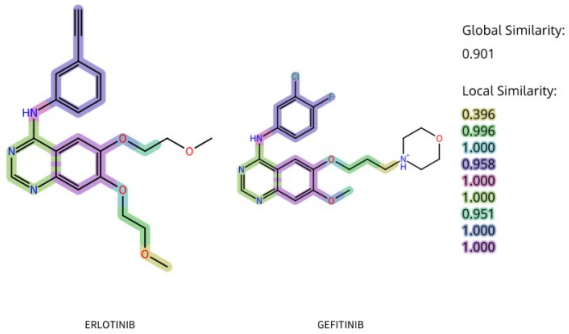
Analogue of metronidazole




ERLOTINIB

2004

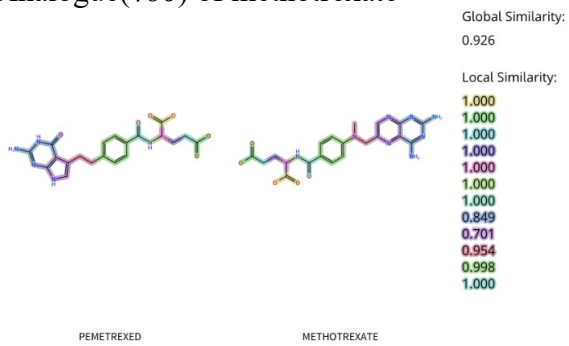
Analogue(*486, 542*) of gefitinib




PEMETREXED

2004

Analogue(*486*) of methotrexate




CONIVAPTAN

2005

"**Target-based screening** […]

Conivaptan was developed in a programme to identify orally active arginine vasopressin (AVP) antagonists for both the $V_{1A}$ and $V_2$ receptors, based on the hypothesis that blocking the properties of both receptors — vasoconstriction and water reabsorption, respectively — would be beneficial in congestive

heart failure(*486*)."

SORAFENIB

2005

"**Target-based screening: optimized MMOA subsequently identified** […]

Considerable biological data supported the choice of targeting Raf kinase as an anticancer target. Additionally, drug discovery assays were available to allow initiation of a high-throughput screening (HTS) approach, followed by medicinal chemistry optimization. These efforts lead to the discovery of sorafenib(*486*)."

From the discovery paper:

"The lead series for the Raf kinase project can be broadly defined as bis-aryl ureas. Many thousand medicinal chemistry compounds, from either medicinal chemistry directed syntheses or numerous combinatorial libraries, were screened through the Raf kinase biochemical assay. Compounds were first analyzed for in vitro activity against recombinant, activated human Raf kinase.

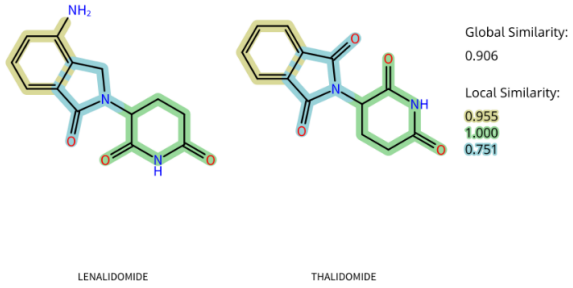
Active compounds (<500 nM) were then tested in a mechanistic cellular assay. The activity of endogenous phosphorylated MEK was assayed by a high throughput immunoprecipitation assay of MEK in response to estradiol stimulation of an estrogen receptor (ER) fused to a Raf kinase construct within a mouse 3T3 cell line.

Compounds that demonstrated inhibition of Raf kinase-mediated MEK phosphorylation in cells were then analyzed for their ability to inhibit HCT116 tumor cell proliferation in vitro, as well as for inhibition of soft agar growth (both HCT116 and MiaPaca-2 cell lines), a hallmark of transformation. Finally, the lead compounds were also tested in a tumor cell-based mechanistic assay monitoring the inhibition of MEK and ERK phosphorylation in HCT116 tumor cells. Counter-screening was performed using biochemical assays for MEK and ERK activity, as well as a cell-based assay for insulin receptor function. This drug discovery effort led to the selection of BAY 43-9006 as a candidate for clinical development(*543*)."

LENALIDOMIDE

2005

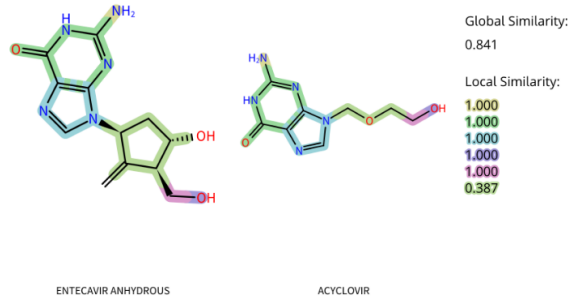
Analogue of thalidomide(*1*)




ENTECAVIR

2005

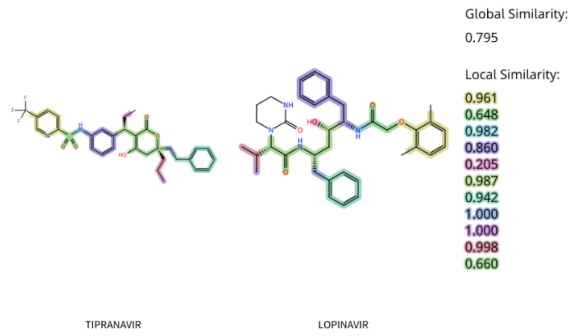
Analogue of acyclovir




TIPRANAVIR

2005

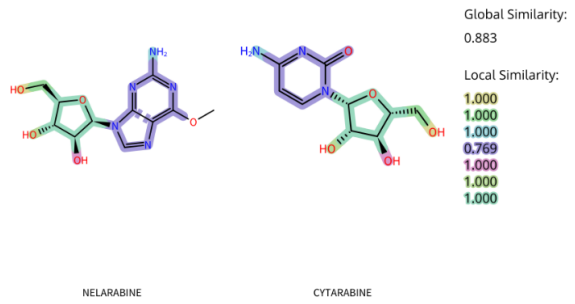
Analogue(*486*) of lopinavir



## NELARABINE

2005

Analogue of cytarabine




"**Phenotypic screening of compound-specific libraries based on significant prior knowledge of compound properties** […]

Nucleoside analogues have proven to be a highly successful class of cytotoxic drugs for the treatment of haematological cancers. These compounds, such as cytarabine, work primarily by incorporation of their triphosphate form into DNA, resulting in apoptosis. The deoxyguanosine analogue 9-b- D -arabinofuranosylguanine (ara-G), was discovered in the 1960s, but was not used clinically because of its poor solubility characteristics. However, studies starting in the 1970s on a naturally occurring disease, purine nucleoside phosphorylase deficiency (PNP), provided a rationale for developing deoxyguanosine analogues. Ara-G was found to be selectively toxic to T cells compared with B cells, and a water-soluble prodrug of ara-G, nelarabine (also known as compound 506U78), was subsequently developed(*486*)."

## HYALURONIDASE (HUMAN)

2005

Endogenous-based biopharmaceutical

## MECASERMIN

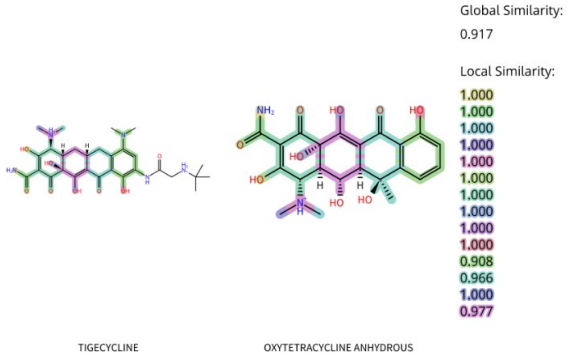
2005

Recombinant-DNA-engineered human insulin-like growth factor-1(*2*)

## TIGECYCLINE

2005

Analogue of oxytetracycline




## MICAFUNGIN

2005

Analogue(*486*) of caspofungin

Error in similarity calculation by FTrees because of the unsupported macrocycle

"The lead compounds from which micafungin was derived, FR901379, and several related compounds were discovered from amongst about 6000 broth samples, and were detected by antifungal activity against *C. albicans* and *Aspergillus fumigatus*. These new compounds were found to be members of the echinocandin-like class of lipopeptides. Echinocandin B, pneumocandin B0, and other echinocandin-like lipopeptides are characterized structurally by a cyclic hexapeptide acylated with a long side chain, and have excellent anti-*Candida* activity(*544*)"

## PRAMLINTIDE

2005

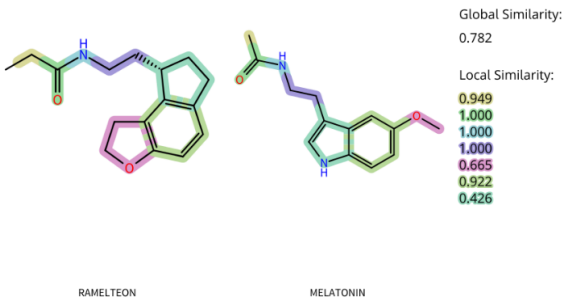
Analogue of human amylin(*1*)

"The synthetic analogue pramlintide acetate differs from amylin in that the amino acid residues at 25 (alanine), 28 (serine), and 29 (serine) have been replaced by proline residues. These substitutions increase the solubility of the drug and decrease its aggregation and adhesion properties, which have been noted with amylin(*486*)."

## RAMELTEON

2005

Analogue of the endogenous substance, melatonin(*486*)




"Ramelteon was synthesized as part of a program aimed at limiting the conformational flexibility of the methoxy group of melatonin, whose orientation is important for optimal binding to the MT1 receptor(*486*)."

From the discovery paper of melatonin:

"During the past forty years investigators have reported that injection of pineal gland extracts into tadpoles, frogs, toads and fish produces lightening of skin color. Recently it was found that such extracts, by causing aggregation of melanin granules within the melanocytes of isolated pieces of frog skin, reverse the darkening effect of the melanocyte stimulating hormone (MSH). We wish to report isolation from beef pineal glands of the active factor that can lighten skin color and inhibit MSH. It is suggested that this substance be called melatonin. […]

Bioassay was performed using isolated *Rana pipiens* skin darkened with caffeine. The lightening effect of the test substance on the melanocytes was measured photometrically with transmitted light. This revealed that 95% of recoverable biologic activity was present at the position of the blue spot. […]

In preventing darkening of frog skin by MSH, melatonin, the active pineal gland factor, was at least 100 times as active on a weight basis as adrenaline or noradrenaline, 200 times as active as tri-iodothyronine and 5,000 times as active as serotonin. Melatonin had no adrenaline nor noradrenaline-like activity on rat uterus and no serotonin-like activity on clam heart. No melatonin activity was detected in beef pituitary, hypothalamus, thymus, thyroid, adrenal, ovary, testis or eye(*545*)."

From an early paper on the effect of light on melatonin synthesis:

"The mass, morphology, and biochemical composition of the mammalian pineal gland can be altered by varying the amount of light or darkness to which the animal is exposed: constant exposure to light decreases the weight of the pineal gland in the rat; this effect does not require the presence or normal functioning of the pituitary gland, gonads, adrenals, or thyroid. Constant illumination also decreases the size of pinealocyte nucleoli and the level of cytoplasmic basophilia. This has been interpreted as indicating a decrease in pineal RNA synthesis. The reverse histologic picture is found when rats are placed in continuous darkness.

It has recently been demonstrated that the administration of minute amounts of melatonin subcutaneously over long periods inhibits ovarian growth and the incidence of estrus in young rats. Larger doses produce a decrease in the size of seminal vesicles in male rats, and inhibit the response of the thyroid to methylthiouracil. […]

The physiological disposition of intravenously-administered tritiated melatonin is altered in the rat exposed to continuous light, while minute doses of this compound interfere with the persistent estrus induced by light. Since the actions and disposition of melatonin seem to be related to light exposure in the mammal, studies were undertaken to determine whether the capacity of the rat pineal gland to synthesize melatonin from its immediate precursor was also subject to photic regulation. Our experiments show that

exposure of rats to constant darkness for as little as 6 days induces a striking increase in the activity of HIOMT in the pineal gland.

Sprague-Dawley female rats were placed in constant light(*546*)"

From the discovery paper of melatonin's effect on sleep:

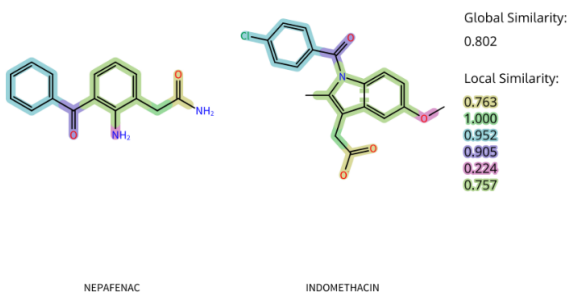
"The relatively high level of melatonin in the pineal gland of the mammalian brain 1 suggests that besides its inhibitory action on gonadal function it may also play the role of a modulator substance within the central tryptaminoceptive structures postulated by BRODIE and SHORE. The recent finding that it is capable of preventing thyroid hyperplasia caused by methylthiouracil 4 also suggests such a possibility.

In the present study, carried out upon 11 adult cats, micro-amounts of crystalline melatonin where administered directly through chronically implanted stainless steel cannulae into three subcortical structures according to Jasper, Ajmone-Marsan coordinates: preoptic region, nucleus centralis medialis and to the brain stem reticular formation. The general behavior of the animals was observed in a relatively sound-proof box and EEG recordings made simultaneously. After 3-5 experiments repeated on each animal at 6-8 day intervals the brains were fixed in formalin and the sites of deep electrodes and of cannulae checked histologically(*547*)."

## NEPAFENAC

2005

Analogue of indomethacin




## EXENATIDE

2005

"Exenatide is a synthetic derivative of 39-amino acid GLP1 agonist isolated from the salivary gland venom of the lizard *Heloderma suspectum* (Gila monster). This peptide has 53% amino acid similarity to mammalian GLP1(*486*)"

"The major interest in heloderma venoms is in their biologically active peptides designated helospectins, helodermin, exendin-3 and exendin-4, all of which, through different receptors, activate adenylyl cyclase. Discussion of helospectins and helodermin which bind to and stimulate VIP and secretin receptors, is beyond the scope of this article. However, these peptides were discovered with the knowledge that crude venom of both *Heloderma horridum* and *Heloderma suspectum* stimulates adenylyl cyclase activity and amylase release from guinea-pig dispersed pancreatic acini(*548*)."

From the discovery paper of the secretagogue effect of the venom cited in the previous quotation:

"In the present study, we undertook a systematic examination of the effects of venoms from various arthropods and reptiles on dispersed acini from guinea pig pancreas. Venom from Gila monster (family Helodermatidae) was found to increase pancreatic enzyme secretion by interacting with vasoactive intestinal peptide (VIP) receptors to activate adenylate cyclase and increase cellular cAMP. […]

*Tissue preparation*. A guinea pig was killed by a blow to the head. The pancreas was removed and trimmed of fat and mesentery. Dispersed acini were then prepared using purified collagenase and mild shearing forces as described previously(*549*)."

## DEFERASIROX

2005

Iron-chelating agent

ABATACEPT

2005

"Abatacept is a soluble fusion protein, which links the extracellular domain of human cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) to the modified Fc (hinge, CH2, and CH3 domains) portion of human immunoglobulin G1 (IgG1)(*2*)."

GALSULFASE

2005

"Galsufase is a variant form of the polymorphic human enzyme N-acetylgalactosamine 4-sulfatase of recombinant DNA origin(*2*)."

INSULIN DETEMIR

2005

Long-acting analogue of human insulin(*1*)

ECAMSULE

2006

"Ecamsule affords broad spectrum protection against the sun's UVB and UVA rays. Exposed to UV, ecamsule undergoes reversible photoisomerization, followed by photoexcitation. The absorbed UV is then released as thermal energy, without penetrating the skin(*1*)."

RANOLAZINE

2006

"**Phenotypic screening of compound-specific libraries based on significant prior knowledge of compound properties** […]

Ranolazine (RS-43285) was first identified by screening potential channel blockers in a canine model of myocardial ischaemia(*486*)."

RANIBIZUMAB

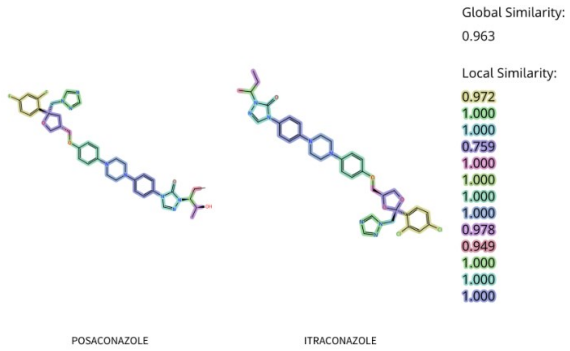
2006

Monoclonal Antibody

POSACONAZOLE

2006

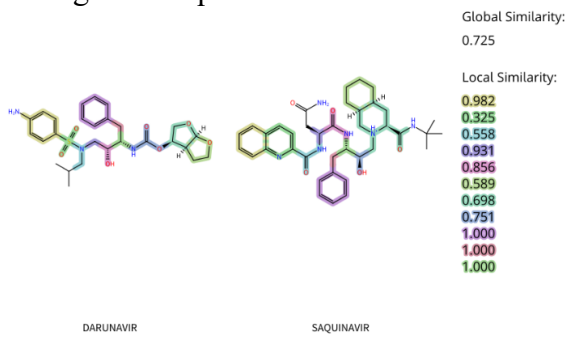
Analogue(*486*) of itraconazole(*2*)




DARUNAVIR

2006

Analogue of saquinavir




VORINOSTAT

2006

"**Phenotypic screening: serendipitous discoveries** […]

Charlotte Friend was studying murine erythroleukaemia cells (MELC) and in an effort to 'soften them' for transfection, she cultured the cells with 280 mM DMSO in aqueous buffer. Approximately two-thirds of these cancer cells turned red — suggesting the presence of haemoglobin. Subsequently, other polar, small-molecule solvent species were observed to also induce the cytodifferentiation and growth arrest of MELCs and that simple amides were in fact somewhat more potent than DMSO. The molecular mechanism of action (MMOA) was identified using cell-based screens. It was

subsequently discovered that suberoylanilidehydroxamic acid (SAHA, vorinostat) inhibits the activity of histone deacetylases (HDACs), including all 11 known human class I and class II HDACs(*486*).”

SITAGLIPTIN

2006

“**Target-based screening** […]

Advances in the understanding of the actions of endogenous glucoregulatory peptide hormones, known as incretins, identified new therapeutic targets for type 2 diabetes. Two incretins — glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP1) — potentiate glucose-dependent insulin secretion from islet b-cells by activating specific G-protein-coupled receptors. However, although native GLP1(7–36) amide effectively lowers blood glucose, it is rapidly degraded by the ubiquitous serine protease dipeptidyl peptidase-4 (DPP4). Sitagliptin, a DPP4 inhibitor, was discovered in an iterative discovery approach aimed at optimizing metabolic properties while retaining efficacy(*486*).”

From the discoverer(s):

“Following the completion of the studies described above, the objective of the internal program was to identify a potent DPP-4 inhibitor for development with 41000-fold selectivity over related proline peptidases, especially DPP-8 and DPP-9. […]

High throughput screening led to the identification of surprisingly few hits, and only two, b-aminoacyl amide 9 and piperazine 10, were deemed worthy of extensive follow-up(*550*).”

ANIDULAFUNGIN

2006

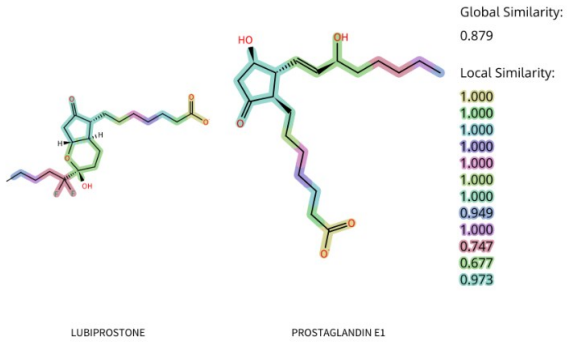
Analogue(*486*) of caspofungin

Error in similarity calculation by FTrees because of the unsupported macrocycle

LUBIPROSTONE

2006

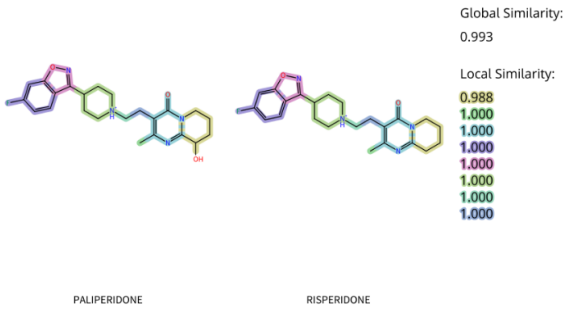
Analogue of Prostaglandin $E_1$




PALIPERIDONE

2006

Analogue of risperidone, the primary active metabolite of risperidone(*2*).




SUNITINIB

2006

“**Target-based screening: optimized MMOA subsequently identified** […]

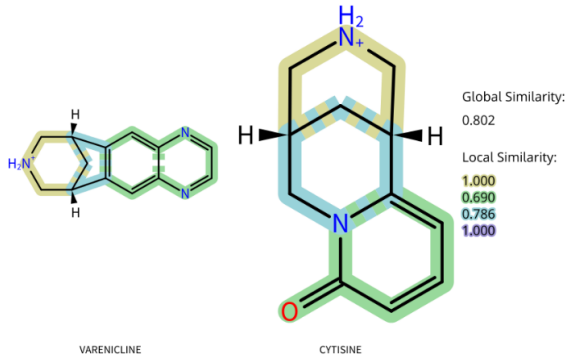
Sunitinib (SU11248) was identified as a potent inhibitor of the VEGFR and platelet-derived growth factor receptor (PDGFR) kinases. VEGFR2 and PDGFR are important in cancer-cell proliferation and survival, and also in tumour angiogenesis. Data from preclinical and animal models suggested that simultaneous inhibition of VEGFR2 and PDGFR might produce greater antitumour effects than inhibition of either receptor tyrosine kinase alone, leading to the development and prioritization of agents that inhibited both of these receptors(*486*).”

VARENICLINE

2006

Analogue of cytisine(*551*)

"Cytisine was first discovered in 1818 and




was isolated in 1865. In 1912, cytisine's biological effects were reported to be nearly identical to those of nicotine, and cytisine was proposed as an inexpensive, readily available replacement for tobacco. Consequently, the Cytisus plant was reportedly smoked during World War II by German and Russian soldiers as a tobacco substitute. In 1964, a Bulgarian pharmaceutical company named Sopharma marketed cytisine as a smoking cessation aid under the brand name 'Tabex.' Although clinical trials during the 1960's and 1970's reported that cytisine produced quit rates between 21–30% at six-month follow-up, these studies were not conducted systematically. A later placebo-controlled trial published in the *New England Journal of Medicine* reported more modest effects of cytisine on sustained abstinence at 12-month follow up: 8.4% of subjects remained abstinent on cytisine compared to 2.4% on placebo. Similarly, a more recent meta-analysis based on two studies deemed to be of high quality reported a ~three-fold increase (random ratio = 3.29) in the likelihood of maintaining abstinence at six-month follow-up with cytisine use compared to placebo. Cytisine's low efficacy may be due in part to poor absorption and crossing of the blood brain barrier. […]

Varenicline tartrate was originally developed as a smoking cessation agent by Pfizer in 1997 based on the molecular structure of cytisine(*551*)."

"**Phenotypic screening: intentional/known target seeking improved MMOA** […]

Varenicline was discovered through the synthesis of a series of compounds inspired by the natural product (–)-cytisine, which was previously known to have partial agonist activity at nAChRs(*486*)."

"**Phenotypic screening of compound-specific libraries based on significant prior knowledge of compound properties** […]

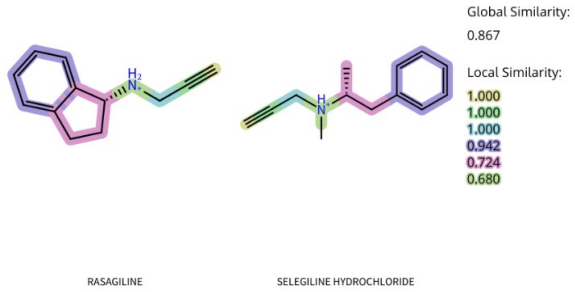
Lubiprostone is a derivative of prostaglandin E1 (PGE1). The first evidence that lubiprostone increased intestinal water secretion and intestinal fluid chloride concentrations was reported in 2002. The exact MMOA is still unclear although some controversial evidence suggests a role for chloride channels. We could not identify a report that explicitly described the method of discovery. However, we deduce for the literature that it was discovered using phenotypic assays. It is marketed for the treatment of chronic constipation(*486*)."

"In vivo testing of specific compounds probably based on the finding that a known side effect of prostaglandins is diarrhea(*542*)."

RASAGILINE

2006

Analogue(*486*) of selegiline




ARFORMOTEROL

2006

Enantiopure formoterol

SINECATECHINS

2006

"**Phenotypic screening: serendipitous discoveries** […]

The mode of action of sincatechins in the clearance of genital and perianal warts is unknown. In vitro, they have antioxidative activity; however, the clinical significance of this finding is unknown. Archaeological evidence suggests that tea plant culture is likely to have originated in China more than 5,000 years ago, from where it was brought to India, Japan, Thailand, Korea and Sri Lanka. The medicinal properties of tea leaves first appeared in a Chinese book on pharmaceutical plants (~200 BC). Later, in the KissaYojoki (Book of Tea, ~1191), tea was listed as a remedy to control bleeding, help wounds heal, regulate body temperature, control blood sugar and promote digestion(*486*)."

ALISKIREN

2007

"**Target-based screening**

*Aliskiren*. It took nearly 100 years following the discovery of the protease renin, which is a key regulator of blood pressure, for an orally active renin inhibitor, aliskiren to be approved for the treatment of hypertension. The breakthrough came in the 1980s when medicinal chemists identified inhibitors of renin that were more drug-like than substrate-like.(*486*)"

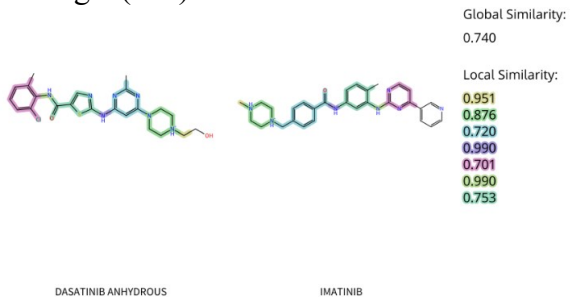
From the discovery paper:

"We employed a combination of crystal structure analysis of renin–inhibitor complexes and computational methods to design novel, low molecular weight renin inhibitors without the extended peptide-like backbone of previous inhibitors and with favourable pharmacokinetic properties after oral administration to monkeys. Our design approach led to the development of aliskiren, the first in a new class of orally effective, non-peptide renin inhibitors which represent novel potential treatments for hypertension and related cardiovascular diseases(*552*)."

DASATINIB

2006

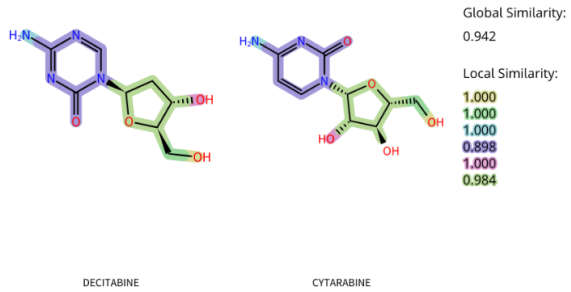
Analogue(*486*) of imatinib




DECITABINE

2006

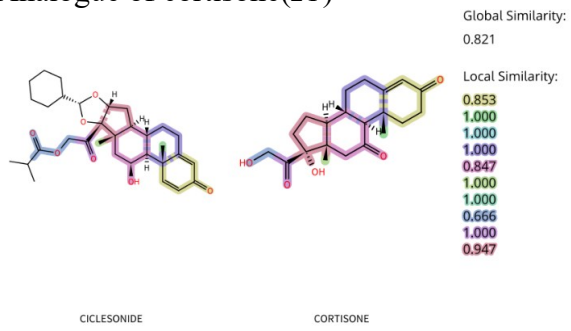
Analogue(*486*) of cytarabine




CICLESONIDE

2006

Analogue of cortisone(*21*)




PANITUMUMAB

2006

Monoclonal Antibody

IDURSULFASE

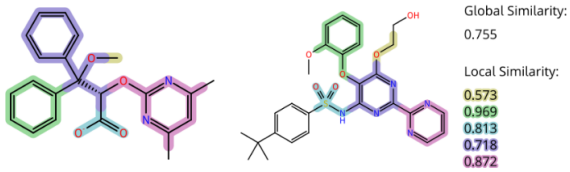
2006

human iduronate-2-sulfatase, a lysosomal enzyme.(*2*)

AMBRISENTAN

2007

Analogue(*486*) of bosentan

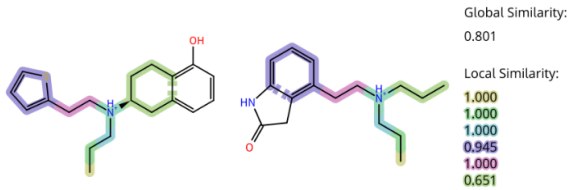



AMBRISENTAN BOSENTAN ANHYDROUS

ROTIGOTINE

2007

Analogue(*486*) of ropinirole

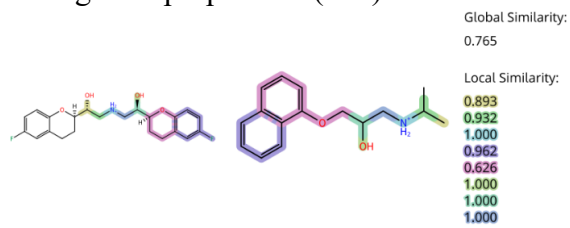



ROTIGOTINE ROPINIROLE

NEBIVOLOL

2007

Analogue of propranolol(*253*)




NEBIVOLOL PROPRANOLOL

RALTEGRAVIR

2007

**"Target-based screening: optimized MMOA subsequently identified**(*486*)"

From the discovery paper:

"4-Aryl-2,4-diketobutanoic acids (DKAs) were the first class of true HIV-1 strand transfer inhibitors and provided the first proof-of-concept for HIV-integrase inhibitors as antiviral agents in the cell based assay. DKAs were also discovered as active site HCV NS5b RNA-dependent RNA polymerase inhibitors. The mechanism of action of these inhibitors is likely a consequence of the interaction with metals in the active site, resulting in a functional impairment by chelation of the critical metal cofactors. Within Merck Research Laboratories (MRL), the two groups working on HIV-integrase and HCV polymerase discovered a series of scaffolds characterized by improved druglike qualities that dialed out the undesirable DKA properties. In particular, we discovered that the dihydroxypyrimidine carboxamide derived from the evolution of DKA in the HCV polymerase program was a potent, reversible, and selective HIV-integrase strand transfer inhibitor showing nanomolar activity in the enzymatic assay ($IC_{50}$ = 0.085 μM) while being completely inactive on the HCV polymerase. Extensive structure activity relationship studies on the carboxamide moiety led to the identification of the p-fluorobenzyl as the optimal amide residue (**1**) and of the gem-dimethyl as the optimal 2-substituent for the dihydroxy pyrimidine core (**2**). Parallel efforts led to the identification of the related N-methylpyrimidone scaffold showing equal or enhanced activity for the HIV-integrase (**3**). Both 2 and 3 showed good potency in the antiviral cell based assay in the presence of 50% normal human serum (NHS) and favorable oral bioavailability in preclinical species.

Raltegravir (**27**) is the result of our continued

efforts to optimize these inhibitors, addressing issues presented by previously reported inhibitors. These include metabolic stability, pharmacokinetic profile, antiviral activity against a panel of HIV-1 integrase mutations previously shown to be associated with resistance to 1,3-diketoacid inhibitors and other classes of inhibitors, and genotoxicity(*553*)."

## RETAPAMULIN

2007

Analogue of pleuromutilin(*486*)

From the discovery paper:

"Several species of the genus Pleurotus have been found in this laboratory to form substances inhibitory for *Staphylococcus aureus*. Among these were two species, *Pleurotus mutilus* (Fr.) Sacc. and *P. Passeckerianus* Pilat, obtained from the Centraalbureau voor Schimmelcultures at Baarn. An antibacterial substance formed by these fungi was isolated in crystalline form from culture liquids; it was named pleuromutilin.

*P. mutilus* grown on corn-steep, thiamine-peptone, or potato-dextrose agars for two days and tested by the streak-method, markedly inhibited *Staphylococcus aureus*, inhibited incompletely *Mycobacterium smegma*, and had no effect on *Escherichia coli*. Agar disks cut from colonies 10 days old formed inhibition zones 20 mm. in diameter with *S. aureus* and a small zone of incomplete inhibition with *M. smegma*. *P. Passeckerianus* produced similar zones of inhibition(*554*)."

## TEMSIROLIMUS

2007

Analogue of sirolimus(*2*)

Error in similarity calculation by FTrees because of the unsupported macrocycle

## SAPROPTERIN

2007

Endogenous-based biopharmaceutical

## NILOTINIB

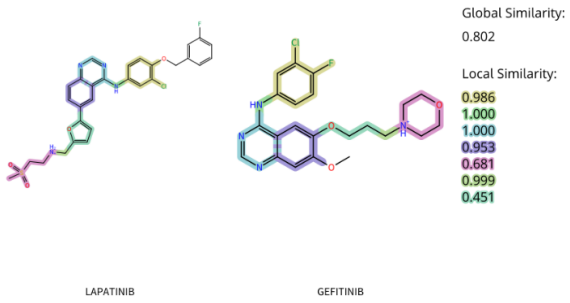
2007

Analogue(*486*) of imatinib


## LAPATINIB

2007

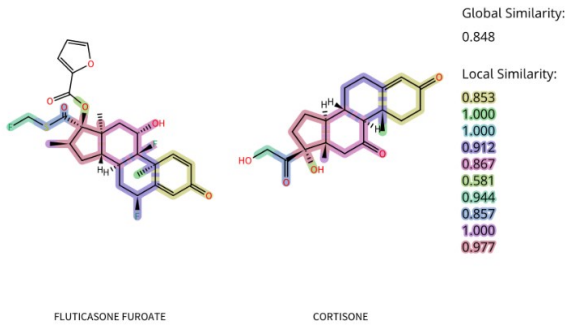
Analogue(*486, 542*) of gefitinib




## FLUTICASONE FUROATE

2007

Analogue of cortisone(*21*)




## METHOXY POLYETHYLENE GLYCOL-EPOETIN BETA

2007

Pegylated recombinant erythropoietin

IXABEPILONE

2007

From the discoverer(s):

"The epothilones were originally isolated from the myxobacterium Sorangium cellulosum by Profs. Hans Reichenbach and Gerhard Höfle in the early 1990s. In the original German patent application from GBF, the epothilones were noted to have antifungal activity and cytotoxic activity, but it was not until the 1995 article from Bollag et al. that the mechanism of the cytotoxicity was revealed(*555*)."

From Gerhard Höfle:

"In July 1985 *Sorangium cellulosum*, strain So ce90, the first producer of epothilone, was isolated by Hans Reichenbach from a soil sample collected at the banks of the river Zambesi in southern Africa in August 1980. Only two years after isolation, the strain was introduced in an antifungal screening of *Sorangium* strains by *Klaus Gerth* and identified as one of several hits inJanuary 1987. Later, *Florenz Sasse*, responsible for cell culture tests, noticed high cytotoxicity of the culture extract. From these and other preliminary tests we were dealing with a new compound and *Norbert Bedorf* from the chemistry group immediately started to isolate the compound and elucidate its structure. Guided by biological activity, he isolated two closely related antifungal compounds later named epothilone A and B(*556*)"

LANREOTIDE

2007

Analogue of the endogenous somatostatin(*2*)

Error in similarity calculation by FTrees because of the unsupported macrocycle

ECULIZUMAB

2007

Monoclonal Antibody

MARAVIROC

2007

"**Target-based screening: optimized MMOA subsequently identified** […]

Maraviroc was discovered through the medicinal chemistry optimization of a hit compound identified from high-throughput screening(*486*)."

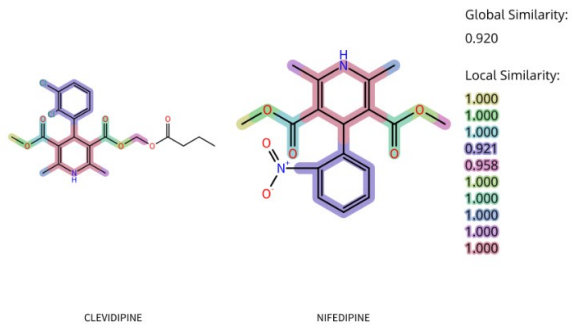
"Pfizer scientists screened their library of compounds, using a chemokine radioligand binding assay to identify a small-molecule CCR5 ligand. The imidazopyridine UK107,543 was one of the most potent lead compounds identified and was the starting point of an intensive medicinal chemistry program, which included parallel screening to optimize the binding potency, antiviral activity, absorption, pharmacokinetics, and specificity for CCR5. The result of this massive effort was maraviroc(*557*)."

CLEVIDIPINE

2008

Analogue(*486*) of nifedipine

IOBENGUANE SULFATE I-123




2008

Radiopharmaceutical

DIFLUPREDNATE

2008

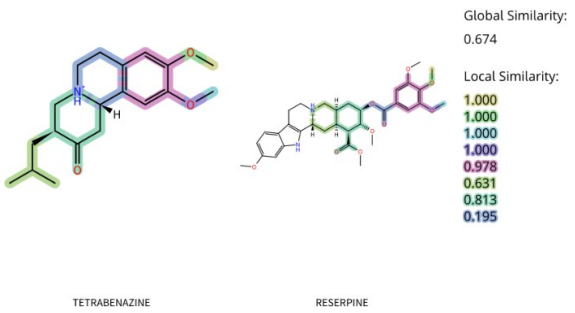
Analogue of cortisone

Error in similarity calculation by FTrees

TETRABENAZINE

2008

Analogue(*486*) of reserpine




Discovery: phenotypic screening(*486*)

Discovery of reserpine:

From a 1954 article:

"Although it is an ancient drug, *Rauwolfia serpentina* received little notice from clinicians interested in hypertension, even in its native land, India, until 1940, or in this country until 1950. This rather slow acceptance of a new therapeutic agent in a field as urgent as hypertension was due in part, no doubt, to the 'slow' nature of the drug itself. I well remember our first clinical trials of increasingly large, single doses of the crude root, and that we were about to conclude it was inactive, when we observed one patient who had taken such doses for several days consecutively. She had developed a slow pulse and a definite fall in blood pressure, but she also had so much sedation that we felt the drug to be impractical given in this way. Some time later, when I placed a group of my long- and well-known cases on small doses of the drug for several weeks, I was surprised to have them report uniformly good symptomatic effects. I was still somewhat dubious about the hypotensive results, although the bradycardia was definite. After several months, however, I became convinced of the hypotensive, as well as the bradycrotic and sedative, effects of the drug as compared with placebo controls. […]

Prior to our own studies, all the reports on the drug were from India. Thus, Bhatia, in 1942, observed that *Rauwolfia* caused a moderate lowering of blood pressure in both renal and essential hypertensive patients and, in addition, was particularly effective in relieving the nervous symptoms of the disease, such as headache, tinnitus, vertigo, giddiness, insomnia, *etc*. He postulated that the drug somehow produced its action through the central nervous system. He did not comment on the pulse-rate-slowing effect of the drug, but the following year Gupta, Deb, and Kahali, in a paper on its use in mental disorders noted that it slowed the pulse rate as well as lowered the blood pressure. […]

I have told many psychiatrists and others interested in psychotherapy that '*Rauwolfia* is good psychotherapy in pill form.'(*558*)."

**Note the attitude towards using chemicals for psychiatric disorders before the advent of chlorpromazine and iproniazid.

"*R. serpentina* has an ancient history. It is said to appear in Sanskrit as an Ayurvedic medicine named Sarpagandha and Chandrà. Chandrà means moon and refers to the use of the plant in the 'moon's disease' or lunacy; Sarpagandha, snake's smell or repellent, refers to the use as an antidote for snake-bite. Rheede in 1686 probably mentioned this species, at least in part, under the name Tsjovanna (or Sjouanna) Amel-Podi; he noted the use of the root against snake-bite and the sting of scorpions. Kaempfer in 1712 described the plant and its curative properties under the name Radix Mungo. Burman in 1737 applied the term Lignum Colubrinum to it. Linnaeus in Materia Medica, 1749, used the pharmacopoeic appellation Serpentini Lignum. Rumphius named the plant Radix Mustelae, in reference to the legend that the mongoose has recourse to it when bitten by a poisonous snake; he stated that the species came to his notice in 1693. Various other curative properties were early attributed to the plant, and it has accordingly been regarded as

a febrifuge, tonic, stomachic, sedative, soporific, eclampsia relief, cough-sedative, diuretic, purgative and anthelmintic. Trimen noted its use against hydrophobia. Dymock (1879) stated that in Bombay most of the laborers who came from southern Koncan kept a small supply of the root which they valued as a remedy in dysentery and other painful affections of the intestines. Roxburgh reported that it was administered to promote delivery in child-birth; Wight added that it was supposed to act on the uterine system somewhat in the manner of Ergot; Khory stated the root was said to cause abortion if given to pregnant women. Rama Rao described the 'whole plant dried in shade, powdered and given in honey as a remedy in rheumatism, all poisons, insanity, epilepsy, fits and eczema.' 'The juice of the fresh leaves has been mentioned for the treatment of corneal opacities' (Kapur). Dalzell and Gibson reported the plant used 'to poison tigers.' It will be noticed that many of the empirical uses have a common denominator, the proven sedative or relaxing efficacy of the drug(*559*)"

## ELTROMBOPAG

2008

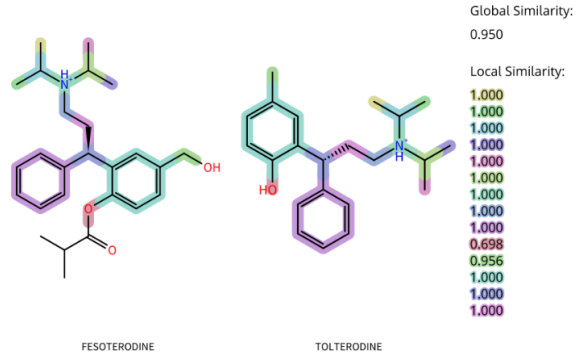
"**Target-based screening** […]

Eltrombopag is a thrombopoietin receptor (TPO) agonist approved for the treatment of thrombocytopenia in patients with chronic immune (idiopathic) thrombocytopenic purpura. It interacts with the transmembrane domain of the human TPO-receptor and initiates signalling cascades that induce proliferation and differentiation of megakaryocytes from bone marrow progenitor cells. Eltrombopag was identified through screening of small molecule libraries for the ability to activate a reporter molecule in TPO-dependent cell lines. Lead compounds were initially identified and then optimized for their biologic effects and pharmaceutical properties(*486*)."

## FESOTERODINE

2008

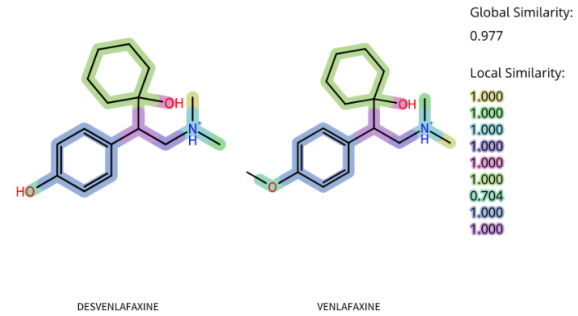
Analogue of tolterodine(*2*)




## DESVENLAFAXINE

2008

The major active metabolite of venlafaxine(*2*)




## REGADENOSON

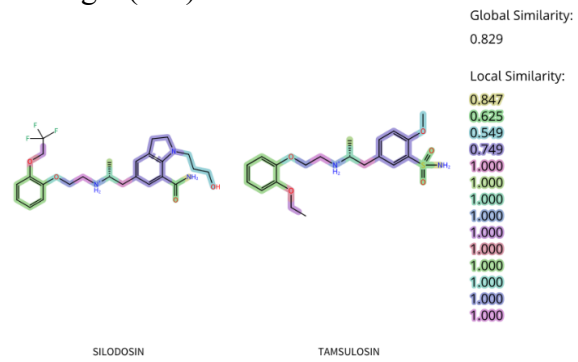
2008

Diagnostic

## SILODOSIN

2008

Analogue(*486*) of tamsulosin



## PLERIXAFOR

2008

"Plerixafor (Mozobil®, AMD3100) is a small organic molecule consisting of two cyclam rings connected by a 1.4-phenylenebis(methylene) linker. The pharmacological activity of bicyclam molecules was first identified in the search for new agents to treat HIV. Plerixafor evolved through an intensive medicinal chemistry effort from these early alkyl-linked bicyclams.

Mechanistic studies suggested that the bicyclams acted at the early stages of the HIV infection process, but it was not until the discovery that HIV required a chemokine co-receptor, either CCR5 or CXCR4, along with CD4, for host cell entry, that the molecular target for plerixafor was discovered(*560*)."

From the discovery paper of the bicyclams cited in the previous quotation:

"A series of bicyclams have been shown to be potent and selective inhibitors of human immunodeficiency virus (HIV). The compounds are inhibitory to the replication of various HIV-1 and HIV-2 strains in various human T-cell systems, including peripheral blood lymphocytes, at 0.14-1.4 μM, without being toxic to the host cells at 2.2 mM. The bicyclam JM2763 is active against 3'-azido-3'-deoxythymidine (zidovudine; AZT)-resistant HIV-1 strains and acts additively with AZT. Mechanism of action studies revealed that the bicyclams (i.e., JM2763) interact with an early event of the retrovirus replicative cycle, which could be tentatively identified as a viral uncoating event(*561*)."

## RILONACEPT

2008

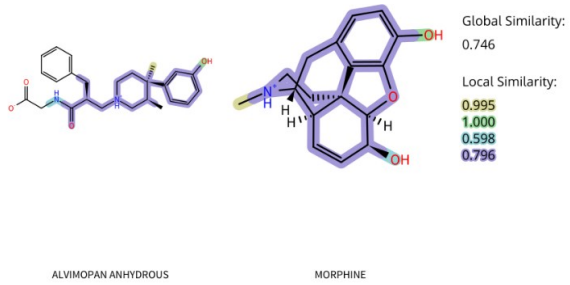
"Rilonacept is a dimeric fusion protein consisting of portions of IL-1R and the IL-1R accessory protein linked to the Fc portion of immunoglobulin G1(*2*)."

## ALVIMOPAN

2008

Analogue(*486*) of morphine

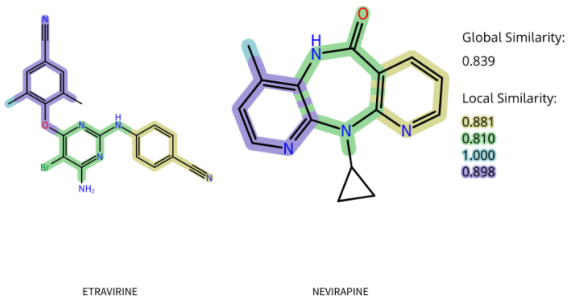
Also see the fentanyl entry and refer to Paul Janssen's article cited there.




## ETRAVIRINE

2008

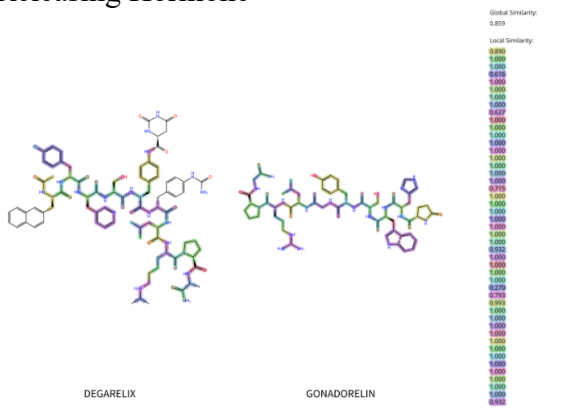
Analogue of nevirapine(*562*)




## DEGARELIX

2008

Analogue of the endogenous Gonadotropin Releasing Hormone




## CERTOLIZUMAB PEGOL

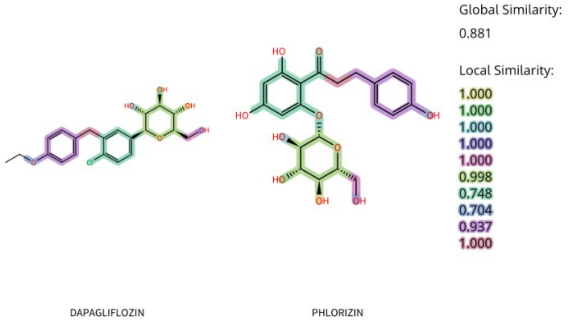
2008

Monoclonal Antibody

## DAPAGLIFLOZIN

2008

Analogue of phlorizin




"Phlorizin is a glucoside consisting of a glucose moiety and two aromatic rings (aglycone moiety) joined by an alkyl spacer. In the 19th century, French chemists isolated it from the bark of apple tree to be used in treatment of fever and infectious diseases, particularly malaria. Von Mering observed in 1886 that phlorizin produces glucosuria. It has been used as a tool for physiological research for more than 150 yr. In 1975, DeFronzo *et al*. showed that infusion of phlorizin in dogs increased fractional excretion of glucose by 60%, whereas glomerular filtration rate and renal plasma flow remained unchanged.

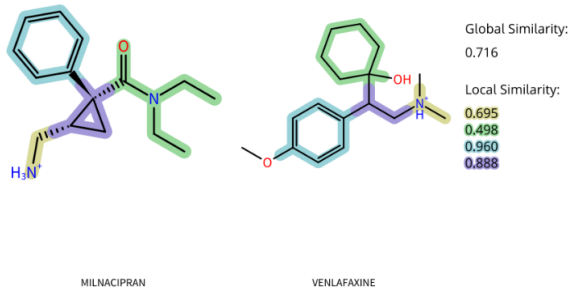
In 1986, Unger's group reported that iv glucose failed to suppress the marked hyperglucagonemia found in insulin-deprived alloxan-induced diabetic dogs; however, when hyperglycemia was corrected by phlorizin, the hyperglucagonemia became readily suppressible. Phlorizin treatment of partially pancreatectomized rats completely normalized insulin sensitivity but had no effect on insulin action in controls, suggesting that the effect on insulin sensitivity was by reversal of glucotoxicity, rather than by a direct effect on insulin sensitivity.

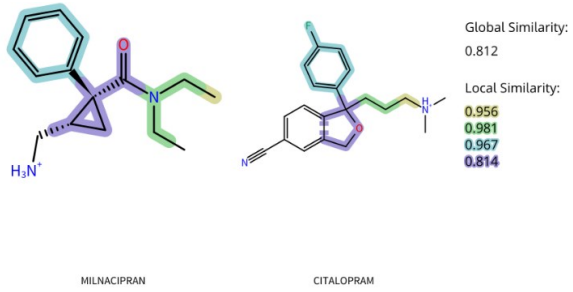
Several specific and potent SGLT2 inhibitors have undergone preclinical testing. Most SGLT2 inhibitors are glucosides, structurally related to phlorizin, which is an o-glucoside. The o-glucosides have to be administered as their prodrug esters to avoid degradation by β-glucosidase in the small intestine. Sergliflozin and remogliflozin etabonate, which are orally administered, are the ethyl carbonate prodrug esters of sergliflozin A and remogliflozin, respectively. Creating a carbon-carbon bond between the glucose and aglycone moiety converts o-glucosides to c-glucosides, which have a different pharmacokinetic profile, making them unsusceptible to β-glucosidase. Dapagliflozin is the first c-glucoside to be discovered that is currently in phase III trials(*563*)."

## MILNACIPRAN

2009

Analogue of venlafaxine

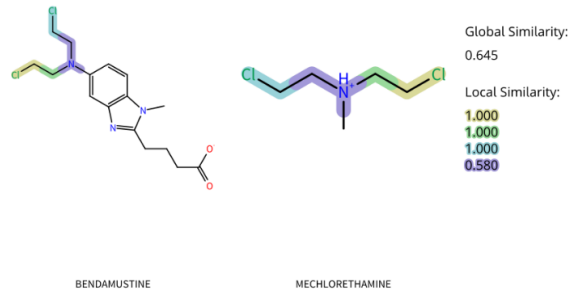



## BENDAMUSTINE

2008

Analogue(*486*) of mechlorethamine



RUFINAMIDE

2008

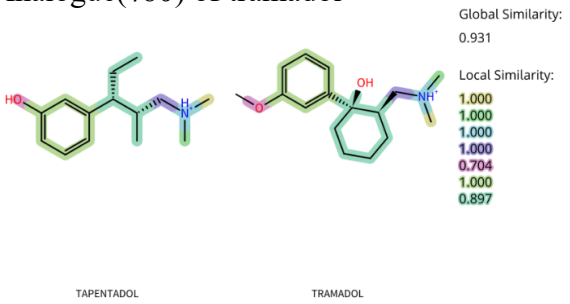
"**Phenotypic screening of 'random' compound library** […]

Rufinamide was discovered by Novartis and initially evaluated within the framework of NIH-sponsored anticonvulsant drug screening program. Rufinamide has a distinctive profile in animal testing — activity in both MES and PTZ models and a very high protective index — that differentiates it from other anti-epileptic drugs(*486*)."

TAPENTADOL

2008

Analogue(*486*) of tramadol




LACOSAMIDE

2008

From the discoverer(s):

"In 1985, we discovered a novel class of anticonvulsant agents, termed functionalized amino acids (FAA). More than 250 FAAs were synthesized and screened in animal model systems. Where possible, we also compared the anticonvulsant activities for the FAA's (*R*)- and (*S*)-stereoisomers. We found that the anticonvulsant activity resided in the (*R*)-enantiomer. The ratio of the potency of the more active (eutomer) to the less active (distomer) isomer ranged from 10 to >22. The lead FAA, lacosamide ((*R*)-*N*-benzyl-2-acetamido-3-methoxypropionamide), is an emerging drug for the treatment of epilepsy and neuropathic pain and has entered phase III clinical trials in the United States and Europe(*564*)."

FOSAPREPITANT DIMEGLUMINE

2008

Prodrug of aprepitant

METHYLNALTREXONE BROMIDE

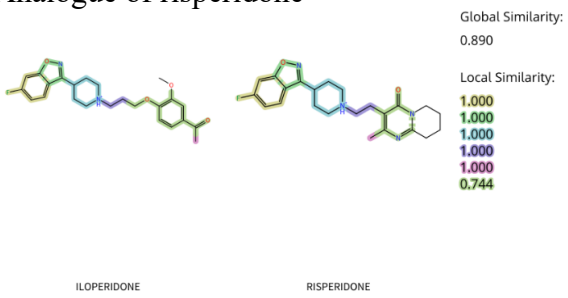
2008

Secondary

ILOPERIDONE

2009

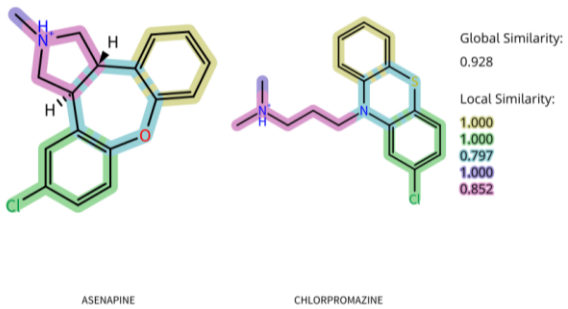
Analogue of risperidone

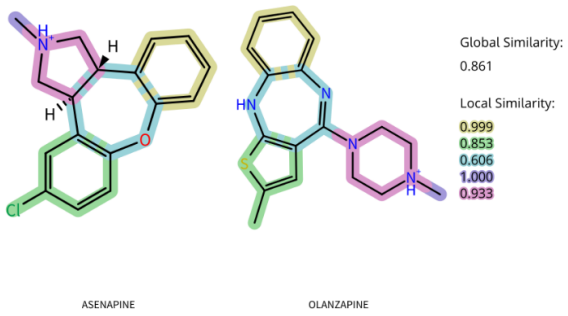



ASENAPINE

2009

Analogue of chlorpromazine




LEVOMILNACIPRAN

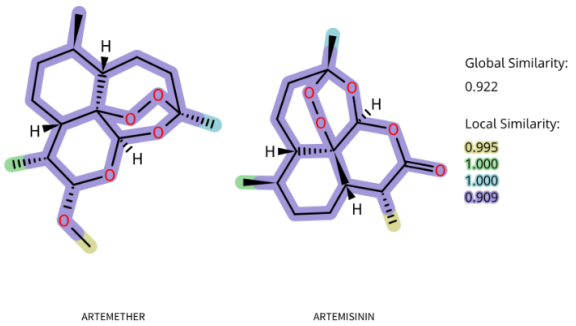
2009

Enantiopure milnacipran

ARTEMETHER

2009

Analogue of artemisinin




Discovery of artemisinin:

In 1967 the government of the People's Republic of China embarked on a systematic examination of indigenous plants used in traditional remedies as sources of drugs. One such plant, a pervasive weed with a long history of use, is known as *qing hao* (*Artemisia annua* L., sweet wormwood, annual wormwood). Its earliest mention occurs in the Recipes for 52 Kinds of Diseases found in the Mawangdui Han dynasty tomb dating from 168 B.C. In that work, the herb is recommended for use in hemorrhoids. This plant is mentioned further in the *Zhou Hou Bei Ji Fang* (Handbook of Prescriptions for Emergency Treatments) written in 340 A.D. The author, Ge Hong, advised that to reduce fevers one should soak one handful of *qing hao* in 1 sheng (about 1 liter) of water, strain the liquor, and drink it all. Later, Li Shizhen, the famous herbalist, whose death 390 years ago was recently commemorated in China, wrote in his *Ben Cao Gang Mu* (Compendium of Materia Medica) of 1596, that chills and fever of malaria can be combated by *qing hao* preparations. A decoction of *A. annua* and *Carapax trionycis* was suggested in the *Wenbing Tiaobian* in 1798 as a treatment for malaria.

Attempts to confirm the antipyretic and antimalarial activity of a hot-water extract of *A. annua* were disappointing. In 1971, it occurred to an investigator that low-temperature extraction of the plant, that is, with ethyl ether, should be tried. Crude ether extracts produced encouraging results in mice infected with the malaria parasite *Plasmodium berghei*(*565*)."

From the discoverer(s):

"Q: What made you and your team think of using artemisinin to treat malaria?

A: Project 523 included two groups engaged in antimalarial drug development: one to devise chemical medicines, another to examine traditional Chinese medicines. The latter group included researchers as well as traditional Chinese medicine doctors, who, as part of Chairman Mao's barefoot scheme, scoured the nation to collect folk remedies. By the time Project 523 had got under way, the Cultural Revolution had started and the research provided shelter for scientists facing political persecution. From 1970, the focus of the project shifted to traditional Chinese medicine because producing antimalarials became less of a priority after China produced chemical combination antimalarials and provided them to North Viet Nam. Experts screened a list of herbs and folk remedies, a few of which were found to have a curative effect against malaria. In the end, the *Artemisia annua* plant was chosen for further research. In the early 1970s, a Project 523 team first isolated artemisinin from the plant. Clinical trials confirmed its antimalarial effects. Between 1976 and 1978, the molecular structure of artemisinin was identified and more artemisinin derivatives were developed. In 1979, artemisinin-based antimalarial drugs were first used in the battlefield in the Sino-Vietnamese War (the Third Indo-China War). Chinese scientists in Project 523, unlike Western researchers looking to find new medicines, identified herbs with curative effects first, before

targeting active ingredients, drawing on their knowledge of traditional Chinese medicine.

*Q: What was* artemisia annua *traditionally used for in China?*

A: As early as the second century BC, the Qinghao plant (sweet wormwood) had appeared as an anti-fever medicine in the *Fifty-two remedies*, a medical treatise. In 340 BC, the *Artemisia annua* plants were first described as having antimalarial properties by Ge Hong, an alchemist and medical expert of the East Jin Dynasty. The folk remedies that Project 523 collected around the 1970s also registered these usages(*566*)."

From some other discoverer(s):

"The department of general affairs of CACMS compiled a mimeographed *Collection of Simple and Secrete Antimalarial Remedies* with 640 recipes selected from thousands of letters sent by the public over several years. At the same time, it sent extracts from a few herbal remedies out of the collection to the AMMS for rodent malaria tests. They found that pepper and chilli-alum extracts had an over 80% malaria inhibition rate on rodent malaria. From July to October, Tu Youyou, Yu Yagang, and Lang Linfu carried out on-site clinical trials in Hainan using these two extracts. Out of 44 cases, only one case in each extract group showed parasite clearance. Eventually, these poor results terminated the trial on these extracts. Then, in early 1970, the National Project 523 Head Office dispatched Gu Guoming from the AMMS, where he was researching herbal antimalarials, to work with Yu to produce herbal extracts and test them on rodent malaria. Because of her other responsibilities, Tu did not continue with the team but remained at its head.

**First Indications of Qinghao's Antimalarial Properties**

Yu and Gu continued combing through the Chinese medical literature, preparing and sending herb extracts to AMMS for rodent malaria tests. As his main resources, Yu used the *Special Compilation on Malaria*—a collection of ancient Chinese antimalarial prescriptions edited by the Shanghai Literature Institute of Traditional Chinese Medicine—and the malaria section of the Qing-dynasty *Complete Medical Works of the Library Collection, Ancient and Modern* compiled in 1723. He concluded after in-depth study that 'black plum, aconite root, shell of fresh-water turtle *Carapax Trionycis*, qinghao, and others' should be singled out, believing that these remedies 'had been used in isolation and appeared frequently in combined prescriptions and are worthy of multiple animal tests.' With 'Project 523 Team' as the author, Yu edited a manuscript titled *Malaria Remedies in Chinese Medical Literature*. Yu's manuscript noted that *qinghao* remedy was first recorded in *A Handbook of Prescriptions for Emergencies* written by Ge Hong (AD 284–364), prepared thus: 'One bunch of *qinghao* in two *sheng* of water, mash it and administer the juice.' The extracts prepared by him and Gu were tested against rodent malaria by Jiao Xiuqing of the AMMS. Gu reported that 'Herbs that appeared more frequently among the traditional antimalarial remedies were selected as objects of study. Among them were *qinghao*, fresh-water turtle shell etc. Extracts were obtained via boiling in water or ethanol extraction, and sent to the screening group for rodent malaria tests. It was found that *qinghao* (dried aerial part of *Artemisia annua* L. purchased) had definite antimalarial properties, with an inhibition rate of around 60–90%(*567*)."

LUMEFANTRINE

2009

Like artemisinin, it was developed in project 523. See the artemether entry(*566, 567*).

CANAKINUMAB

2009

Monoclonal Antibody

CAPSAICIN

2009

“Capsaicin is the main active component found in chilli peppers (*Capsicum annuum*). However, this plant species contains other constituents such as dihydrocapsaicin, nordihydrocapsaicin, homodihydrocapsaicin and homocapsaicin, all of which are known as capsaicinoids. It is currently believed that these chemicals are synthesised by the plant as a defence mechanism against the attack of mammalian herbivores and fungi. Capsicum species have been used in culinary and folk medicine since 7000 BC. Native Americans used Capsicum to cure cramps, diarrhoea and dyspepsia. The capsaicinoids were used for treating toothache in the nineteenth century(*568*).”

TOLVAPTAN

2009

Analogue of conivaptan

From the discoverer(s):

“No reports about nonpeptide vasopressin receptor antagonists or agonists were found in patents or in the literature; therefore, in-house compound library screening was initiated. The competition binding experiments were performed using $^{3}$H-AVP as a natural ligand with rat $V_{1a}$ and rat $V_2$ receptors. No receptor cloning was reported when the binding experiment was initiated; therefore, experiments in a HTS manner could not be performed.

After about 20,000 compounds from the in-house library were screened, several compounds were found that showed potent inhibition of binding at the $3 \times 10^{-4}$ M concentration.(*569*)”

TELAVANCIN

2009

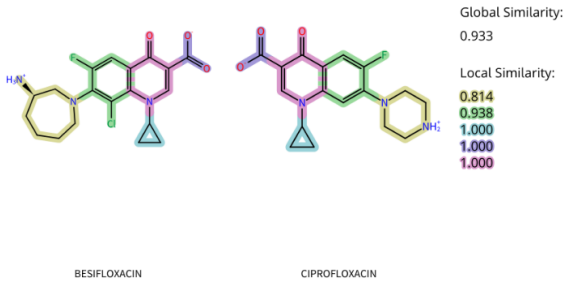
Analogue of vancomycin(*2*)

Error in similarity calculation by FTrees because of the unsupported macrocycle

BESIFLOXACIN

2009

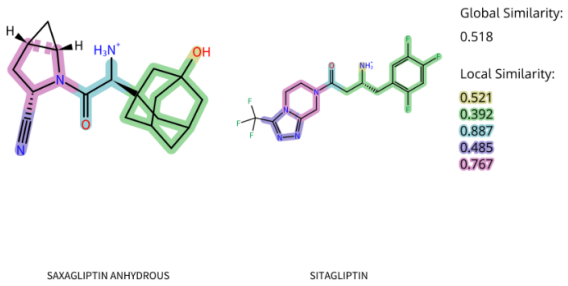
Analogue of nalidixic acid(*2*)




SAXAGLIPTIN

2009

Analogue of sitagliptin




ECALLANTIDE

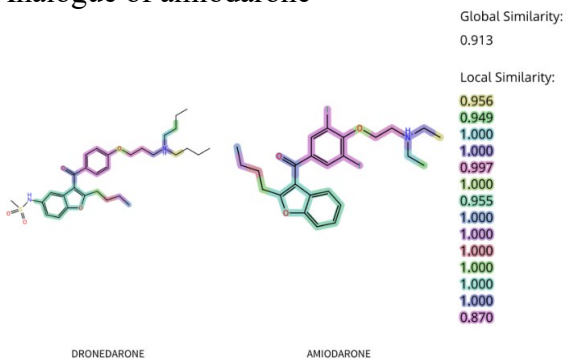
2009

Endogenous-based biopharmaceutical

DRONEDARONE

2009

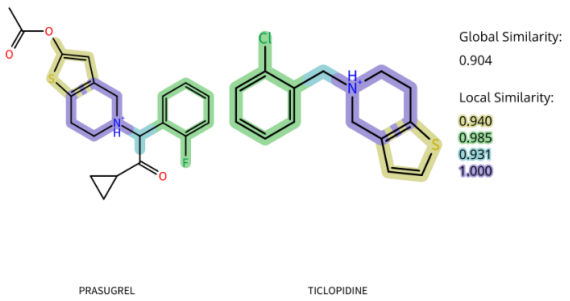
Analogue of amiodarone



## PRASUGREL

2009

Analogue of ticlopidine(*1*)




## ROMIDEPSIN

2009

From the discovery paper:

"During the course of our research program, we found a novel antitumor antibiotic, FR901228 from the fermentation broth of a strain of *Chromobacterium violaceum* No. 968. This compound reversed the transformed morphology of Ha-*ras* transformant to normal. […]

Antimicrobial Activity

Antimicrobial activity was determined by a serial broth dilution method in Nutrient broth for Gram-positive and Gram-negative bacteria and in Sabouraud broth for fungi and yeast. The inoculum was adjusted to 5 x $10^5$ cfu/ml for bacteria and 1 x $10^6$ cfu/ml for fungi and yeast. […]

Ha-*ras* Transformed Cells

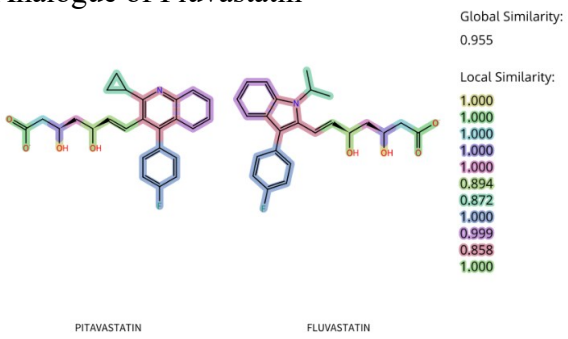
Human bladder carcinoma EJ cells were kindly provided by Dr. M. Tachibana, Keio University. Mouse established normal fibroblast NIH3T3 cells were a kind gift from professor M. Saito, Jichi Medical School. The Ha-*ras* transformed NIH3T3cell line was obtained from transfection of DNA from EJ cells to NIH3T3 cells according to the method described by Parada *et al*. Ras-1 cells, a clonal cell line used in these studies, were obtained from the parental transformant by the limiting-dilution method and had more malignant properties. Ras-1 cells expressed high levels of the Ha-*ras* product, exhibited the transformed phenotype, and was tumorigenic in nude mice. […]

Strain No. 968 was isolated from a soil sample obtained from Yamagata-prefecture, Japan(*570*)."

## PITAVASTATIN

2009

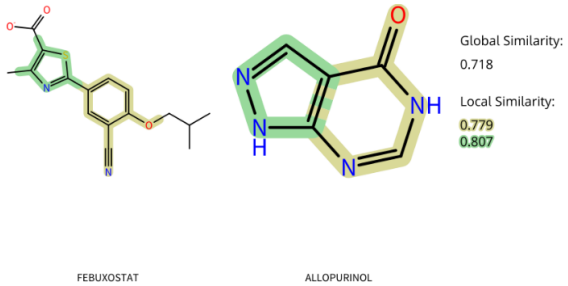
Analogue of Fluvastatin




## FEBUXOSTAT

2009

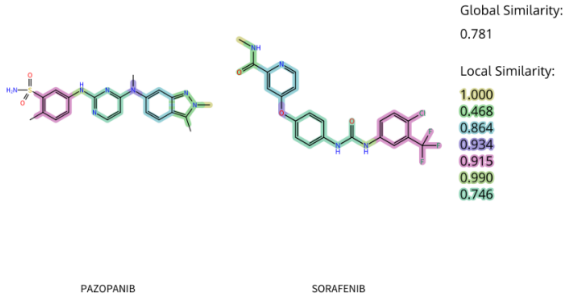
Analogue(*542*) of allopurinol




## PAZOPANIB

2009

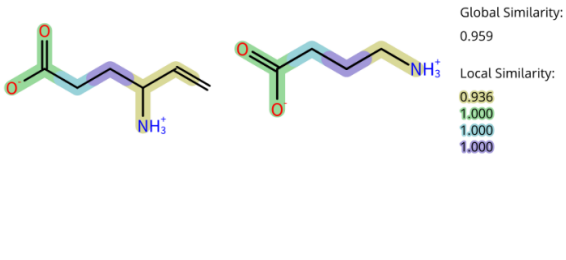
Analogue(*542*) of sorafenib(*571*)



## VIGABATRIN

2009

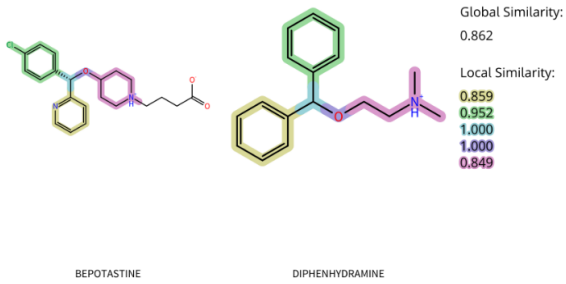
Analogue of GABA(*2*)




## BEPOTASTINE

2009

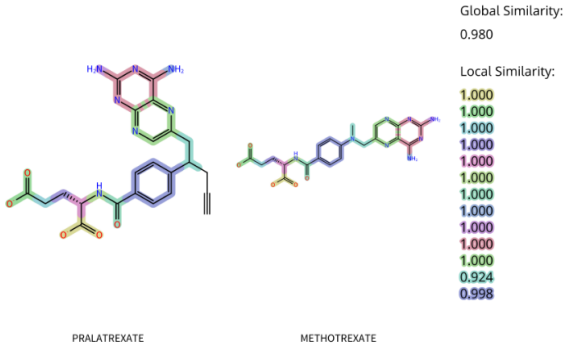
Analogue of diphenhydramine




## PRALATREXATE

2009

Analogue of methotrexate




## DALFAMPRIDINE

2010

"4-Aminopyridine is a broad-spectrum potassium-channel blocker that has been used in electrophysiologic studies for characterizing voltage-gated potassium channels. In vitro studies from the mid 1970s to early 1980s, using isolated nerves in nonmyelinated systems, revealed that 4-AP selectively blocked voltage-sensitive potassium channels, reduced the potassium current, and increased the action potential duration. The ability of 4-AP to restore conduction in demyelinated axons with little effect in normal myelinated axons was further demonstrated using rat dorsal root sensory nerve fibers. These results were subsequently confirmed using isolated rat sciatic nerve fibers under conditions of demyelination as well as in central demyelinated nerve fibers in mammalian models of traumatic spinal cord injury (SCI).

Based on its potential to enhance neuronal conduction in demyelinated axons, 4-AP was assessed from the 1970s to the 1990s, in individual human cases and small studies, as a potential therapy in a variety of conditions, including Eaton–Lambert and related myasthenia syndromes, SCI, and MS. Administration was by intravenous infusion or oral dosing, mainly with an immediate-release formulation, and variable results were reported for different symptoms. […]

Despite characterization of 4-AP, a lipid-soluble compound that readily crosses the blood–brain barrier, and its widespread use in vitro and in vivo, the mechanism of action of dalfampridine has not been fully elucidated because the specific potassium channels that are blocked during therapeutic response have not been identified.(*572*)"

## BOTULINUM TOXIN TYPE A

1989

See the botulinum toxin type B entry

FINGOLIMOD

2010

From the discoverer(s):

"A potent immunosuppressive natural product, **myriocin** (ISP-I), was isolated from a culture broth of *Isaria sinclairii*, a kind of vegetative wasp that is an 'eternal youth' nostrum in traditional Chinese medicine. Mycestericins, structurally resembling myriocin, were also isolated from another fungus. Myriocin at nanomolar concentrations strongly inhibited the proliferation of T cells in mouse allogeneic mixed lymphocyte reaction by culturing BALB/c mouse spleen cells as responder cells with mitomycin C-pretreated C57BL/6 mouse spleen cells as stimulator cells *in vitro*. Moreover, myriocin (0.3 mg/kg, intraperitoneally) significantly prolonged rat skin allograft survival in major histocompatibility complex-compatible rat strain combination between LEW donor and F344 recipient; however, a higher dose of myriocin induced strong toxicity *in vivo*. Myriocin is a rather complicated amino acid with three successive asymmetric centers, some functionalities and has been a challenging synthetic target of synthetic chemists.

**Discovery of fingolimod**

Based on the results of myriocin, we performed lead optimization using both mouse allogeneic mixed lymphocyte reaction *in vitro* and rat skin allograft *in vivo* as screens(*573*)."

From the discovery paper of fingolimod(*573*):

"Compounds 2a-h were evaluated for their ability to inhibit mouse allogeneic MLR (IC50) *in vitro*. […]

Compounds 1a and 2c were evaluated in rat skin allograft in combination with LEW donor and F344 recipient *in vivo*. FTY720 displayed remarkable immunosuppressive activity *in vivo* and prolonged rat skin allograft survival in a dose dependent manner. It was approximately 3-fold more potent than 1a(*574*)."

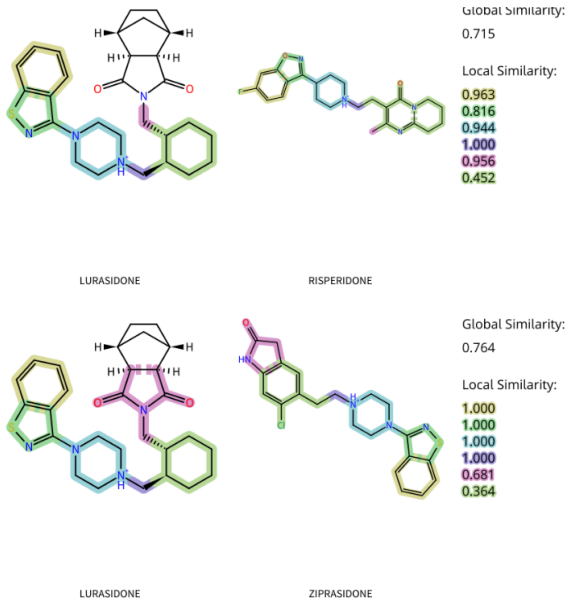
From the discoverer(s):

"In 1994, it has been reported that a potent immunosuppressive activity was found in the culture broth of the fungus *Isaria sinclairii* (ATCC 24400), which is the imperfect stage (the asexual reproductive form in the life cycle) of *Cordyceps sinclairii*. Cordyceps is a genus of fungus which belongs to Hypocreaceae, in the family of Ascomycetes, and parasitic on insects such as *Lepidoptera adonata*. *Cordyceps sinensis* Sacc. (Chinese name: Dong Chong Xia Cao) has been used in a Chinese traditional medicine as a drug for cough, night crying of child, or eternal youth. The culture broths from five strains of Isaria (*I. atypicola* IFO 31160, *I. japonica* IFO31161, *I. felina* ATCC 26680, *I. sinclairii* ATCC 24400, *I. sulfurea* ATCC 22280) were prepared and their immunosuppressive activity was evaluated as inhibition of lymphocyte activation by using mouse allogeneic mixed lymphocyte reaction (MLR)(*575*)."

LURASIDONE

2010

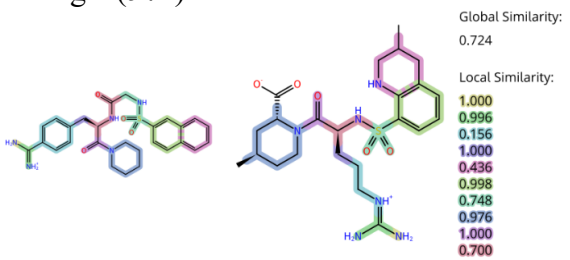
Analogue of ziprasidone

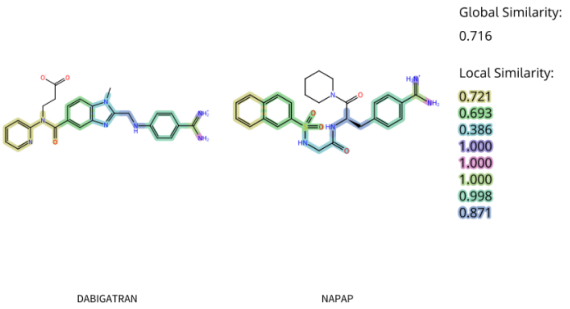


## DABIGATRAN

2010

Analogue(*542*) of NAPAP




From the discovery paper of dabigatran:

"The starting point of our search for noncovalent, nonpeptide thrombin inhibitors was the X-ray crystal structure of the bovine thrombin complex formed with the peptidelike, benzamidine-based inhibitor NAPAP(*576*)."

NAPAP is based on the template of argatroban(*577*).

## ERIBULIN

2010

Analogue of halichondrin A(*578*)

From the discovery paper of halichondrin A:

"In our continuing search for physiologically active substances from marine sources, we recently found several antitumor compounds from *Halichondria okadai* Kadotae. One of them, norhalichondrin A, is a new type macrolide; in this report, we describe the structure determination of norhalichondrin A, a major component in a series of halichondrins.

*Halichondria okadai* Kadota is a common, widely distributed sponge in the Pacific coast of Japan. Prior studies by Scheuerand and Tsukitani resulted in the identification of okadaic acid as a cytotoxic constituent of this animal. However, our interest in the same animal focused on the fact that sponge extracts exhibited remarkable in vivo antitumor activity. Bioassay against B-16 melanoma cells guided the isolation of halichondrins in low yield, including norhalichondrin A.(*579*)"

From the study of Scheuer and Tsukitani cited in the previous quotation:

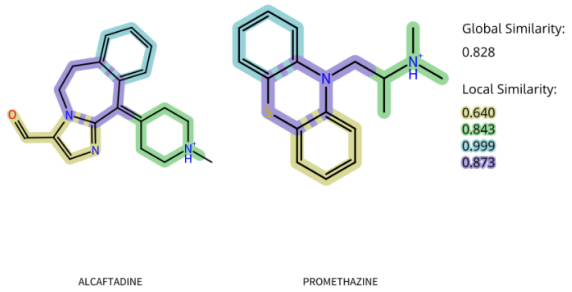
"A new polyether derivative of a C38 fatty acid, okadaic acid, has been isolated independently from two sponges, *Halichondria* (*syn Reniera*) *okadai* Kadota, a black sponge, commonly found along the Pacific coast of Japan, and *H. melanodocia*, a Caribbean sponge collected in the Florida Keys.

Mammalian toxicity of a crude extract of *H. okadai* guided the isolation of a colorless crystalline solid(*580*)."

## ALCAFTADINE

2010

Analogue of promethazine




## PEGLOTICASE

2010

"Pegloticase is a recombinant porcine-like uricase drug indicated for the treatment of severe, treatment-refractory, chronic gout. Similarly to rasburicase, pegloticase metabolises the conversion of uric acid to allantoin(*2*)."

## HEXAMINOLEVULINATE

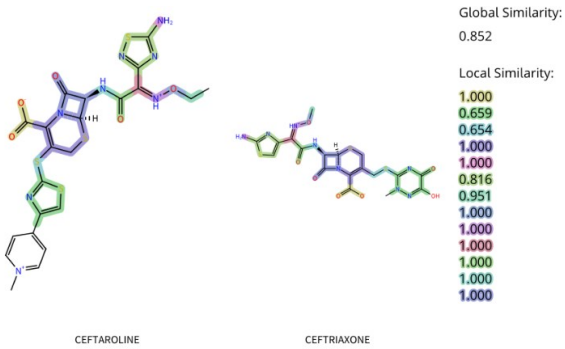
2010

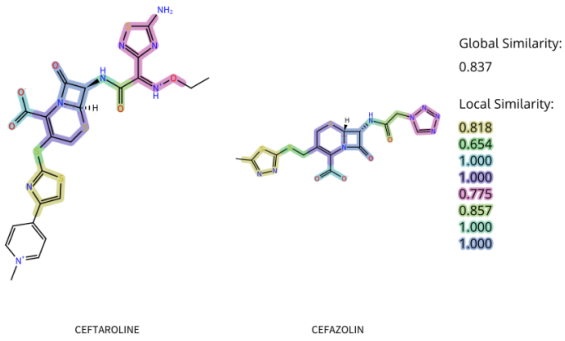
Diagnostic

CEFTAROLINE

2010

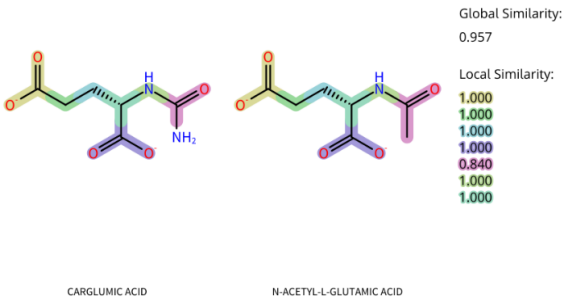
Analogue of cefalexin(*2*)




CARGLUMIC ACID

2010




"discovery strategy: Phenotype […]

Target informed phenotypic assays were required to identify this therapeutically useful MMOA. Other MMOAs for genetic informed discoveries also used a target informed phenotypic assay including the potentiator for the CTFR mutant protein, ivacaftor. As noted above carglumic acid is a structural analog of an essential allosteric activator and product of the deficient enzyme(*581*)."

From the first paper reporting its use in N-acetylglutamate synthase deficiency:

"Because Brown et al. had advocated the use of carbamylglutamate (CG) and arginine in hepatic coma and Kim et al. actually used it in rats, we tried it on the patient."

From the 1958 discovery paper of Brown and colleagues cited in the previous quotation:

"Krebs urea cycle should function with adequate enzymes, intermediates, and substrate concentrations; therefore increasing only one substrate (presumably ornithine from the administered arginine) may not necessarily increase the overall rate of urea formation in the normal liver.

Therefore, ideal therapy based on present knowledge should include (*a*) elimination of the source of ammonia, and (*b*) the administration of arginine and carbamyl glutamate, the latter for acute or chronic hepatic failure as well as for liver regeneration.

Since carbamyl glutamate is easier and cheaper to make than acetyl glutamate we have been using this catalytic agent for some nine months (intravenously as 3 g. of the potassium salt combined with 10 g. of arginine, oral dose 1-2 g. daily), with good results. Finally, this treatment may be reinforced by binding the excess ammonia via formation of glutamine analogues in vivo as a temporary measure to aid the overloaded urea cycle. Attempts are in progress to combine these therapeutic measures(*582*)."

From the discovery paper of Kim and colleagues cited in the first quotation in this entry:

"While N-acetyl-L-glutamate has been shown to be the naturally occurring activator of carbamoyl phosphate synthetase, and to be the most effective of a series of compounds tested, other closely related analogues (e.g.,

*N*-carbamoyl-L-glutamate, 2-acetoxyglutarate) are also able to activate the enzyme, but with different $K_m$ values.

In an attempt to determine whether factors involved in the operation of the urea cycle other than ornithine (or compounds capable of rapidly forming ornithine) would be effective in protection against ammonia intoxication, Kim studied the effect of N-acetyl-L-glutamate and N-carbamoyl-L-glutamate. The former proved to have relatively little beneficial effect, even though it is the naturally occurring and most effective activator of carbamoyl phosphate synthetase, while the latter was strikingly effective. At doses of 1 mmol/kg, carbamoylglutamate was even more effective than arginine. Kim also investigated the metabolic fate of [$^{14}$C]carbamoyl-labeled carbamoylglutamate in rats. About 65% of the carbamoylglutamate injected was excreted unchanged in the urine within 6 hr after intraperitoneal injection, and a total of 75% was accounted for in the urine after 48 hr. No radioactivity was observed after 48 hr in extracts of liver, spleen, kidney, intestine, muscle, and brain. The remaining 25% was presumably catabolized.

Because of the limited number of animals used in the earlier studies, we reinvestigated the effect of carbamoylglutamate with a larger number of experimental animals(*583*).”

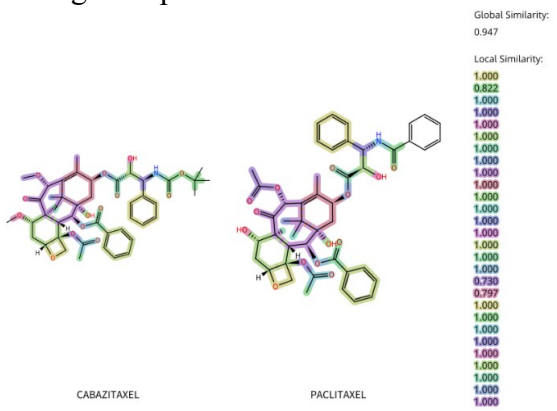
From the discovery paper of its effect on the urea cycle whose authors were cited in the previous quotation:

“The carbon dioxide fixation reaction in the initial step of the urea cycle has been assumed to involve the direct carboxylation of the α-amino group of ornithine. A more detailed study of this reaction, with use of the washed residue from potassium chloride-homogenized rat liver revealed that glutamic acid was acting as the initial acceptor for carbon dioxide In the study of a large series of compounds which might be expected to behave as intermediates in this reaction, it was observed that carbamyl-L- glutamic acid was highly active in the conversion of ornithine to citrulline. Thus this compound could be shown to be 2 to 3 times more active than L-glutamic acid in citrulline synthesis in the presence of carbon dioxide, and 10 to 15 times more active in the absence of carbon dioxide(*584*).”

## CABAZITAXEL

2010

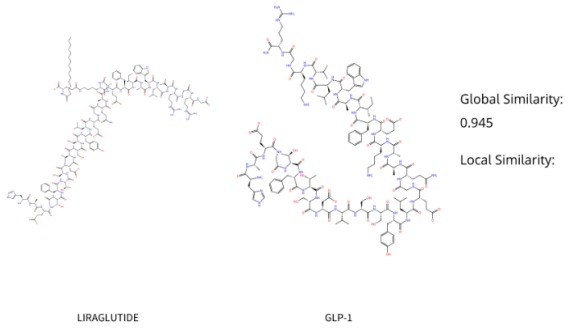
Analogue of paclitaxel




## LIRAGLUTIDE

2010

Analogue of the native human glucagon-like peptide-1 with 97% homology(*2*)




## VELAGLUCERASE ALFA

2010

Recombinant human glucocerebrosidase

## POLIDOCANOL

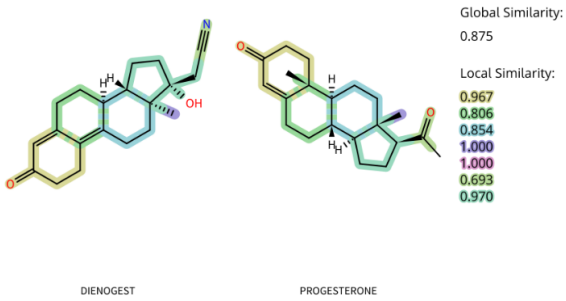
2010

A non-ionic surfactant sclerosing agent(*1*)

DIENOGEST

2010

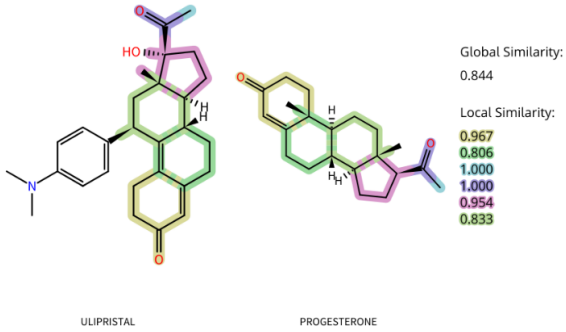
Analogue of progesterone(*2*)




ULIPRISTAL

2010

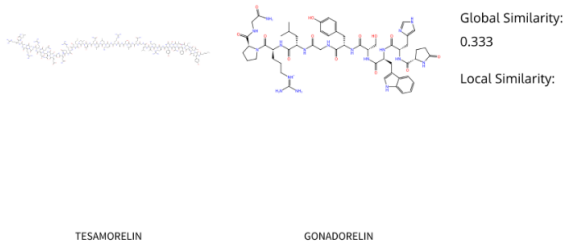
Analogue of progesterone(*2*)




TESAMORELIN

2010

Analogue of the endogenous Gonadotropin Releasing Hormone(*2*)




BELATACEPT

2011

"Belatacept is a soluble fusion protein, which links the extracellular domain of human cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) to the modified Fc (hinge, CH2, and CH3 domains) portion of human immunoglobulin G1 (IgG1)(*2*)."

SPINOSAD

2011

From the discoverer(s):

"**Figure 1.** A brief history of events leading to the introduction of spinosyns.

1982 – Vacationing chemist from Natural Products Research collects interesting soil samples near an abandoned sugar rum still in the Carribean

1984 – Entomology Screen modified to accommodate 96-well format and increased sensitivity needs via adoption of a novel mosquito larvicide bioassay

1985 – A83543 A is positive in the fermentation screen and subsequent refermentation confirmed the presence of a biologically active product

1985 – Oral and contact activity against Lepidopteran insects identified

1986 – New species of Actinomycete identified(*585*)"

"In the course of our screening culture broths from the fermentation of random soil microorganisms, a broth was found that exhibited activity against larvae of the mosquito, *Aedes aegypti*. This activity was produced by a microorganism, designated as A83543, that had been isolated from a soil sample collected in the Virgin Islands. Subsequent taxonomic studies indicated that this organism was a new species within the rare genus Saccharopolyspora. It has now been classified as *Saccharopolyspora spinosa*(*586*)."

IPILIMUMAB

2011

Monoclonal Antibody

## CRIZOTINIB

2011

From the discoverer(s):

"The cocrystal structure of 3 (PHA-665752), bound to c-MET kinase domain, revealed a novel ATP site environment, which served as the target to guide parallel, multiattribute drug design. A novel 2-amino-5-aryl-3-benzyloxypyridine series was created to more effectively make the key interactions achieved with 3. In the novel series, the 2-aminopyridine core allowed a 3-benzyloxy group to reach into the same pocket as the 2,6-dichlorophenyl group of 3 via a more direct vector and thus with a better ligand efficiency (LE). Further optimization of the lead series generated the clinical candidate crizotinib (PF-02341066) […]

The search for leads started in a potent class of kinase inhibitors, the 3-substituted indolin-2-ones, where one representative, sunitinib, is now approved for GIST and RCC treatment. The selectivity of indolin-2-ones for particular kinases is mediated by substituentsbuiltontotheindolin-2-onecore. Both 4-substituted indolin-2-ones and 5-substituted indolin-2-ones were evaluated for c-MET inhibition and attractive lead matter was found. From this starting point, key cocrystal structures guided both prioritization decisions and drug design strategy. […]

Compound 2 (SU11274) was identified as a c-MET inhibitor with isolated enzyme $IC_{50}$ of 10 nM. 2 inhibited HGF-induced c-MET autophosphorylation in a dose dependent manner with complete inhibition at 1 μM in A549 c-MET cellular assay. Optimization of 2 led to 3 (PHA-665752) a c-MET RTK inhibitor with a significantly improved cellular potency ($IC_{50}$ =9 nM in GTL-16 cell line) and selectivity (>50-fold for c-MET compared with a panel of diverse tyrosine and serine-threonine kinases).

The design concept was tested with a small set of compounds shown in Figure 5. Compound 7 displayed moderate inhibition against c-MET with an enzymatic $K_i$ of 3.83 μM (LE= 0.29, LipE = 0.35). […]

To investigate kinase selectivity, crizotinib was evaluated against a panel of more than 120 human kinases from Upstate Inc. Of these, 13 kinases were inhibited with enzymatic potency within a 100-fold selectivity window of crizotinib enzymatic c-MET potency(*587*)."

"Shortly after in 2007, anaplastic lymphoma kinase (ALK) was fortuitously identified as a drug target in NSCLC. Initially, the industry researchers who developed crizotinib, the first-in-class oral ALK TKI, were searching for a mesenchymal–epithelial transition factor (MET) inhibitor(*588*)."

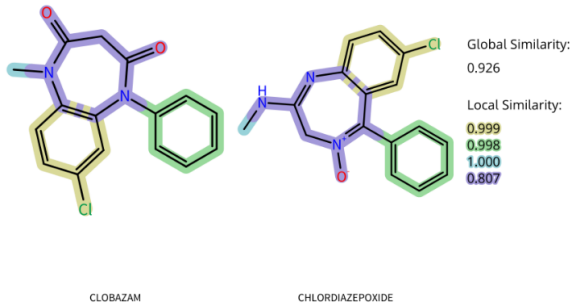
From the discovery paper:

"The present studies describe the identification and characterization of PF-2341066, an orally available ATP-competitive and selective small-molecule inhibitor of c-Met. PF-2341066 potently inhibited c-Met phosphorylation and signal transduction, as well as c-Met–dependent oncogenic phenotypes of tumor cells and endothelial cells in vitro and showed antitumor efficacy in tumor models at well-tolerated doses *in vivo*(*589*)."

## CLOBAZAM

2011

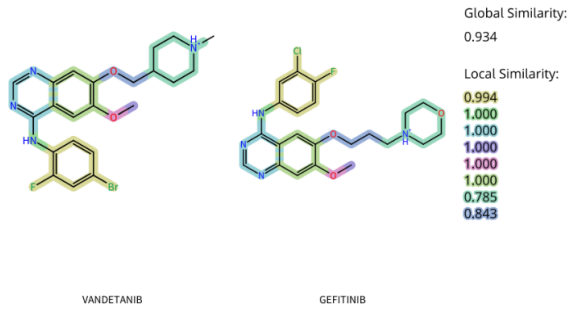
Analogue of chlordiazepoxide




## VANDETANIB

2011

Analogue(*542*) of gefitinib(*571*)




## RUXOLITINIB

2011

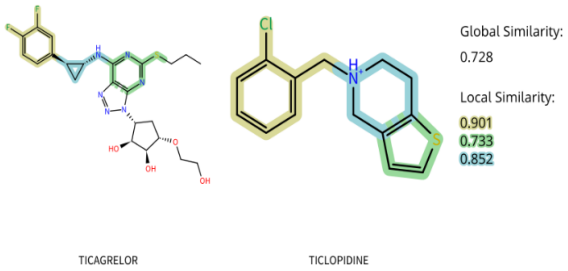
From the discoverer(s):

"The discovery programme that targeted JAK1 and JAK2 at Incyte began in 2003. Following careful consideration of the biology of JAK signalling, phenotypes of JAK knockout mice, and the potential roles for different JAK family members in oncogenic, inflammatory and immune function, we decided to focus on JAK1 and JAK2 and deliberately build selectivity against JAK3 in the target compound profile. The decision to avoid JAK3 inhibition was based on the absence of a role for JAK3 in the signalling of key cytokines, such as IL-6 and IL-12/23, which are believed to be important for oncology and inflammatory diseases, and on the desire to minimise the risk for immunosuppression. Given the absence of a specific and dominant role for TYK2 in any cytokine signalling pathway, we decided to accept some degree of TYK2 cross-reactivity. A rational design process utilising known chemical scaffolds with JAK inhibitory activity, rather than computational chemistry or chemical library screening, was used to discover novel pharmacophores. A series of cell-based assays, including isolated cellular assays using peripheral blood monocytes and T-cells and whole blood assays with IL-6 or TPO stimulation and phosphoSTATs as readouts, was used to identify compounds with good cellular activity. As a result of this effort, several potent and selective JAK1 and JAK2 inhibitors were identified, among which ruxolitinib (INCB018424) was one. Selection of ruxolitinib as a development candidate was based on *in vitro* and *in vivo* pharmacology data, its pharmacokinetic profile and toxicology data(*590*)."

## TICAGRELOR

2011

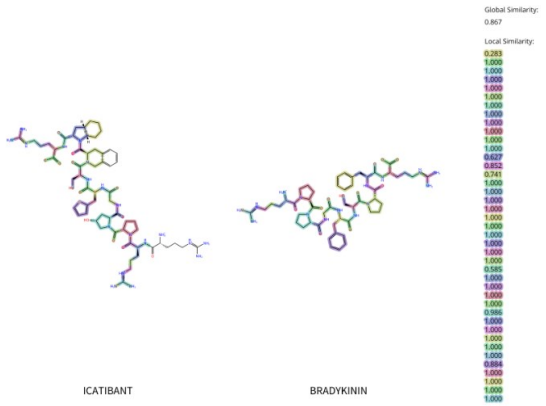
Analogue of ticlopidine




## ICATIBANT

2011

Analogue of the endogenous bradykinin




Discovery of bradykinin:

From the discovery paper:

"IN THE course of experiments on the physiological action of the venom of *Bothrops jararaca*, we found that some blood samples taken from a dog after the injection of minute doses of the venom had a stimulating effect upon the isolated gut of the guinea pig. This was not due to direct action of the venom since the gut had been previously made refractory to it; no desensitization could be observed after several additions of the serum to

the perfusing bath containing the piece of guinea pig ileum(*591*).”

## VEMURAFENIB

2011

From the discoverer(s):

“Vemurafenib, formerly known as PLX4032, was built around the 7-azaindole scaffold. This novel scaffold was identified from a target-naive screening library, utilizing a combination of biochemical and high-throughput cocrystallography screening filters. Plexxikon’s screening library (scaffold library) of more than 20,000 low molecular weight (150–350Da) compounds were identified using a novel approach described by Zhang *et al*. The process of low-affinity biochemical screening of the scaffold library at high concentrations (100–200mM) against multiple members of target protein family yielded scaffolds for further screening by cocrystallography. This approach (scaffold-based drug discovery) has been successfully utilized in identifying small-molecule inhibitors for targets in several protein families, including phosphodiesterases, and nuclear receptors. Recently, we have described the expansion of this strategy to discover 7-azaindole as a scaffold targeting protein kinases, using Pim-1 kinase as a robust system for cocrystallography. This novel kinase scaffold was one among 70 different compounds bound in the ATP binding pocket and was the starting point to rationally design the selective oncogenic BRAF inhibitor vemurafenib, as well as a selective dual FMS–KIT kinase inhibitor PLX647.

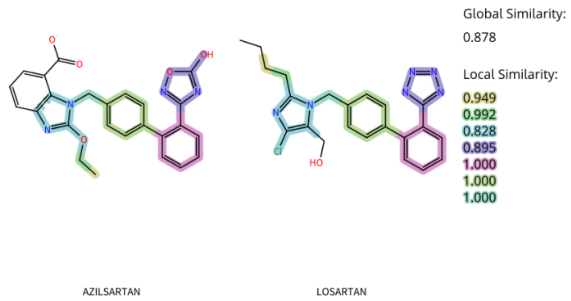
The 7-azaindole profiler library was built through diverse chemical modifications at the productive sites of the scaffold as guided by the cocrystal structures. This proprietary library was screened against recombinant BRAF V600E kinase to identify potential leads. The initial submicromolar hits revealed a set of compounds, containing a difluorophenol substituent connected through a ketone linker to the 7-azaindole scaffold. […]

The next step of optimization was focused on substitutions at the 5-position of azaindole. Halogens Cl and Br were equivalent, showing ~10-fold improvement in activity compared to compound 8. In addition, a number of aromatic and heteroaromatic substituents at the 5-position of the azaindole were synthesized and screened through the oncogenic BRAF biochemical assay, […]. The various 5-substitutions did not significantly affect biochemical potency; however, these substituents had impact on the *in vivo* exposure and efficacy (xenograft) studies. Due to their pharmaceutical properties, *in vitro* safety profile, and consistent rodent pharmacokinetic properties, both PLX4032 and PLX4720 were chosen for preclinical evaluation. Finally, based on the favorable pharmacokinetic properties in higher species, vemurafenib was chosen for further development(*592*).”

## AZILSARTAN

2011

Analogue of losartan




## AFLIBERCEPT

2011

“Aflibercept is a recombinant protein composed of the binding domains of two human vascular endothelial growth factor (VEGF) receptors fused with the Fc region of human immunoglobulin gamma 1 (IgG1)(*593*).”

## ROFLUMILAST

2011

From the discovery paper:

"From a series of benzamide derivatives, roflumilast (3-cyclo-propylmethoxy-4-difluoromethoxy-N-[3,5-di-chloropyrid-4-yl]-benzamide) was identified as a potent and selective PDE4 inhibitor. It inhibits PDE4 activity from human neutrophils with an $IC_{50}$ of 0.8 nM without affecting PDE1 (bovine brain), PDE2 (rat heart), and PDE3 and PDE5 (human platelets) even at 10,000-fold higher concentrations.

PDE4 was tested in the cytosol of human neutrophils as described by Schudt et al. using cAMP as substrate(*594*)."

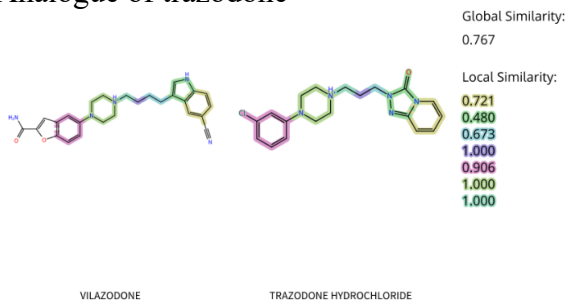
From an earlier article of the discoverer(s), cited in the previous quotation, that describes the used assay:

"Chromatographic analysis of 3′,5′-cyclic nucleotide phosphodiesterase (PDE) isoenzymes in the cytosol of human neutrophils shows the predominant presence of PDE IV (cAMP specific) and PDE V (cGMP specific). PDE IV is characterized by (1) cAMP selectivity, (2) a KM for cAMP of 1.2 M and (3) a typical rank order of IC 50-values for PDE inhibitors: 0.13, 0.17, 47 and 9.5 µM for PDE IV selective rolipram, PDE III/IV selective zardaverine, PDE III selective motapizone and unselective 3-isobutyl-l-methylxanthine (IBMX), respectively. Functions of polymorphonuclear leukocytes (PMN) such as N-formylmethionyl-leucyl-phenylalanine (fMLP)-stimulated superoxide release and fMLP/thimerosal elicited leukotriene (LT) biosynthesis are inhibited by these PDE inhibitors with the same rank order and even lower IC50-values. Measurements of changes in cytosolic Cai in Fura-2 loaded PMN demonstrate a transient Cai increase after stimulation with 0.1 µM fMLP and an additional sustained elevation of Cai levels in the presence of thimerosal. PDE inhibitors suppress this sustained phase of Cai release with the same rank order of IC50-values as LT biosynthesis. The correlation between fMLP/thimerosal-induced LT biosynthesis and Cai levels reveal a Cai threshold of 150 nM for arachidonic acid metabolism. cAMP levels in PMN were elevated by PDE inhibitors alone by less than 2-fold. In the presence of fMLP however, cAMP was increased up to 10-fold and the efficacy of PDE inhibitors to increase cAMP paralleled their potency to inhibit PDE IV. It is concluded that (1) suppression of PMN functions is achieved by PDE IV inhibition(*595*)"

## VILAZODONE

2011

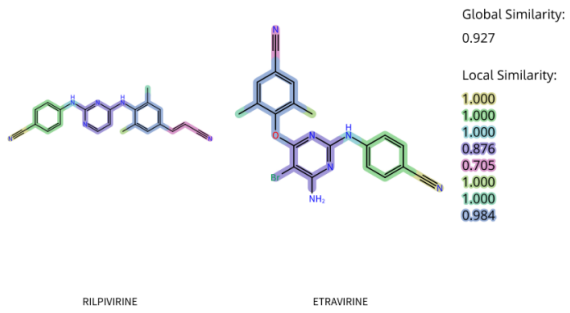
Analogue of trazodone




## RILPIVIRINE

2011

Analogue of etravirine




## IOFLUPANE I-123

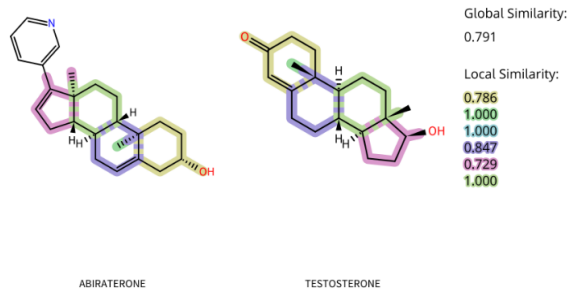
2011

Radiopharmaceutical

## ABIRATERONE

2011

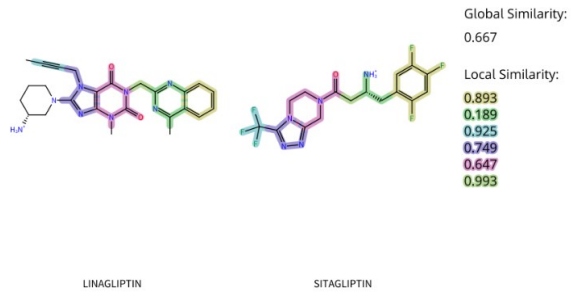
Analogue of testosterone




## LINAGLIPTIN

2011

Analogue of sitagliptin




## RIVAROXABAN

2011

"Although factor Xa was identified as a promising target for the development of new anticoagulants in the early 1980s, the viability of factor Xa inhibition was not tested before the end of that decade. In 1987, the first factor Xa inhibitor, the naturally occurring compound antistasin, was isolated from the salivary glands of the Mexican leech *Haementeria officinalis*. Antistasin is a 119 amino-acid polypeptide; kinetic studies revealed that it is a slow, tight-binding, potent factor Xa inhibitor that also inhibits trypsin. Another naturally occurring factor Xa inhibitor, the tick anticoagulant peptide (TAP), a single-chain, 60 amino-acid peptide, was isolated in 1990

from extracts of the soft tick *Ornithodoros moubata*. Similarly to antistasin, tAP is a slow, tight-binding inhibitor of factor Xa.

TAP and recombinant forms of antistasin and TAP 38–40 were used to validate factor Xa as a viable drug target and to improve understanding of the role of factor Xa in thrombosis. the antithrombotic effects of these compounds were compared with those of direct thrombin inhibitors and of indirect thrombin and factor Xa inhibitors in animal models of thrombosis. these studies suggested that direct factor Xa inhibitors might be a more effective approach to anticoagulation, and might also offer a wider therapeutic window, particularly with regard to primary haemostasis. […]

High-throughput screening of approximately 200,000 compounds revealed several hits that selectively inhibited the cleavage of a chromogenic substrate by human factor Xa. the most potent of these hits was on a minor impurity in a combinatorial library — a phosphonium salt with an $IC_{50}$ of 70 nM. We proposed that this positively charged phosphonium moiety might serve as an arginine mimic and could be interchangeable with an amidine group. this resulted in the synthesis of lead compound 2 with similar potency ($IC_{50}$ of 120 nM). Further optimization resulted in the synthesis of compounds of the isoindolinone class(*596*)"

## FIDAXOMICIN

2011

= Tiacumicin B

From the discoverer(s):

"From a soil sample collected in Hamden, CT, his team isolated a novel subspecies of *Dactylosporangium aurantiacum*, which, when grown in one of our primary screening media, yielded activity against MRSA. This activity led to the scale-up fermentation and isolation, by Jill Hochlowski, of a family of 18-membered macrolides, which we named the tiacumicins. […]

In the hamster model, which was later

improved by Jeff Alder to develop an impressive data package, all vancomycin-treated animals died shortly after treatment ceased, whereas tiacumicin B-treated animals survived without apparent development of colitis. Recurrence of the infection is a major drawback of vancomycin treatment of colitis, and, on the basis of our results, Jake Clement delivered a presentation to Abbott management proposing Tiacumicin B as a product candidate. […]

Although tiacumicins were discovered for their activity against MRSA, the relative potency, and the pharmacokinetics of tiacumicin B in animals, directed its development toward the treatment of C. difficile-induced colitis(*597*).”

## DEACETYLBISACODYL

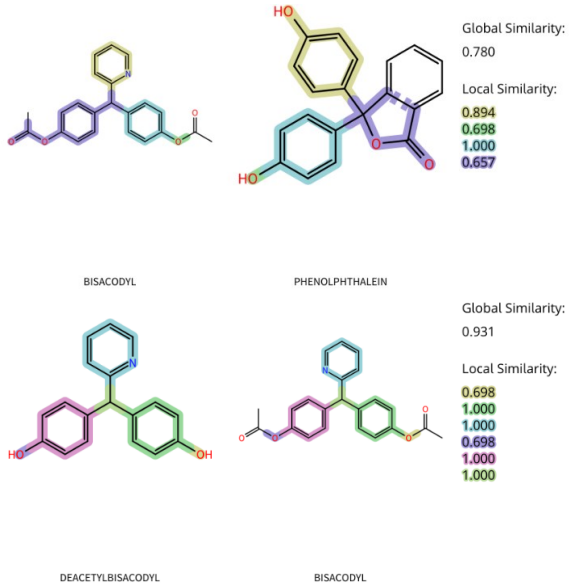
2012

Analogue of bisacodyl which is itself an analogue of phenolphthalein

“Bisacodyl is an active ingredient in many rectal chemical stimulant preparations for defecation. This compound, a diphenylmethane derivative (bis (p-acetoxyphenyl)-2-pyridylmethane) which was first introduced for use as a laxative in 1953 due to its structural similarity to phenolphthalein(*598*).”

Discovery of phenolphthalein:

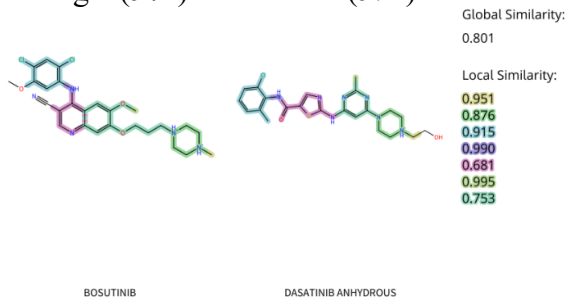
“A coal tar derivative synthesized in the 1870s and initially used as an acid-base indicator, phenolphthalein moved from the laboratory into the clinic at the very beginning of this century thanks, as has so often been the story in pharmacy, to serendipity. The Hungarian government desired to mark artificial wines with some chemical indicator to distinguish them from the genuine product. Phenolphthalein was tentatively chosen, and in 1900 pharmacologist Zoltan Vamossy was entrusted with the evaluation of the compound’s toxicity. After animal tests indicated it to be harmless, Vamossy and a colleague took small doses of the substance to determine its effects on humans. When both experienced attacks of diarrhea the same day, ‘I became convinced,’ Vamossy later recounted, ‘that I had discovered a laxative of great merit.’(*599*).”




## BOSUTINIB

2012

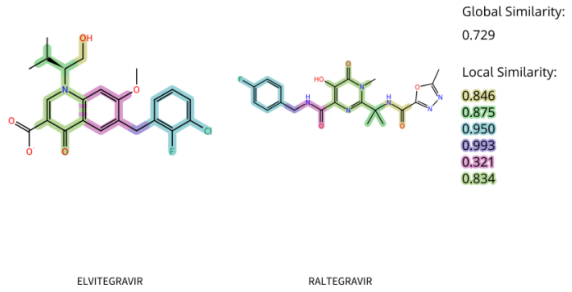
Analogue(*542*) of dasatinib(*571*)




## ELVITEGRAVIR

2012

Analogue of raltegravir



## VISMODEGIB

2012

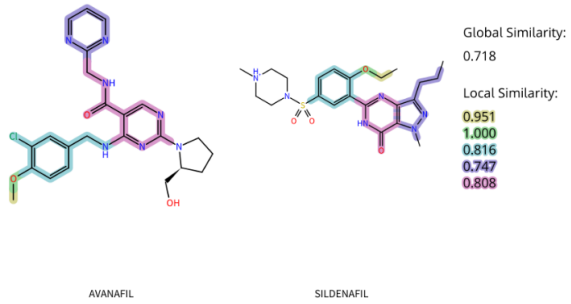
"The first indication that small molecules could block the Hh pathway was demonstrated when the mechanism of action for the natural product cyclopamine was discovered based on the similarity of SHH loss-of-function phenotypes with cyclopamine-treated embryos. Cyclopamine was initially identified in 1968 as the component of the plant *Veratrum californicum* responsible for inducing cyclopia in newborns of pregnant sheep grazing in areas where the plant was endemic. This steroidal alkaloid was subsequently shown to bind directly to SMO and block Hh signaling with an EC 50 of ~ 300 nM. However, its structural complexity, scarcity, poor aqueous solubility and poor chemical stability in acid led us to identify small-molecule Hh antagonists of a different chemical class.

The suggestion that the pathway could be drugged and the potential for small-molecule antagonists as therapies for BCC and medulloblastoma and agonists in neurodegenerative diseases led Curis to initiate the first small molecule screen of the pathway. A series of high-profile papers published in 2003 and 2004 suggesting a role for Hh ligands driving autocrine or juxtacrine (adjacent cell-to-cell signaling) signaling spurred many companies to initiate small-molecule programs around this time frame. However, careful analysis of large panels of cell lines with a number of Hh pathway inhibitors (HPIs) revealed that these effects on proliferation were off-target activities and that Hh-ligand associated cancers rely on paracrine signaling. Small-molecule inhibitors of the Hh pathway were identified via a high-throughput screen using murine CH310T½ embryonic fibroblast cells stably expressing a luciferase reporter gene under transcriptional control by GLI. The use of this GLI-luciferase assay was critical to enable identification of potent and selective Hh pathway inhibitors. When these cells are stimulated with exogenous SHH, luciferase activity and thus Hh-pathway activity can be measured by standard optical assays(*600*)."

## AVANAFIL

2012

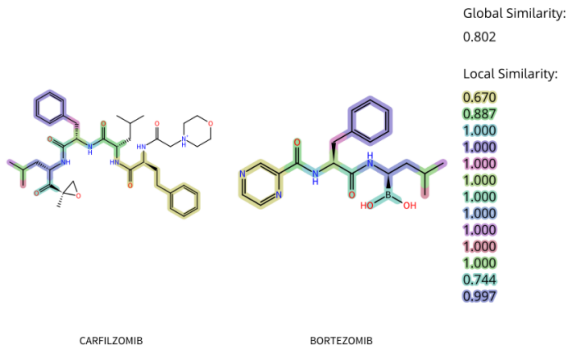
Analogue of sildenafil




## CARFILZOMIB

2012

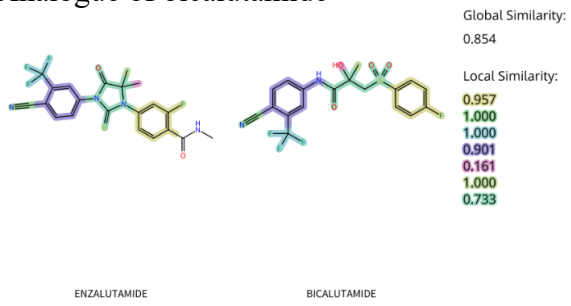
Analogue of bortezomib




## ENZALUTAMIDE

2012

Analogue of bicalutamide




## RAXIBACUMAB

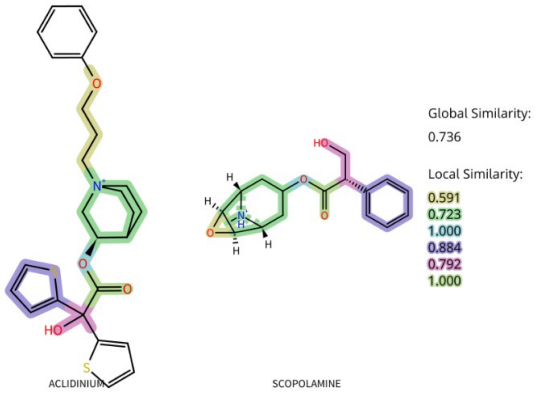
2012

Monoclonal Antibody

ACLIDINIUM

2012

Analogue of scopolamine




LOMITAPIDE MESYLATE

2012

"A potentially effective therapy for homozygous familial hypercholesterolemia would be to reduce low-density lipoprotein (LDL) production. The MTP is responsible for transferring triglycerides onto ApoB within the liver in the assembly of very-low-density lipoprotein (VLDL), the precursor to LDL. In the absence of functional MTP, as in the rare recessive genetic disorder abetalipoproteinemia, the liver cannot secrete VLDL, leading to the absence of all lipoproteins containing ApoB in the plasma. Thus, the pharmacologic inhibition of MTP might be a strategy for reducing LDL production and plasma LDL cholesterol levels. Preclinical studies in animal models lacking LDL receptors had shown that the inhibition of MTP significantly reduces serum cholesterol levels. Lomitapide whose precursors were discovered in a high through put screen, directly binds and inhibits MTP, which resides in the lumen of the endoplasmic reticulum, thereby preventing the assembly of apoB-containing lipoproteins in enterocytes and hepatocytes. This inhibits the synthesis of chylomicrons and VLDL. The inhibition of the synthesis of VLDL leads to reduced levels of plasma LDL-C(*581*)."

From the discovery paper of the lead compound, cited in the previous quotation:

"**Inhibition of Lipid Transport.** The inhibition of lipid transfer activity in the presence of BMS-200150 was measured in an assay similar to one that has been previously described. Donor and acceptor small unilamellar vesicles (SUVs) were prepared by bath sonication in 15 mM Tris HCl, pH 7.5/1 mM EDTA acid/40 mM NaCl/0.02% sodium azide (assay buffer). The lipid transfer assay mixture contained donor membranes (40 nmol egg PC/7.5 mol % cardiolipin/0.25 mol % radiolabeled substrate), acceptor membranes (240 nmol egg PC), 5.0 mg BSA, and various concentrations of BMS-200150 in a total volume of 0.68 ml assay buffer. BMS-200150 was dissolved in dimethyl sulfoxide (DMSO) and added to the reaction mixture. The final concentration of DMSO was 0.5%. The reaction was started by the addition of MTP in 20 µl assay buffer. After a 60-min incubation at 37°C, the reaction was terminated by the addition of 0.5 ml of DE-52 cellulose (Whatman) pre-equilibrated in 15 mM Tris-HCl, pH 7.4/1.0 mM EDTA/ 0.02% sodium azide (1:1, vol/vol). The mixture was agitated for 5 min and centrifuged at maximum speed in a Biofuge B centrifuge for 3 min to pellet the DE-52 bound donor vesicles. First order kinetics were used to calculate the lipid transfer rate using the equation $[S] = [S]_0 e^{-kt}$, where $[S]_0$ and $[S]$ are the fraction of the available labeled lipid in the donor membrane at times 0 and t, respectively, and k is the fraction of the available labeled lipid transfered per unit time. This calculation corrects for the depletion of labeled lipid in donor vesicles that occurs with time.

**Identification and Characterization of BMS-200150.** High-throughput screening of the Bristol-Myers Squibb compound collection identified BMS-200150 as a potent inhibitor of bovine MTP-mediated transport of

TG between SUVs. The $IC_{50}$ for inhibition of TG transfer was 0.6 µM(*601*).”

## OMACETAXINE

2012

From the 1969 discovery paper:

“We wish to report the structure of cephalotaxine, and three related alkaloids isolated from Cephalotaxus harrigtonia variety drupacea. These were obtained from an ethanol extract of the seed by countercurrent distribution and subsequent thin-layer chromatography of an alkaloid concentrate. An ester of cephalotaxine, for which we propose the name harringtonine, has shown significant inhibitory activity against the experimental lymphoid leukemia systems L1210 and P388 in mice at 1.0 mg./kg. […]

Assays were performed under the auspices of the Cancer Chemotherapy National Service Center(*602*).”

## IVACAFTOR

2012

“After the CFTR gene was discovered in 1989, there was considerable hope that gene therapy could be rapidly developed. However, this has proven to be extremely challenging. There have been over 25 gene therapy trials using either viral or cationic lipid-based vector systems which have shown limited success. Even after successful uptake of the CFTR gene, the cells lose expression after a few weeks. Gene therapy, should it prove to be therapeutically effective, could be used to treat all patients with CF regardless of CFTR mutation. […]

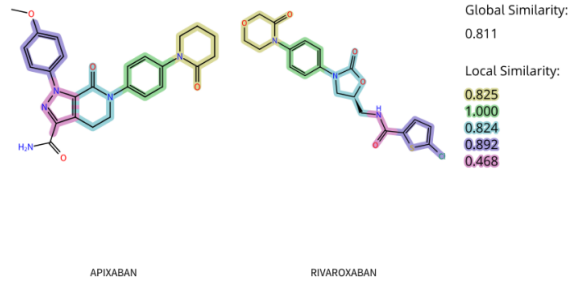
An alternative to gene therapy, which shows more promise, is the development of small-molecule compounds that target specific CFTR mutations. […]

Ivacaftor was identified by screening over 228,000 small-molecule compounds using high throughput screening with a cell-based fluorescence membrane potential assay designed to identify CFTR potentiators(*603*).”

## APIXABAN

2012

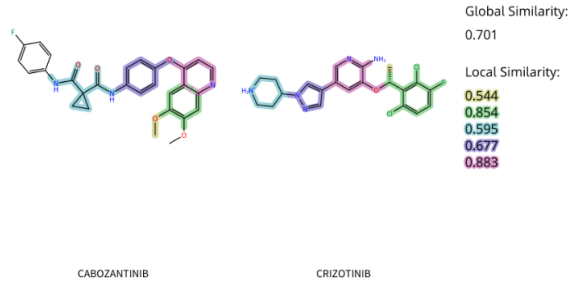
Analogue of rivaroxaban




## CABOZANTINIB

2012

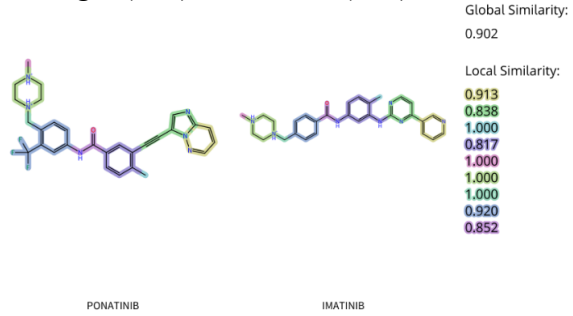
Analogue(*542*) of crizotinib




## PONATINIB

2012

Analogue(*542*) of imatinib(*571*)




## PASIREOTIDE

2012

Analogue of the endogenous somatostatin

Error in similarity calculation by FTrees because of the unsupported macrocycle

## LINACLOTIDE

2012

Analogue of the endogenous uroguanylin

Error in similarity calculation by FTrees because of the unsupported macrocycle

"The approach to its discovery exploited the mechanisms of enterotoxigenic *Escherichia coli* to produce traveler's diarrhea and the discovery of the endogenous hormones guanylin and uroguanylin regulating intestinal fluid homeostasis(*604*)."

From the discovery paper of guanylin:

"Pathogenic strains of *E. coli* and other bacteria produce a family of heat-stable enterotoxins (STs) that activate intestinal guanylate cyclase. STs are acidic peptides that contain 18 or 19 amino acids with six cysteines and three disulfide bridges that are required for full expression of bioactivity. The increase of intestinal epithelial cyclic GMP elicited by STs is thought to cause a decrease in water and sodium absorption and an increase in chloride secretion. These changes in intestinal fluid and electrolyte transport then act to cause secretory diarrhea. In developing countries, the diarrhea resulting from STs causes many deaths, particularly in the infant population. STs are also considered a major cause of traveler's diarrhea in developed countries. They have also been reported to be a leading cause of morbidity and death in domestic animals.

In the present study, we designed a bioassay to search for a potential endogenous ligand that activates the intestinal guanylate cyclase. This bioassay is based on the demonstration that T84 cells in culture respond to ST in a selective and sensitive manner with graded increases of intracellular cyclic GMP. This bioassay revealed that the intestine as well as the kidney possessed an active material. Purification of this material from the rat intestine was accomplished and the structure was determined to be a 15-amino acid peptide with 4 cysteines that must be disulfide-linked for bioactivity. The peptide, termed guanylin, also possesses a high degree of homology with STs(*605*)."

Regarding the discovery of the relationship between *E. coli* and diarrhea:

"The first reports of E. coli-associated diarrheal disease came from nursery epidemics in the mid 1940s. Prior to this time *E coli* was not recognized as a pathogen as long as it was confined to the gastrointestinal tract. During these nursery outbreaks, mortality rates were high, often as much as 50%; autopsy studies showed minimal inflammation of the small bowel, somewhat edematous mucosa, and an absence of ulceration. Bacteriologically, specimens of small intestine and stool showed a predominantly *E. coli* flora belonging to common serotypes that could be identified with specific antisera. One of the early and widely recognized enteropathogenic isolates, originally designated as D433, was later classified as serotype O111, the designation by which we now recognize it. Although these serotypes could be identified in low frequency from normal children and adults, they were found in as high as 80-100% of children with diarrhea and were thus epidemiologically incriminated as the cause of diarrhea and designated enteropathogenic. With the investigation of more epidemics, the number of enteropathogenic serotypes grew, until at present there are approximately 20-25 recognized, depending upon the geographical areas involved.

In addition to this epidemiologic evidence for pathogenicity, volunteer experiments in both adults and a child with two of these serotypes confirmed that the ingestion of large numbers of these organisms regularly resulted in diarrhea and that the strains could be recovered in large numbers from the feces(*606*)."

## FLORBETAPIR F-18

2012

Radiopharmaceutical

MIRABEGRON

2012

“At the Institute for Drug Discovery Research (Astellas Pharma Inc., Ibaraki, Japan), Maruyama et al. chose as their lead compound in the search for novel potent and selective human β3-AR agonists, the benzenesulfonanilide derivative reported in 1998 by Merck scientists to be one of the first selective human β3-AR agonists. Maruyama et al. hypothesized that the position of the two benzene rings in the benzenesulfonanilide moiety of would play an important role in its β3-AR agonistic activity and/or its selectivity. This compound and its derivatives had an excellent activity profile but an extremely poor oral bioavailability, presumably due to the polar and highly solvated urea moiety. Their huge experimental efforts led to the design and synthesis of phenyl-acetanilide derivatives by converting the sulphonamide moiety in the RHS of into an acetamide moiety. Extensive structure-activity relationship (SAR) studies on the RHS substituents of these novel compounds were conducted using human β-ARs. The biological agonistic activity *in vitro* was measured evaluating the increase in cAMP levels in CHO cells expressing cloned human β3-, β2- and β1-ARs. The *in vivo* evaluation was performed measuring the reduction on plasma glucose levels in a rodent model of type 2 diabetes(*607*).”

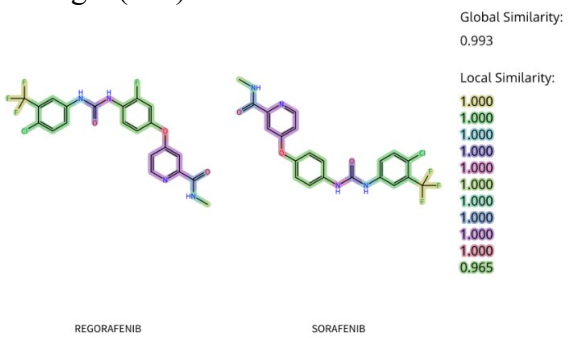
From the discovery paper:

“In the search for potent and selective human β3-adrenergic receptor (AR) agonists as potential pharmacotherapies for the treatment of obesity and non-insulin dependent (type II) diabetes, we prepared a novel series of phenylethanolamine derivatives containing acetanilides and evaluated their biological activities at the human β3-, β2-, and β1-ARs. Among these compounds, the 6-amino-2-pyridylacetanilide, 2-amino-5-methylthiazol-4-ylacetanilide, and 5-amino-1,2,4-thiadiazol-3-ylacetanilide derivatives showed potent agonistic activity at the β3-AR with functional selectivity over the β1- and β2-ARs. In addition, these compounds exhibited significant hypoglycemic activity in a rodent diabetic model(*608*).”

REGORAFENIB

2012

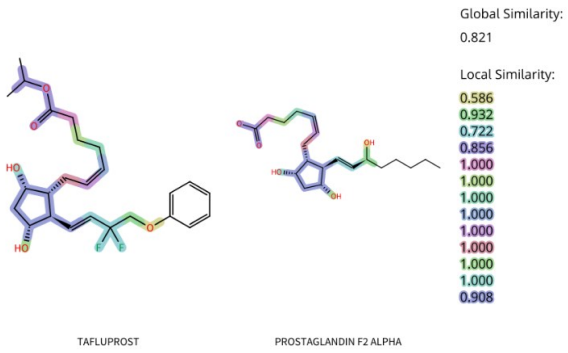
Analogue(*542*) of sorafenib




TAFLUPROST

2012

Analogue of prostaglandin $F_2$ alpha




TALIGLUCERASE ALFA

2012

“Taliglucerase alfa is the recombinant active form of the human lysosomal enzyme, β-glucocerebrosidase(*2*).”

GLUCARPIDASE

2012

Secondary

PERAMPANEL

2012

From the discoverer(s):

"Perampanel was built on a chemical template discovered via high-throughput screening (HTS). At the time of initiation of the perampanel discovery program, AMPA receptor antagonists of a variety of structural classes were known. The search for new AMPA receptor antagonists was stimulated by the recognition that many competitive AMPA receptor antagonists failed to penetrate the blood–brain barrier, and for compounds such as NBQX that did enter the brain, there were safety concerns due to poor solubility. At the same time, while 2,3-benzodiazepine AMPA receptor antagonists did show good blood–brain barrier penetration, they had modest potency. The objective was to discover structures with improved safety and higher potency. HTS was performed using a [$^3$H]AMPA-binding assay to search for compounds that competitively displaced binding at the glutamate recognition site (competitive antagonists). AMPA-induced neuronal cell death in rat primary cortical neuron cultures served as a functional assay of AMPA receptor blockade. To exclude neuroprotective compounds that did not act on the AMPA receptor target, compounds were tested for their ability to inhibit AMPA-induced $Ca^{2+}$ influx, a more direct assay of AMPA receptor antagonist activity. No promising new compounds were identified with the [$^3$H]AMPA-binding assay. However, among hits in the functional assay, 2,4-diphenyl-4H-[1,3,4]oxadiazin-5-one – which showed AMPA receptor blocking activity with an $IC_{50}$ value of about 5 μm – was selected as the starting point for a medicinal chemistry effort. Initial efforts focused on increasing potency and water solubility, with the aim of creating a drug to be administered intravenously in the treatment of acute stroke. Subsequently, the focus changed to developing a compound with oral efficacy that could be used in the treatment of chronic neurological diseases. This reduced the requirement for water solubility and expanded the options for chemical modification. The core structure 1,3,5-triaryl-1H-pyridin-2-one was identified following this change in strategy. Perampanel [2-(2-oxo-1-phenyl-5-pyridin-2-yl-1,2-dihydropyridin-3-yl)benzonitrile hydrate 4:3] was discovered by optimization of the core structure, mainly focusing on increasing oral efficacy(*609*)."

TEDUGLUTIDE

2012

Endogenous-based biopharmaceutical

Different from the endogenous glucagon-like peptide-2 (GLP-2) in only one amino acid (glycine instead of alanine)(*2*)


ICOSAPENT

2012

Polyunsaturated fatty acid found in fish oils

OCRIPLASMIN

2012

Recombinant truncated form of human plasmin(*2*)

PERTUZUMAB

2012

Monoclonal Antibody

COBICISTAT

2012

Secondary

CROFELEMER

2012

Secondary

BEDAQUILINE

2012

"TMC207 (also known as R207910 or the 'J' compound) is a diarylquinoline that inhibits the proton pump of *M. tuberculosis*'s ATP synthase, a novel mechanism of action. It was discovered by Johnson & Johnson (J&J) via a screening program of more than 70,000 compounds with activity against the saprophytic *Mycobacterium smegmatis*, a more rapidly growing and manageable mycobacterium compared with *M. tuberculo*sis(*610*)."

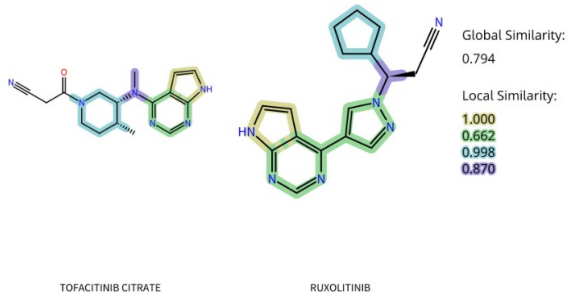
"The development of TMC207 represents an important advance in the chemotherapy of tuberculosis. It is perhaps most amazing because of the defiantly unconventional nature of the effort. At virtually every step, from the original discovery of the diarylquinolines by screening for compounds that would kill *Mycobacterium smegmatis*, a saprophytic distant relative of *M. tuberculosis,* through the phase 2 study by Diacon et al. reported in this issue of the *Journal* this effort flouted conventional wisdom about how to develop new drugs for tuberculosis.

It is also a humbling case study that is worth some reflection. Those of us in the tuberculosis field turned up our noses at looking for compounds that killed anything less than the real human pathogen, and until recently, the whole notion of screening drugs for their ability to provide activity against whole organisms was somewhat anachronistic. Surely we have advanced in the decades since streptomycin was isolated by Selman Waksman after he performed such a screen. Give us a nice, isolated enzyme with a high-resolution x-ray crystallographic structure, and we will use the armamentarium of modern drug discovery to treat the hard-to-treat tuberculosis. The problem, summed up recently by Payne et al., is that this approach does not work for bacteria. The truly disturbing fact is that we do not understand why. We can develop exquisitely potent and selective inhibitors of virtually any target we choose, but these inhibitors rarely translate into anything with activity useful against whole cells(*611*)."

TOFACITINIB CITRATE

2012

From the discovery paper:




"The Pfizer chemical library was screened for inhibitors of in vitro JAK3 kinase activity, providing the lead compound, CP-352,664. Extensive chemical modification led to CP-690,550. Although CP-690,550 was highly potent for JAK3 inhibition [enzyme inhibitory potency of 1 nM], it was 20- to 100-fold less potent for JAK2 and JAK1, respectively. Because JAK2 mediates signaling via many hematopoietic cytokines [e.g., erythropoietin, thrombopoietin, and colony-stimulating factor receptors], potent JAK2 inhibition could result in anemia, thrombocytopenia, and leukopenia in vivo. In addition, CP-690,550 did not have potent activity against 30 other kinases [all median inhibitory concentration ($IC_{50}$) > 3000 nM]. This included Lck, a key T lymphocyte–signaling molecule downstream of the T cell receptor.

Cell-based assays were used to further compare drug effects on signaling via JAK3 (IL-2–induced proliferation of human T cell blasts) with that via JAK2 [granulocyte–macrophage–colony-stimulating factor (GM-CSF)–induced proliferation of HUO3 cells], as well as cellular systems dependent on

other kinases.(*612*)”

INGENOL MEBUTATE

2012

“*E. peplus*, commonly known as ‘petty spurge’ in England or ‘radium weed’ in Australia, has a long history of traditional use for a variety of conditions. For example, the sap from *E. peplus* has been used as a purgative, to treat asthma, catarrh and several internal tumours as well as a topical treatment for warts, corns, waxy growths and skin cancers. A survey of home remedies for skin cancer and actinic keratosis reported the unanimous opinion by the users that topical treatment with *E. peplus* sap was effective

Despite the long history of traditional use of *E. peplus* for the treatment of skin cancers it was only when Dr James Aylward, whose family had used *E. peplus* sap for self-treatment of skin cancer since the mid-1900s, approached Professor Peter Parsons at the Queensland Institute of Medical Research in 1996, that the idea of identifying and isolating the active constituent emerged. Dr Aylward enthusiastically described the significant anti-cancer activity and long term cosmetic effect that he and his family had observed over many years of use of *E. peplus* sap and outlined his vision for the potential discovery of a novel natural product that could be developed as an NCE for the treatment of skin cancer(*613*).”

CITRIC ACID; MAGNESIUM OXIDE; SODIUM PICOSULFATE

2012

Diagnostic preparation

OBINUTUZUMAB

2013

Monoclonal Antibody

FLUTEMETAMOL F-18

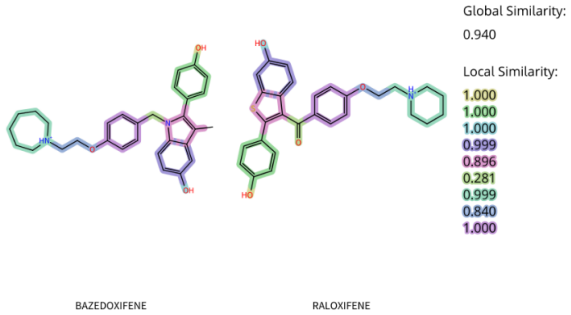
2013

Radiopharmaceutical

BAZEDOXIFENE

2013

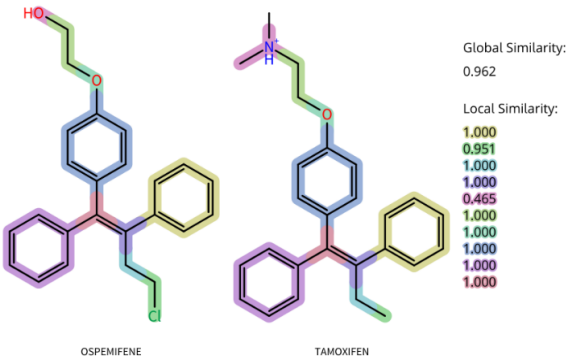
Analogue of raloxifene(*1*)




OSPEMIFENE

2013

Analogue of raloxifene




IBRUTINIB

2013

From the discoverer(s):

“We have previously described the synthesis of a series of Btk inhibitors that bind covalently to a cysteine residue (Cys-481) in the active site leading to potent and irreversible inhibition of Btk enzymatic activity. One of these compounds, PCI-32765, was selected for the present studies because of its potency ($IC_{50}$, 0.5 nM) and selectivity for Btk against a screening panel of kinase enzymes(*614*).”

RADIUM RA-223 CATION

2013

## DIMETHYL FUMARATE

2013

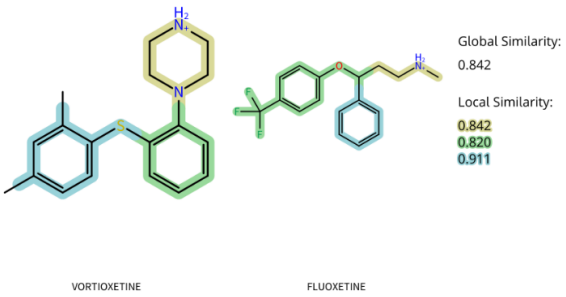
"Dimethyl fumarate (DMF) is derived from the simple organic acid fumaric acid which is named after the earth smoke plant (*Fumaria officinalis*). In the late 1950s, fumaric acid derivates were first used for the treatment of psoriasis based on the erroneous assumption that the disease may be caused by a metabolic deficiency in the citric acid cycle and that exogenous repletion may restore the balance in the Krebs cycle, thus leading to beneficial effects on the disease.

While free fumaric acid is poorly absorbed by the gastrointestinal tract, its ester derivatives, namely monomethyl fumarate (MMF) and DMF proved to be beneficial in treating psoriasis, first administered as a topical ointment and, later, also as an oral formulation. Since the mid-1990s, a combination of ethylhydrogen fumarates and DMF has been licensed in Germany under the brand name Fumaderm® with DMF constituting approximately 60% of the fumaric acid mixture. This medication was proven to be clinically effective in the treatment of moderate to severe forms of psoriasis in large clinical trials and nowadays is one of the most widely used oral compounds for psoriasis therapy in Germany. Ultimately, DMF was found to be a major effective principle in the preparation. As the immunopathology of psoriasis was unveiled, first dermatologic *in vitro* and *ex vivo* studies rapidly pointed at the immunomodulatory properties of DMF. Fostered by the well-described safety profile of fumaric acid esters in psoriasis, the immunomodulatory potential of Fumaderm® and DMF was also explored in other immune-mediated diseases which ultimately led to rigorous testing of DMF in large multi-center phase II and III studies of relapsing-remitting multiple sclerosis (RRMS)(*615*)."

## VORTIOXETINE

2013

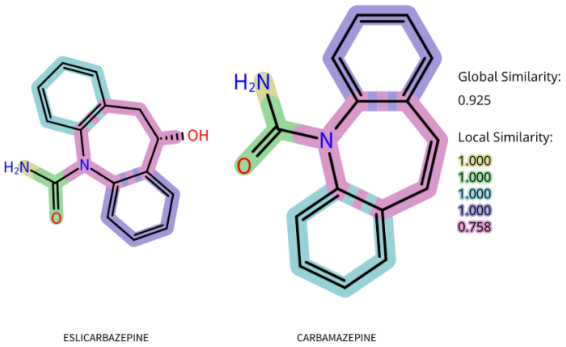
Analogue of fluoxetine(*616*)




## ESLICARBAZEPINE

2013

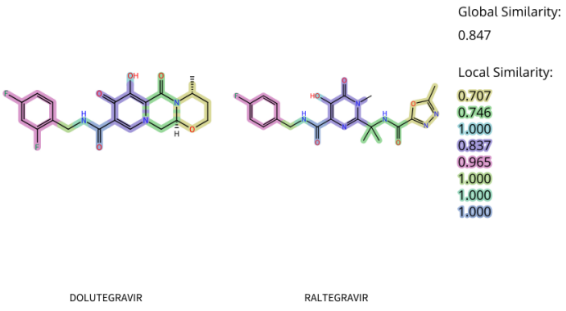
Analogue of carbamazepine




## DOLUTEGRAVIR

2013

Analogue of raltegravir




## TECHNETIUM TC-99M TILMANOCEPT

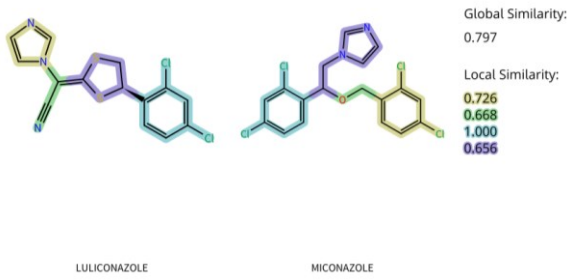
2013

Radiopharmaceutical

## LULICONAZOLE

2013

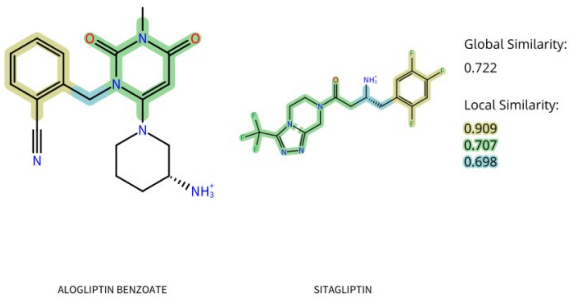
Analogue of miconazole(*1*)




ALOGLIPTIN BENZOATE

2013

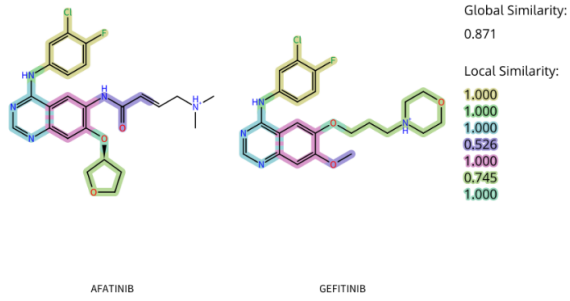
Analogue of sitagliptin




AFATINIB

2013

Analogue(*542*) of gefitinib(*571*)




NINTEDANIB

2014

From the discoverer(s):

"Inhibition of VEGFR2 was a potential mode of action to suppress neoangiogenesis in tumour tissue. Consequently, a lead optimisation programme aimed at the identification of a new chemical entity displaying potent and selective inhibition of VEGFR2 was initiated

High-throughput screening (HTS) was the state-of-the-art hit-finding strategy at the time, and accordingly an HTS campaign targeting VEGFR2 inhibition was instigated at the Boehringer Ingelheim facilities. In parallel, Boehringer Ingelheim scientists made an intriguing observation during an exploration of structure–activity relationships (SARs) around the potent cyclin-dependent kinase 4 (CDK4) inhibitor lead compound **2**: they found that transferring the amido group on the oxindole core from the 5- to the 6-position abolished CDK4 inhibition. Interestingly, however, the resulting oxindole (compound **3**) retained VEGFR2 inhibition, making it a potential hit candidate for the angiogenesis programme. To this end, compound **3** was evaluated in a small in-house kinase assay panel (insulin-like growth factor 1 receptor (IGF1R), insulin receptor (INSR), CDK1, CDK2, CDK4, epidermal growth factor receptor (EGFR), human epidermal growth factor receptor 2 (HER2), polo-like kinase 1 (PLK1)) and, quite remarkably, displayed selectivity against all of the kinases in this panel. Indeed, this specificity pattern was superior to those of other hit structures identified, and therefore compound **3** was nominated as the sole lead compound of the VEGFR2 programme. […]

Initial synthesis efforts were aimed at improving the biochemical potency of compound **3**(*617*)."

DABRAFENIB

2013

From the discovery paper:

"Our early efforts aimed at discovering inhibitors of B-Raf$^{V600E}$ suitable for clinical evaluation led to the identification of thiazole **1**. This compound shows potent in vitro kinase inhibitory activity against the B-Raf$^{V600E}$ enzyme, and in both cellular mechanistic (pERK) and proliferation assays in the

B-Raf$^{V600E}$ SKMEL28 melanoma cell line. Thiazole **1** also had low clearance and good overall oral systemic exposure in rats. However, this compound displayed very high clearance and poor bioavailability in non-rodent species. Additionally, metabolite identification studies conducted in dog and monkey liver microsomes identified several major metabolites clustered in the tail and core regions of the molecule. We hypothesized that drug exposure after an oral dose in the higher species was limited by rapid compound metabolism. Medicinal chemistry efforts were thus focused on improving pharmacokinetic properties in dog while preserving the favorable target potency, selectivity, and rodent pharmacokinetic properties inherent in this template.

Having established the sulfonamide as a key pharmacophore required for potent cellular inhibition of B-Raf$^{V600E}$, we performed significant structural modifications elsewhere to lower the molecular weight and reduce the number of metabolic sites contained within the template. Truncation of the tail by replacing the aminopyridine in **1** with a small alkyl group (**5**) or polar functionality (**6–8**) largely preserved enzyme potency, cellular mechanistic potency (pERK), and inhibition of proliferation in B-Raf$^{V600E}$ SKMEL28 cells but resulted in significantly higher clearance in rat(*618*)."

From the discovery paper of the lead compound, cited in the previous quotation:

"Compound 1, a B-Raf lead identified from our oncology-directed kinase programs, features an imidazopyridine core and a large hydrophobic benzamide headgroup. Although this compound displayed good activity in the B-Raf V600E enzyme assay, it had little activity in either mechanistic (pERK) or antiproliferative cell-based assays using the B-Raf V600E mutant SKMEL28 cell line.

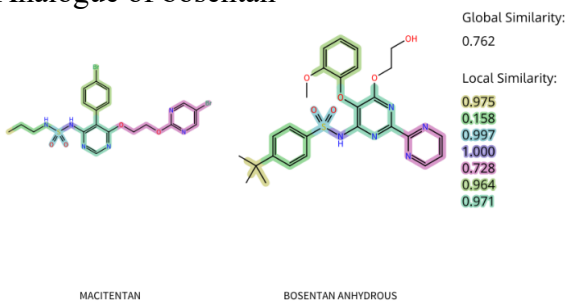
In an effort to improve the cellular activity of the series, SAR in the headgroup, core and tail regions of compound 1 were explored in parallel. […]

Evaluation of several different headgroup linkers (1 and 9–11) revealed that the sulfonamide-containing analog 11 showed a substantial improvement in cellular potency, particularly in the pERK mechanistic assay run in B-Raf V600E mutant SKMEL28 cells. Interestingly, sulfonamide 11 had similar potency in the cellular pERK assay and B-Raf biochemical assay, although activity in the SKMEL28 anti-proliferative assay was still inadequate(*619*)."

## MACITENTAN

2013

Analogue of bosentan




From the discoverer(s):

"Approximately 2,500 novel compounds targeting both ET receptors were synthesized, characterized, and tested for ET receptor affinity. The most potent compounds were then tested in a selection cascade, which included functional inhibition assays and in vivo models. Approximately 300 compounds were assessed for in vivo efficacy in several animal models of hypertension or PH, and 40 compounds were tested in a hepatic safety model after intravenous injection in rats. At the end of this process one compound met the required criteria and emerged as a highly attractive candidate for further studies. This compound was macitentan […]

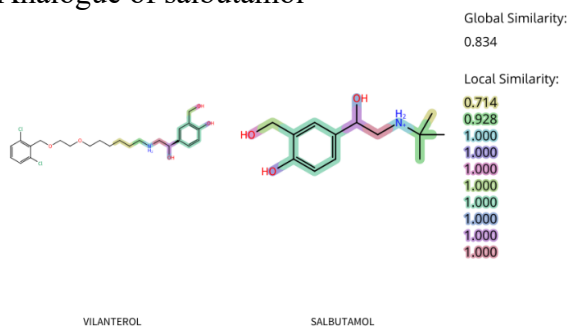
The structure of macitentan was derived from the structure of bosentan, taking into account all other patented structures of ERAs. The

sulfonamide moiety present in bosentan was replaced with a sulfamide moiety, resulting in an increased receptor affinity and an overall increase in lipophilicity(*620*).”

## VILANTEROL

2013

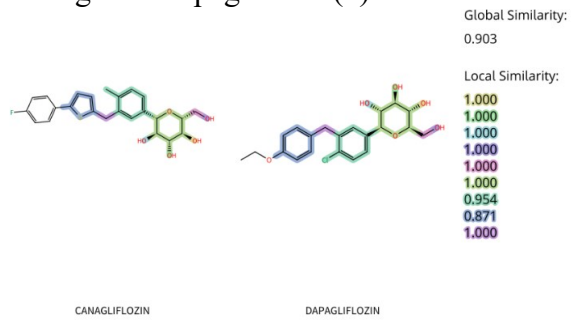
Analogue of salbutamol




## CANAGLIFLOZIN

2013

Analogue of dapagliflozin(*1*)




## RIOCIGUAT

2013

From the discovery paper:

“Direct NO-independent sGC stimulation was first demonstrated in 1994 when Ko and colleagues reported cGMP-stimulating properties for benzylindazole YC-1. Our ini tial chemical optimization program based on YC-1 as a lead structure resulted in the identification of the sGC stimulators BAY 41-2272 and BAY 41-8543 with a pyrazolopyridinyl pyrimidine core. The mode of action of these two compounds is similar to that of YC-1, but they demonstrate greatly increased potency and specificity for sGC. […]

In the course of our optimization we investigated more than 800 pyrimidine derivatives differing mainly at C5 […]

As primary in vitro assays to evaluate sGC-stimulating potency we monitored cGMP formation in a sGC-overexpressing Chinese hamster ovarian (CHO) cell line and the inhibition of phenylephrine-induced contractions of rabbit aortic rings. In the former case we used the minimum effective concentration (MEC) for cGMP formation rather than the $EC_{50}$ values for our SAR studies, as this provides a better correlation with the relaxation of isolated vessels and effective plasma concentrations in vivo. Apart from biological variability, deviations between the primary assays may be explained by differences in cell and tissue penetration. Blood pressure lowering effects were evaluated in conscious, spontaneously hypertensive rats equipped with a radiotelemetric device for continuous recording of hemodynamic parameters. Oral in vivo potency, efficacy, and duration of action in this model also provided initial hints on the PK profile.

Our lead compounds BAY 41-2272 and BAY 41-8543 stimulated the sGC-overexpressing cell line starting at 0.03 mm and inhibited the phenylephrine-induced contractions of rabbit aorta with $IC_{50}$ values of 0.30 and 0.10 mm, respectively.[…]

Throughout the project we synthesized numerous pairs of pyrimidine 4-amines and 4,6-diamines as exemplified by the pairs shown in Table 1 and Table 2. Overall, no major differences in in vitro potency were observed. In most cases, however, the diamino analogues displayed a slightly more potent relaxation of rabbit aorta than their monoamino counterparts. A seven- to tenfold loss in potency for relaxing rabbit aorta was observed upon replacement of the amino group of BAY 41-8543 by methyl or hydrogen. The weak blood pressure lowering effect of compound 9

suggests that the potency loss was even more dramatic in vivo, indicating a positive impact of the amino group on oral exposure(*621*).”

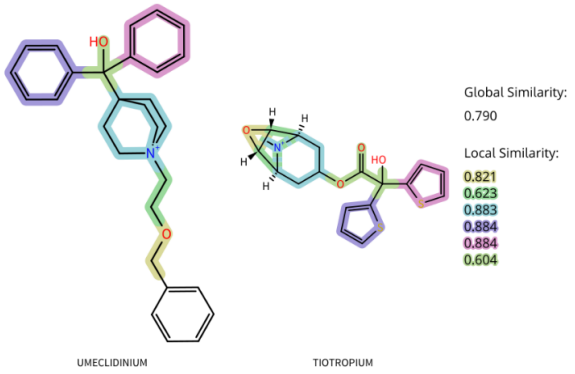
The 1994 paper reporting YC-1, cited in the previous quotation, does not narrate how YC-1 was discovered, yet it initially reports its antiplatelet activity this way:

“YC-1 [3-(5’-hydroxymethyl-2’-furyl)-1-benzylindazole] inhibited the aggregation of and ATP release from washed rabbit platelets induced by arachidonic acid, collagen, U46619, platelet-activating factor, and thrombin in a concentration-dependent manner(*622*).”

## UMECLIDINIUM

2013

Analogue of tiotropium




## TRAMETINIB

2013

“Systems-based, phenotypic screening(*542*)”

From the discovery paper:

“Our synthetic efforts, beginning from the lead compound 2, were directed at improving antiproliferative activity against cancer cells as well as various drug properties.

During a high-throughput screening for compounds that can induce expression of the cyclin-dependent kinase (CDK) 4/6 inhibitor $p15^{INK4b}$, we identified **2**. Subsequent experiments confirmed that **2** has an antiproliferative activity against human cancer cell lines ACHN (renal adenocarcinoma) and HT-29 (colorectal adenocarcinoma) with $IC_{50}$ values of 4800 and 990 nM, respectively. We conducted a medicinal chemistry campaign, chemically modifying **2** to optimize for these antiproliferative effects. Our synthetic efforts led to the discovery of orally bioavailable GSK1120212 (JTP-74057 DMSO solvate) **1**, demonstrating selective inhibition of proliferation in various BRAF mutant cancer cell lines. This compound was confirmed through molecular target analyses to be a highly potent and selective inhibitor of MEK1/2. We describe herein the structure−activity relationship (SAR) studies on **2** guided by ACHN and HT-29 cancer cell lines growth inhibitory activity […]

Because the molecular target of this compound series was still unknown at that time, we carried out a compound-immobilized affinity chromatography in which the analogues of **8b** were immobilized to resin. As a result, we found that **8b** binds to MEK1/2 and inhibits its kinase activity with high specificity(*623*).”

From the discovery paper of the lead structure cited in the previous quotation:

“Here we report that the pyrido-pyrimidine derivative JTP-70902, identified by screening for p15INK4b-inducing activity, induces cell cycle arrest at G1 phase in the p16INK4a-inactivated human colon cancer cell line HT-29. Analysis of the p15INK4b-inducing mechanism revealed that JTP-70902 binds to MEK1/2 and inhibits its kinase activity. […]

Screening of our compound library for p15INK4b-inducing activity was conducted by a branched-DNA method, using a QuantiGene High Volume Kit for the Direct Quantitation of Cellular mRNA with p15INK4b-specific probes. […]

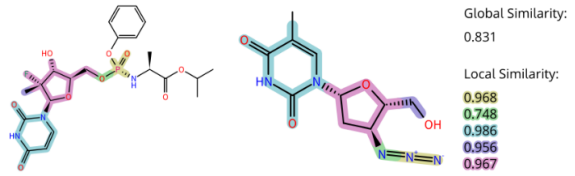
We established a high-throughput branched-DNA assay and screened a total of 160 000

compounds for their ability to induce the expression of p15INK4b mRNA. As a result, a pyrido-pyrimidine derivative, JTP-70902, was identified to have a high p15INK4b-inducing activity. In a time-course analysis using human colon cancer HT-29 cells, 100 nM JTP-70902 slightly induced expression of the p15INK4b protein after 8 h exposure, and the effect was pronounced after 24 h exposure(*624*)."

SOFOSBUVIR

2013

Analogue of zidovudine




ADO-TRASTUZUMAB EMTANSINE

2013

Alteration of trastuzumab:

"DM1, the cytotoxic component of T-DM1, is a derivative of the microtubule depolymerizing agent maytansine. DM1 induces mitotic arrest and triggers apoptosis in a manner similar to vinorelbine and other vinca alkaloids. Maytansine was known as a potent cytotoxic agent for several decades, but its nonselective toxicity curtailed clinical development. DM1 exhibits *in vitro* potency 3–10 times greater than maytansine, and 25–500 times greater than vinblastine or taxanes(*625*)."

Discovery of DM1 (DM1 = MERTANSINE)

Analogue of maytansine

Error in similarity calculation by FTrees because of the unsupported macrocycle

Discovery of maytansine:

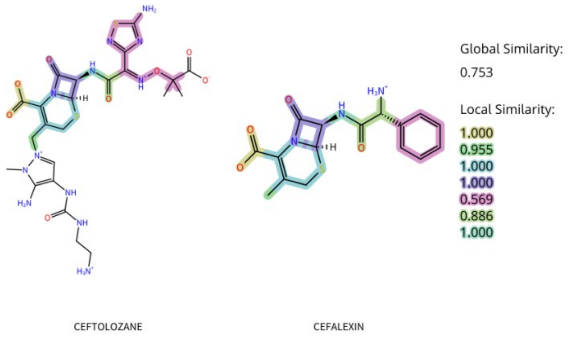
From the discovery paper of maytansine:

"In the course of a continuing search for tumor inhibitors from plant sources, we found that an alcoholic extract of *Maytenus ouatus* Loes. showed significant inhibitory activity *in vitro* against cells derived from human carcinoma of the nasopharynx (KB) and against five standard animal tumor systems(*626*)."

CEFTOLOZANE

2014

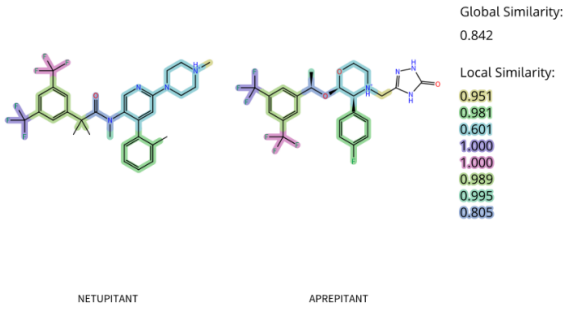
Analogue of cefalexin




NETUPITANT

2014

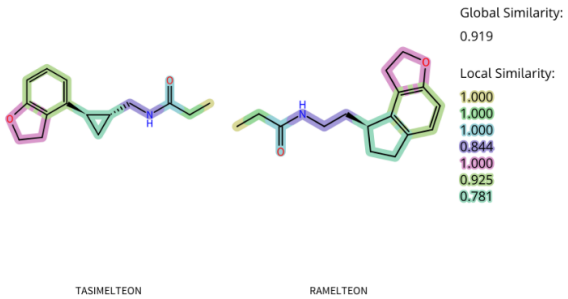
Analogue of aprepitant




TASIMELTEON

2014

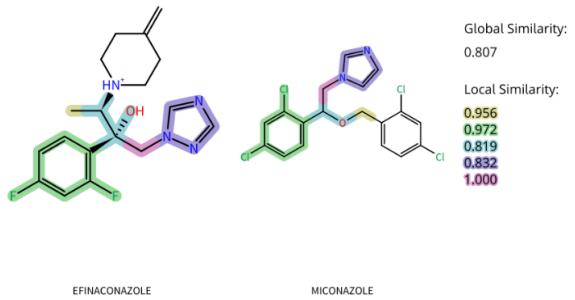
Analogue of ramelteon



## EFINACONAZOLE

2014

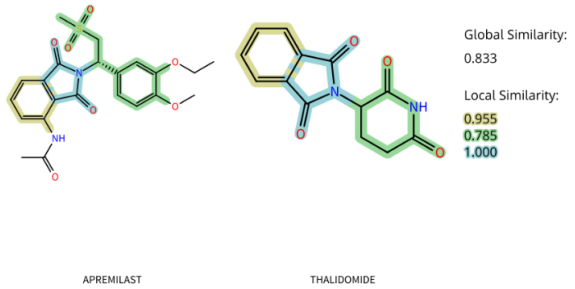
Analogue of miconazole(*2*)




## APREMILAST

2014

Analogue of thalidomide




From the discovery paper:

"We have previously reported on the development of a novel series of PDE4 and TNF-R inhibitors derived from 3-(1,3-dioxo-1,3-dihydroisoindol-2-yl)-3-(3,4-dimethoxyphenyl)propionic acid derivatives. Herein, we report the discovery of 1S (apremilast), a novel orally active PDE4 and TNF-R inhibitor. 1S is currently in clinical trials for the treatment of psoriasis. […]

Three assays were used to assess the in vitro potency of our PDE4 inhibitors. PDE4 inhibitory activity was measured with PDE4 enzyme isolated from U937 cells as previously reported. TNF-α inhibitory activity was measured in lipopolysaccharide (LPS) stimulated hPBMC or WB. The hPBMC and WB cells are human cells, and thus, these cellular assays may have greater clinical relevance than inhibition of purified PDE4. Furthermore, the difference between hPBMC and WB TNF-α inhibitory activity may serve as an indirect indicator of the degree of protein binding, and the WB data are a more realistic view of the clinical situation.

In a previous report, we described a novel series of 3-(1,3-dioxo-1,3-dihydroisoindol-2-yl)-3-(3,4-dimethoxyphenyl)propionic acid and derivatives with TNF-α inhibitory activity. Later, we reported that inhibition of PDE4 was the mechanism of action for TNF-α inhibition by this class of compounds. In the effort to optimize the potency, isosteric replacement of the acid moiety was explored(*627*)."

From a previous related article of the discovery team which was cited in the previous quotation as the discovery paper of the lead structure:

"**Structural Modifications of Thalidomide Produce Analogs with Enhanced Tumor Necrosis Factor Inhibitory Activity** […]

After a few years of use as a sedative, thalidomide was withdrawn from the market when its potent and tragic teratogenic properties became apparent. However, during this time, it was noted that thalidomide was remarkably effective for the treatment of erythema nodusum leprosum (ENL), an acute inflammatory manifestation of lepromatous leprosy. […]

Because of the demonstrated effect of thalidomide on the production of TNFα, and the central role that TNFα plays in the immune response and the inflammatory cascade, we decided to focus on improving the TNFα-inhibiting properties of thalidomide by structure modification. We have designed and synthesized analogs of thalidomide optimized for their ability to control TNFα synthesis. Initial studies demonstrated the importance of an intact phthaloyl ring. Hydrolysis of the glutarimide ring affords either N-

phthaloylglutamine or N-phthaloylisoglutamine. Analogs were therefore prepared based on the hydrolysis of the glutarimide ring of thalidomide. […]

Inhibition of TNFα was measured in the supernatant of human PBMCs stimulated with LPS(*628*).”

VORAPAXAR

2014

“We have previously reported the discovery of PAR-1 antagonists based on a lead generated from the natural product himbacine. These compounds bind to PAR-1 in a competitive manner with high affinity and are highly active in a series of functional assays that measure cellular responses to platelet activation. More importantly, these compounds showed robust inhibition of platelet aggregation in an ex vivo cynomolgus monkey model following oral administration.

As part of our continuing effort to optimize the potency and pharmacokinetic profile of this series, we have further explored the C-7 region of the tricyclic motif, which has been known to undergo considerable in vivo metabolism. Toward this end, various derivatives of the C-7 amine were explored. […] In vitro binding studies were carried out on human platelet membrane-derived PAR-1 using radiolabeled high affinity thrombin receptor activating peptide ([$^3$H]haTRAP) as ligand, according to the previous reports(*629*).”

From the discovery paper of the lead compound, cited in the previous quotation:

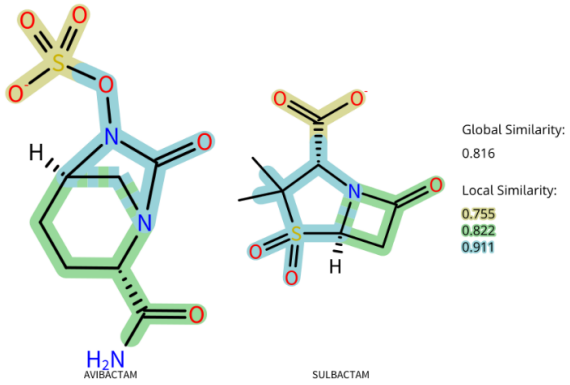
“We report the discovery of high affinity, orally active, low molecular weight non-peptide PAR-1 antagonists based on the natural product himbacine. One of the synthetic analogues of himbacine was identified in high-throughput screening as a lead for the PAR-1 antagonist program. […]

In vitro binding studies were carried out using purified human platelet membrane as PAR-1 source and tritiated high-affinity thrombin receptor activating peptide(*630*)”

AVIBACTAM

2014

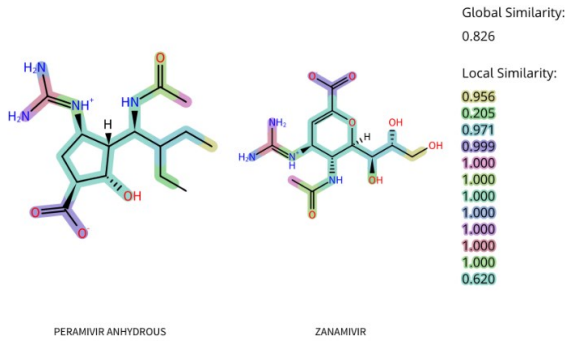
Analogue of sulbactam




PERAMIVIR

2014

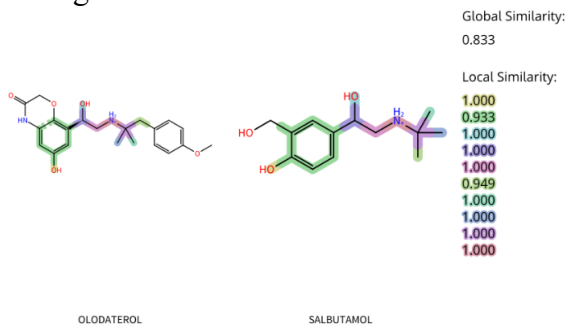
Analogue of zanamivir




OLODATEROL

2014

Analogue of salbutamol




PEGINTERFERON BETA-1A

2014

Pegylated interferon beta-1A

MILTEFOSINE

2014

From the discoverer(s):

"Miltefosine (hexadecylphosphocholine) was also synthesized independently in 1982 by Bill Pendergast and Joseph Chan at Burroughs Wellcome, RTP, NC, USA, as part of an antiinflammatory programme. Miltefosine was one of a series of simple analogues of PAF that had recently been described. Compounds were selected for screening against Leishmania and trypanosomes at the Wellcome Research Laboratories, Beckenham, UK in 1984. […]

Meanwhile, Pendergast and Chan had synthesized several APCs, with different alkyl chain lengths and distances between P and N of the phosphocholine moiety. Seven APCs, including hexadecylphosphocholine (miltefosine), and one alkyl phosphoethanolamine were reported active at <10 μg/ml against *L. donovani* amastigotes and promastigotes. Miltefosine had an activity of 5.0 μg/ml in the mouse macrophage model, not the highest activity but the best tolerated by host cells. Four compounds were selected for in vivo study, of which the three APCs were active, but the phosphoethanolamine was inactive. In a subsequent experiment, the $ED_{50}$ of miltefosine was determined as 12.8mg/kg body weight×5 administrations (subcutaneous route). This information was published in 1987 with the closure of the antileishmanial and antitrypanosomal programme at the WRL, Beckenham.

Subsequently, during a night shift at University Hospital Goettingen, C. Unger and A. Kuhlencord, knowing the results from Croft et al. (1987) and the oral bioavailability of miltefosine from the phase II studies in tumour patients, planned oral testing of miltefosine against *Leishmania* and other protozoa using existing in vivo models in the group of W. Bommer. They were able to confirm the excellent antileishmanial activity after oral treatment in BALB/c mice. Miltefosine produced >95% suppression of both *L. donovani* and *L. infantum* amastigotes in the liver, spleen and bone marrow at 20mg/kg×5 administrations (oral). The activity of miltefosine was markedly superior to that of the standard drug sodium stibogluconate and this study, demonstrating the advantage of oral administration, helped to establish miltefosine as a lead compound for the treatment of VL. These data were the basis for one of us (J.E.) to decide to initiate a development programme within ASTA Medica (later Zentaris) for miltefosine in VL(*631*)."

From a previous study of the discoverer(s), Croft and his team, cited in the previous quotation:

"Several alkyl phosphorylcholines and related derivatives were tested against *Leishmania donovani* amastigotes in mouse peritoneal macrophages *in vitro* and $ED_{50}$ values were determined in the range of 1–12 μM. The three alkyl phosphorylcholines tested against *L. donovani* in BALB/c mice were active, an $ED_{50}$ of 12.8 mg/kg/day × 5 was ascertained for one compound, but an alkyl phosphorylethanolamine was inactive(*632*)."

IDELALISIB

2014

From the discovery paper:

"We identified 5-fluoro-3-phenyl-2-[(*S*)-1-(9*H*-purin-6-ylamino)-propyl]-3*H*-quinazolin-4-one (CAL-101), a potent and selective inhibitor of p110δ, in a kinome-wide screen using purified enzymes and in cell-based PI3K isoform-specific assays(*633*)."

NALOXEGOL OXALATE

2014

Secondary

SUVOREXANT

2014

From the discovery paper:

“A recent publication from our group described the discovery of **4**, a novel diazepane-based DORA identified by hit-to-lead efforts following high throughput screening of the Merck sample collection. Compound **4** demonstrates low nanomolar affinity for the human $OX_1R$ and $OX_2R$ as measured by a radioligand-displacement binding assay (expressed as $K_i$), as well as excellent potency in a fluorometric imaging plate reader (FLIPR) assay that provides a functional readout of orexin receptor antagonism in CHO cells engineered to overexpress the human receptors (expressed as $IC_{50}$)(*634*).”

From the discovery paper of the lead structure cited in the previous quotation:

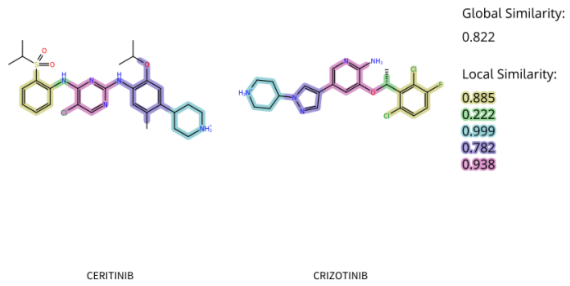
“We now describe a new class of dual orexin receptor antagonists based on a 1,4-diazepane central scaffold, and trace its development from an HTS lead to an optimized compound that demonstrates antagonism of orexin signaling in vivo.

Compound 1 was identified by HTS as a promising lead for optimization based on its potency and modular structure amenable to rapid analogue synthesis. To determine potency, we employed a binding assay that measures displacement of a high-affinity radiolabeled ligand bound to human orexin receptors (expressed as $K_i$ values), and a FLIPR (fluorometric imaging plate reader) assay in which $Ca^{2+}$ flux is measured as a functional determinant of orexin antagonism (expressed as $IC_{50}$ values). In these assays, compound **1** demonstrated good activity on $OX_2R$ ($K_i$ =5 nm; $EC_{50}$ =98 nm), but less affinity for $OX_1R$ ($K_i$ =150 nm; $EC_{50}$ =630 nm). Our initial goal was to improve potency against both receptors by altering the heterocyclic ‘western’ portion and the benzamide ‘eastern’ portion of the HTS lead, while retaining the central 1,4-diazepane core(*635*).”

CERITINIB

2014

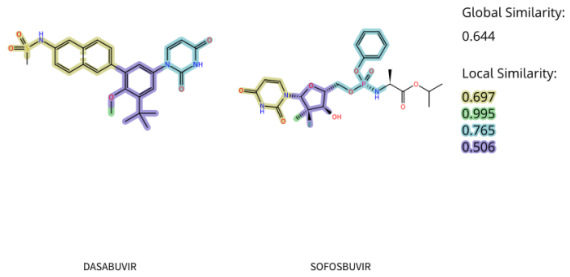
Analogue(*542*) of crizotinib(*571*)




DASABUVIR

2014

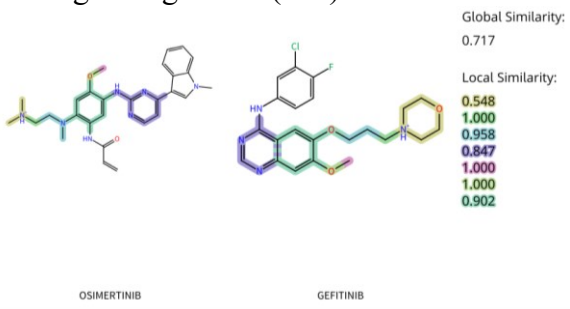
Analogue of sofosbuvir




OSIMERTINIB

2014

Analogue of gefitinib(*571*)




FOSNETUPITANT

2014

Prodrug of netupitant

FLORBETABEN F-18

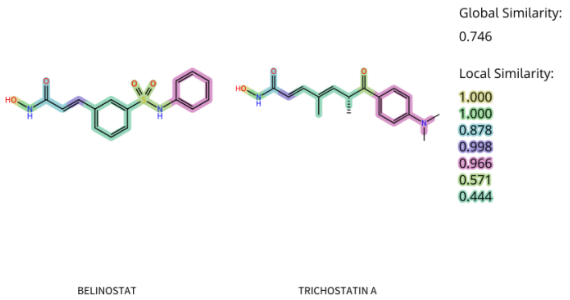
2014

Radiopharmaceutical

BELINOSTAT

2014

Analogue of trichostatin A




From the discovery paper of belinostat:

"We decided to base our design on the structures of hydroxamic acid containing inhibitors of histone-deacetylase known at the initiation of this work, particularly TSA.(*636*)"

Histone deacetylase inhibitory activity of trichostatin A was discovered after it was discovered due to its cellular activity:

"(R)-Trichostatin A (TSA) was originally reported as a fungistatic antibiotic by Tsuji et al. Recently, we demonstrated that the extremely low concentrations of TSA caused induction of Friend leukemia cell differentiation as well as inhibition of the cell cycle of normal rat fibroblasts in both the Gl and G2 phases. […] In the present paper, we show that nanomolar concentrations of (R)-TSA cause a marked accumulation of highly acetylated histones *in vivo* and strongly inhibit the activity of the partially purified histone deacetylase in vitro. In addition, experiments using a TSA-resistant mutant suggest that inhibition of the enzyme is the primary reason for the inhibitory effect of TSA *in vivo*(*637*)."

From the original discovery paper of trichostatin A as a fungistatic antibiotic, cited in the previous quotation:

"In the course of the screening of antifungal antibiotics, we found that a few strains of *Streptomyces hygroscopicus* produce an antifungal antibiotic, though the yield was generally low and variable. In this paper, the isolation and structural elucidation of this antibiotic are described.

The antifungal principle was extracted with organic solvents from the fermentation broth and separated from other inactive products by chromatography on silica gel. The assay organism used was *Aspergillus niger*(*638*)."

OMBITASVIR

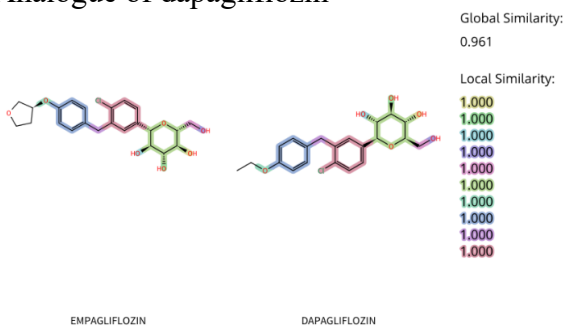
2014

"The availability of subgenomic HCV replicons afforded the opportunity to conduct a cell-based phenotypic screen to identify inhibitors of HCV replication. The following sections in this chapter provide some detail with regard to how a compound identified in the replicon inhibition screen ultimately gave rise to ombitasvir(*639*)"

EMPAGLIFLOZIN

2014

Analogue of dapagliflozin




METRELEPTIN

2014

Recombinant analogue of the human hormone leptin(*2*)

ELOSULFASE ALFA

2014

synthetic version of the enzyme N-acetylgalactosamine-6-sulfatase(*2*)

PIRFENIDONE

2014

“Pirfenidone is a pyridine [5-methyl-1-phenyl-2-(1H)-pyridone] originally synthesized by Gadekar as an agent that had analgesic, antipyretic and anti-inflammatory actions. […]

The precise cellular mechanism whereby pirfenidone modulates fibrogenesis is still not understood in detail, but its effects are probably multitargeted because both antioxidant, antitransforming growth factor (anti-TGF) and antiplatelet derived growth factor effects have been demonstrated(*640*).”

From the disclosing patent cited in the previous quotation:

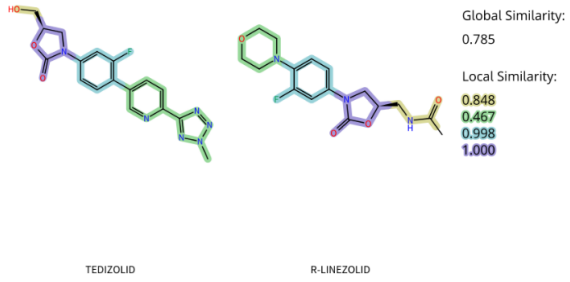
“I have discovered that 5-methyl-1-phenyl-2-(1H)-pyridone (AMR-69) has excellent analgesic activity, marked anti-inflammatory activity and shows excellent anti-pyretic activity in test animals when compared with the standard analgesic drug (aminopyrine). Further as compared to this standard, the compound of the present invention, when formulated into dosage form for oral or intraperitoneal administration, showed markedly lower toxicity in test animals. Moreover, AMR-69 has been observed to show markedly lower toxicity, as well as enhanced therapeutic activity when compared with closely related homologues such as 1-phenyl-2-(1H)-pyridone, 5-ethyl-1-phenyl-2-(1H)-pyridone or 3-methyl-1-phenyl-2-(1H)-pyridone. […]

Furthermore, AMR-69 has been observed to be therapeutically effective in protecting mucous membranes of the respiratory system, in particular those of the nasopharynx and lungs, against noxious agents. Protection against noxious focal respiratory tract pathology (petechiae, edema, hemorrhage, focal infection, etc.) has been demonstrated in gross examination of rat lung tissues and microscopic examination of dog lung tissues following treatment with AMR-69. Special protective effects of the mucous linings of the respiratory system have been confirmed in tests on humans, especially those showing symptoms of sinusitis, post-nasal drip, chronic rhinitis infection, allergic rhinitis, conjunctivitis, headache, earache or sore throat. The therapeutic effectiveness of AMR-69 treatment on skin conditions such as dermatitis, insect sting and poison ivy have also been demonstrated(*641*).”

TEDIZOLID

2014

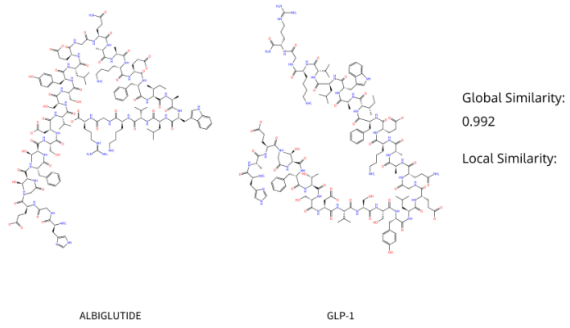
Analogue of linezolid(*2*)




ALBIGLUTIDE

2014

Analogue of liraglutide and GLP-1




RAMUCIRUMAB

2014

Monoclonal Antibody

SILTUXIMAB

2014

Monoclonal Antibody

LEDIPASVIR

2014

From the discovery paper:

"Early NS5A inhibitors were found empirically through screening of the GT1b replicon. Several series of lipophilic proline, proline-mimetic, or alanine-amide inhibitors of the GT1b replicon have been discovered, but these inhibitors typically have ~1000-fold weaker activity against the GT1a replicon. […]

Throughout this work, our optimization of potency focused on GT1a activity; accordingly, the discussion here is restricted to replicon GT1a $EC_{50}$ values, although the GT1b values are provided for comparison(*642*)."

From the discoverer(s):

"We focused on discovering an NS5A inhibitor that could be utilized in a single-tablet regimen in combination with other HCV agents. Further, we sought high antiviral potency and a long PK half-life to reduce the potential for emergence of viral breakthrough or resistance during treatment. A large number of diverse cores were designed and synthesized in the discovery of LDV. In early studies we investigated symmetric core inhibitors. Potency proved challenging to attain against the genotype 1a subtype (GT1a) replicon but was more readily attained against the genotype 1b subtype (GT1b). Thus potency discussions herein most typically refer to GT1a potency, with GT1b potency provided in tables for reference. Throughout this manuscript, potency values represent effective concentration to reduce replication by 50% ($EC_{50}$) in cell lines with engineered replicons(*643*)."

DALBAVANCIN

2014

Analogue of vancomycin(*2*)

Error in similarity calculation by FTrees because of the unsupported macrocycle

ORITAVANCIN

2014

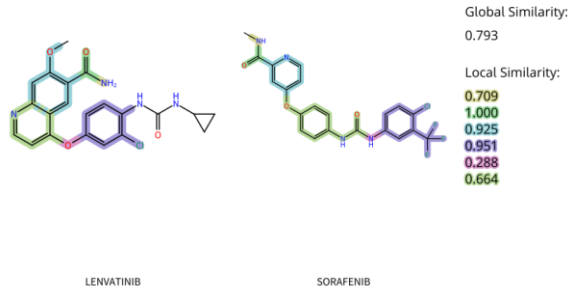
Analogue of vancomycin

Error in similarity calculation by FTrees because of the unsupported macrocycle

LENVATINIB

2014

Analogue of sorafenib




From the discoverer(s):

"We had initially set four preclinical goals: (i) potent inhibition of angiogenesis, (ii) antitumor activity in a wide range of administration doses with a good safety profile, (iii) an acceptable profile for oral administration, and (iv) survival benefit. We established three key assay systems. First, we focused on targeting tube formation by endothelial cells because it is important for angiogenesis and is a specific phenotype of endothelial cells. Our angiogenic-factor-induced sandwich tube formation (sTF) assay is a phenotypic screen system that mimics tube formation driven by individual angiogenic factors. We used VEGF, FGF, or HGF, which were well known as tumor angiogenic factors at that time, and established an sTF assay with human umbilical vein endothelial cells (HUVECs) in 3D collagen gel culture. Lenvatinib was optimized based on quinoline skeleton containing urea moiety selected among Eisai compound libraries by using sTF assay(*644*)."

TAVABOROLE

2014

From the discovery paper:

"Focused screening of our library revealed these dihydrobenzoxaboroles had good antifungal activity against *C. albicans*. Further screening against yeast, filamentous fungi, and dermatophytes showed these compounds had broad spectrum activity against all these fungal pathogens including the major dermatophytes that cause onychomycosis, *T. rubrum* and *T. mentagrophytes*. […]

To determine the antifungal activity of these compounds, we screened for their minimum inhibitory concentrations (MIC) against the major dermatophytes that cause onychomycosis, *T. rubrum* and *T. mentagrophytes*, and against the yeasts and molds *C. albicans*, *C. neoformans*, and *A. fumigatus* to test for their broad spectrum activity(*645*)."

OLAPARIB

2014

From the discovery paper:

"Previously, we and others have described the identification, synthesis, and optimization of a number of potent inhibitors of PARP-1 that bear a common phthalazinone core. The focus of these efforts was to optimize hits, which originated from a medium throughput screen, that identified benzyl phthalazinone **13** as a moderately potent ($IC_{50}$ = 0.77 μM) PARP-1 antagonist. A liability of the early compounds in the series was a lack of cellular activity, which was measured by their ability to sensitize HeLa B cells to the killing effect of the alkylating agent methyl methanesulfonate (MMS). This issue was resolved by the optimization of the pendant benzyl linker to provide potent inhibitors of PARP-1 at both the enzyme and the cellular level. In addition, the intrinsic pharmacokinetics of the series were improved to yield good in vitro and in vivo half lives, which culminated in the disclosure of 4-[[3-(1,4-diazepane-1-carbonyl)-4-fluorophenyl]methyl]-2*H*-phthalazin-1-one **14**. […]

In a logical extension to the homopiperazine series, a number of corresponding piperazine analogs were explored. Interestingly, in the direct comparison with homopiperazine **14**, compound **24** is equipotent for PARP-1 but is marginally less active in the cellular sensitization assay ($PF_{50}$ = 12.6 vs 8.6, respectively), which may be indicative of a reduction in cell permeability. […]

Beyond this observation, convincing structure-$PF_{50}$ relationships have been elusive within the phthalazinone series. Modest changes to structure can have unanticipated effects on $PF_{50}$ values, and, despite the analysis of a large data set, correlations of $PF_{50}$ with permeability parameters such as lipophilicity and solubility have been disappointing. A set of piperazine derivatives that did show transferable $PF_{50}$ profiles is illustrated in Table 3. Here simple alkyl homologation provides compounds with a significant increase in cellular activity from C-1 to C-2 elongation (compounds **39**-**41**). The SAR for the series shows an optimum cellular activity that decreases as lipophilicity increases(*646*)"

"Many of the medicines that were invented starting with a target specific assay required an additional empirical phenotypic assay to prioritize the actives and identify candidates with functional efficacy. The discovery of gleevec, a c-abl kinase inhibitor that works through stabilizing the kinase inactive state, PARP inhibitors such as olaparib(*511*)"

DULAGLUTIDE

2014

"a novel glucagon-like peptide-1 agonist (GLP-1) biologic drug consisting of a dipeptidyl peptidase-IV-protected GLP-1 analogue covalently linked to a human IgG4-Fc heavy chain by a small peptide linker(*2*)."

ELIGLUSTAT

2014

From the discoverer(s):

"The treatment of glycosphingolipid storage diseases by synthesis inhibition was first proposed 40 years ago as an alternative approach to enzyme replacement therapy. We have pursued this strategy through the rational design of potent and selective inhibitors of glucosylceramide synthase, the first step in glycosphingolipid synthesis. Eliglustat tartrate was the result of these efforts(*647*)"

PARITAPREVIR

2014

From the discoverer(s):

"Two cellular assays provided the main biological data collected and examined for compound characterization. The first assay employed cell lines generated to express genotypes 1a (from HCV strain H77) and 1b (from HCV strain Con1) as stably replicating replicons similar in nature to those described previously (referred to herein as the 'stable replicon assay'). As compound development progressed, the impact on antiviral activity of protein binding by human serum was measured by comparing the activity of the compounds measured in the stable replicon assay in the presence of 5% fetal bovine serum (FBS) vs. the activity noted in the presence of 5% FBS plus 40% human plasma to measure the impact of plasma protein binding on potency. The second assay (transient replicon assay) used cells transfected with replicons similar to those used to generate the stable cell lines. The extent of replication of the replicons over 3 days was measured(*648*)."

PEMBROLIZUMAB

2014

Monoclonal Antibody

BLINATUMOMAB

2014

Monoclonal Antibody

VEDOLIZUMAB

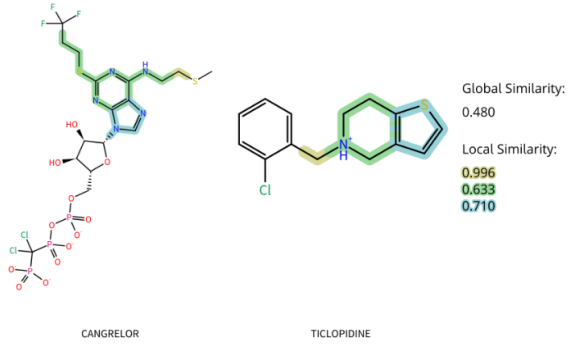
2014

Monoclonal Antibody

CANGRELOR

2015

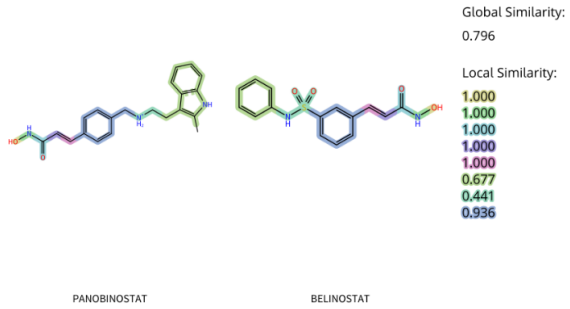
Analogue of ticlopidine




PANOBINOSTAT

2015

Analogue of belinostat




SEBELIPASE ALFA

2015

"Sebelipase alfa is a recombinant form of the enzyme lysosomal acid lipase (LAL) approved for the treatment of lysosomal acid lipase deficiency (LAL-D). The amino acid sequence for sebelipase alfa is the same as the amino acid sequence for human LAL(*2*)."

TIPIRACIL

2015

Secondary

LUMACAFTOR

2015

Empirical screening

“Lumacaftor was discovered with cellular high-throughput screens(*511*).”

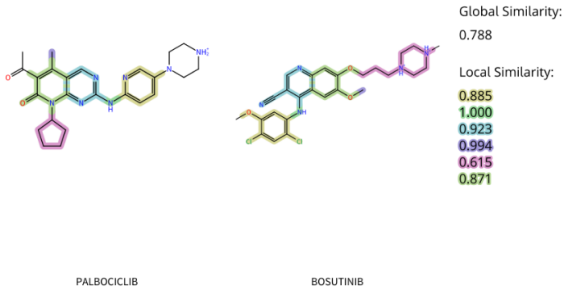
From the discovery paper:

“**Discovery of VX-809.** To discover CFTR correctors, we screened 164,000 small molecules for compounds that increased F508del-CFTR–mediated chloride transport in a recombinant cell-based assay. Active compounds were prioritized based on evidence of improved F508del-CFTR processing in the ER and increased functional F508del-CFTR at the cell surface. Immunoblot techniques were used to measure F508del-CFTR exit from the ER and passage through the Golgi, which is characterized by an increase in the molecular weight of CFTR as a result of glycosylation(*649*).”

PALBOCICLIB

2015

From the discovery paper:




“Our goal is to identify potent (nanomolar) inhibitors of Cdk4/D that possess sufficient selectivity against other kinases to test the hypothesis that pharmacological inhibition of Cdk4/D will provide a mild and effective treatment for the inhibition of tumor growth. Here, we describe structural modifications to a series of pyrido[2,3-d]pyrimidin-7-ones that have led to the discovery of some of the most potent and selective Cdk4/D inhibitors yet reported. […]

The first pyrido[2,3-d]pyrimidin-7-one prepared containing a 2-aminopyridine substituent at C2 was compound **15a**. A comparison of **15a** with its aniline counterpart **15b** identified a remarkable difference in selectivity profile between the two analogues, with the pyridyl analogue (**15a**) substantially favoring inhibition of Cdk4/D over inhibition of Cdk2/A. Contemporaneously, the nonspecific Cdk inhibitor, compound **16**, was identified as a potent inhibitor of Cdk4/D, Cdk2A and the fibroblast growth factor receptor. Bromide **16** was shown to inhibit the growth of human tumor xenografts in mice, demonstrating an ability to reach its molecular target(s) in vivo. Consequently, this compound was selected as a starting point for addressing whether replacing aniline side chains with aminopyridine-containing side chains would provide a general method for achieving selective inhibition of Cdk4/D, with compounds possessing the potential to inhibit this target in vivo.

To our great satisfaction, the next compound pre-pared, compound **17**, was found to exhibit excellent selectivity for Cdk4/D versus other Cdks and the receptor tyrosine kinases FGFr and PDGFr (platelet-derived growth factor receptor). Moreover, compound **17** imposed a $G_1$ block on asynchronously growing Rb-positive MDA-MB453 cells that was maintained at concentrations of inhibitor up to 10 μM. This remarkable observation led to a more thorough exploration of pyrido[2,3-d]pyrimidin-7-ones containing 2-aminopyridine side chains at the C2 position and the resulting SAR trends are detailed below. […]

Attention was turned next to the C6 substituent. Although the bromine atom in compound **17** conferred good potency for Cdk4/D inhibition, the size and lipophilicity of this atom suggested that a more optimal substituent might exist for this position(*650*).”

SECUKINUMAB

2015

Monoclonal Antibody

SACUBITRILAT

2015

From the discovery paper:

"***In Vitro* Assays.** Leu enkephalin, glutaryl-Ala-Ala-Phe-β-naphthylamide, and ANF are used as substrates ($K_{cat}/K_m$ = 56, 37, and 18, respectively) to identify inhibitors of NEP. We have compared the potencies of three different classes of NEP inhibitors, thiols, amino phosphonic acid, and carboxylic acid, in these three assays. The IC50 values determined in these assays for thiorphan (a thiol), an amino phosphonate, and **21a** (a dicarboxylic acid) were similar, although the Leu-ENK assay gave somewhat lower values, and predictive of functional potency in vivo. However, the correlation of inhibitory activity between assays was not always constant. […]

**ANF Potentiation Assay**. Plasma ANF concentrations were determined in animals infused with exogenous ANF before and after administration of NEP inhibitors. Figure 3 shows the effects of **19a** and (±)-candoxatril16 administered at 10 mg/kg PO on plasma ANF levels in conscious rats. Plasma ANF levels are expressed as a percent of those measured in vehicle-treated animals which received the infusion of exogenous ANF. ANF levels were increased significantly at all time points (30-240 min) after the administration of **19a**.

ANF-Induced Diuresis and Natriuresis. In anesthetized rats intraduodenally administered significantly increased ANF-induced natriuresis without affecting diuresis. Prior to the administration of ANF, there were no significant differences in mean arterial pressure, urine flow, or urinary sodium excretion when rats treated with **19a** were compared to controls. In vehicle-treated rats, ANF increased urinary sodium excretion from 0.72 ± 0.25 to 3.26 ± 0.63 μequiv/kg/min. This effect was potentiated in animals which received **19a**.

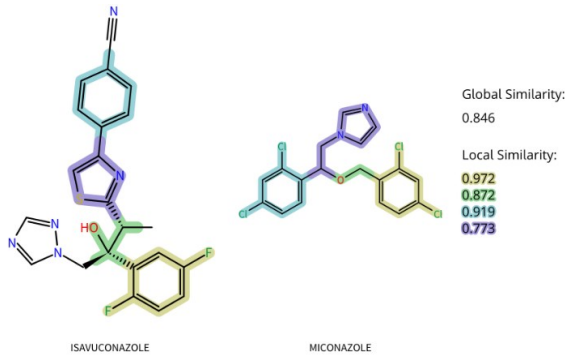
The effects of **21a** on ANF-induced diuresis and natriuresis in mongrel dogs is shown in Figure 5. […]

In summary, *in vitro* data are presented for three series of NEP inhibitors. The pharmacokinetic profile of **19a**/**21a** was determined in three species. The prodrug **19a** was also shown to increase exogenous levels of ANF and enhance ANF's natriuretic and diuretic activity. Although these experiments do not prove **21a** will enhance endogenous ANF levels and natriuretic and diuretic activity, it does demonstrate the potential to elicit these activities(*651*)."

ISAVUCONAZOLE

2015

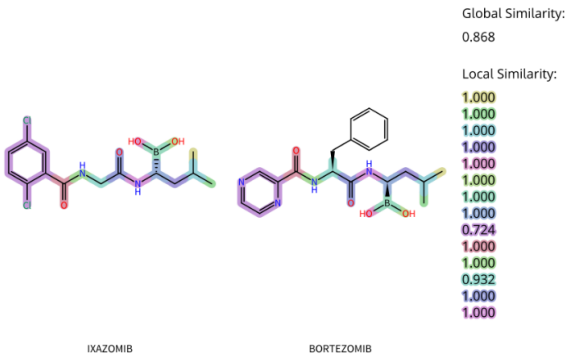
Analogue of miconazole(*2*)




IXAZOMIB

2015

Analogue of bortezomib(*2*)



## IVABRADINE

2015

From the discoverer(s):

"**2. The selection of ivabradine**

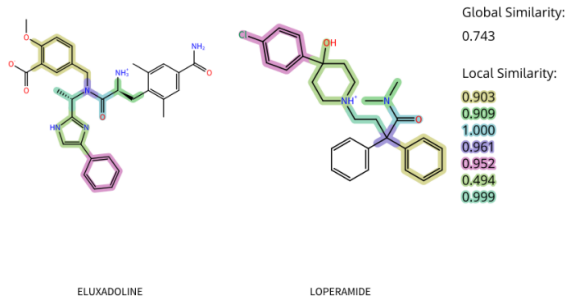
The screening of a series of original benzocycloalkane derivatives consisted in testing the ability of the compounds to directly reduce the spontaneous beating rate of isolated right atria from rat, in analyzing their mechanism of action and electrophysiological selectivity in sinus node preparation from rabbit and in ventricular preparations (guinea pig papillary muscles) and their effect on heart rate and duration of action in the conscious rat.

Among the different compounds studied, the benzocyclobutane or indane derivatives were the most interesting, able to reduce, at micromolar concentrations, the spontaneous beating rate of isolated rat right atria, to decrease the diastolic depolarization slope of the action potential of rabbit sinus node preparations and to reduce selectively the heart rate in conscious rat. The indane derivatives, such as S 16070, which induced marked prolongation of ventricular action potential duration, as was previously observed with UL-FS 49, were excluded to avoid a potential proarrhythmic effect. The benzocyclobutane derivative S 15544 (a racemate compound) was initially preferred as it induced a smaller effect on ventricular action potential duration. The resolution of S 15544 into its two isomers S 16257 (S configuration) and S 16260 (R configuration) has permitted the necessary comparison of their activity. Both isomers were equipotent in reducing the spontaneous firing of rabbit sinus node preparations, but S 16260 induced significant prolongations of action potential duration of ventricular preparation (guinea pig papillary muscle and rabbit purkinje fibers), contrary to S 16257. These in vitro data have been confirmed by in vivo studies in anesthetized pigs showing the equipotence of the two isomers in reducing the heart rate, the absence of effect of S 16257 on the QT interval corrected for heart rate (QTc) in contrast with S 16260 which induced a dose-dependent increase in the QTc, indicating a direct effect on ventricular repolarization. The electrophysiological selectivity of S 16257 was a major inducement to continue preclinical exploration with this particular isomer which was finally chosen for the clinical development and became ivabradine(*652*)."

## ELUXADOLINE

2015

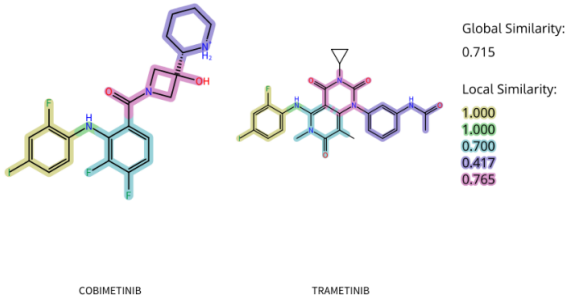
Analogue of loperamide




## COBIMETINIB

2015

Analogue of trametinib




## DARATUMUMAB

2015

Monoclonal Antibody

## NECITUMUMAB

2015

Monoclonal Antibody

## TRABECTEDIN

2015

From the discovery paper:

"Reports of the potent in vivo efficacy of extracts of the Caribbean tunicate *Ecteinascidia turbinata* date back to 1969, when it was reported that such extracts gave T/C to 272 vs P388 murine leukemia, with four of six cures in one experiment. The extracts were also powerful immunomodulators, but repeated attempts to isolate thecompounds responsible for either activity were unsuccessful. Our own concerted efforts to identify the compounds began in 1981, shortly after the Alpha Helix Caribbean Expedition 1978, where a sample of *E. turbinata* showed cytotoxicity in shipboard assays. These efforts culminated in the isolation by 1986 of six compounds-ecteinascidins 729, 743, 745, 759A, 759B, 770-from *E. turbinata*(*653*)"

From another paper of the discoverer(s):

"The most comprehensive survey of pharmacological activity was conducted by the U.S. National Cancer Institute over a period of 15 years, which found that ca. 4% of the marine species (mainly animals) examined contained antitumor compound(s), a figure close to that for terrestrial species (mainly plants). The bioassay employed in that screen was an *in vivo* test vs. P388 murine leukemia, a somewhat more demanding assay than cytotoxicity vs. tumor cells *in vitro*. Criteria for proceeding further with antitumor testing (through preclinical, Phase I, and Phase II stages) before entering the marketplace are progressively more stringent […]

The third antitumor compound from our laboratory currently in clinical trial is Ecteinascidin 743. The antitumor activity of extracts of the tunicate *Ecteinascidia turbinatawere* first noted in the NCI survey referred to earlier(*654*)"

## PARATHYROID HORMONE

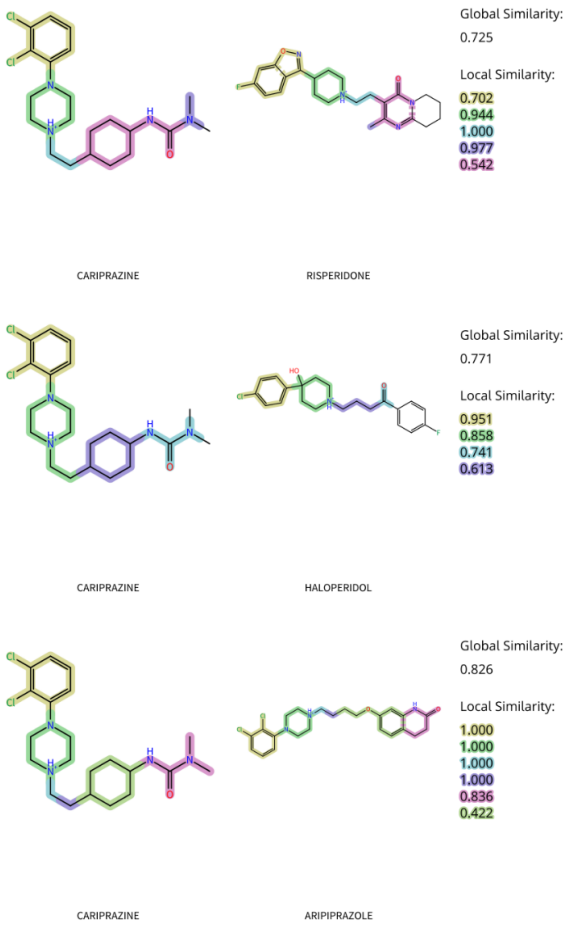
2015

Endogenous-based biopharmaceutical

## CARIPRAZINE

2015

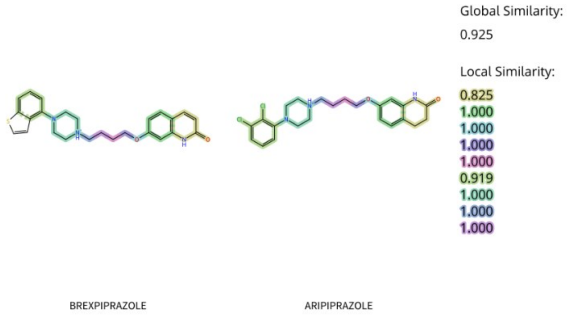
Analogue of haloperidol




## BREXPIPRAZOLE

2015

Analogue of Aripiprazole



## CRISABOROLE

2015

"We previously reported several classes of boron-containing compounds as potential therapeutic agents, including AN0128 as an antibacterial/anti-inflammatory agent and AN2690 as an antifungal agent. As our boron-containing compound library grew and was screened in various assay systems, a series of 5-phenoxybenzoxaborole derivatives was found to exhibit inhibitory activity against the release of cytokines, such as TNF-α and IFN-γ, from peripheral blood mononuclear cells (PBMCs) stimulated by lipopolysaccaride (LPS) or phytohemagglutinin (PHA). We also discovered that this class of compounds inhibited the PDE4 enzyme as part of its mechanism of action. Herein we describe the discovery of a novel series of benzoxaborole derivatives including AN2728 as an optimized developmental candidate and we report the structure–activity relationships (SAR) in terms of PDE4 enzyme inhibition and cytokine release inhibition(*655*)."

From the paper cited in the previous quotation as the previous report of related compounds:

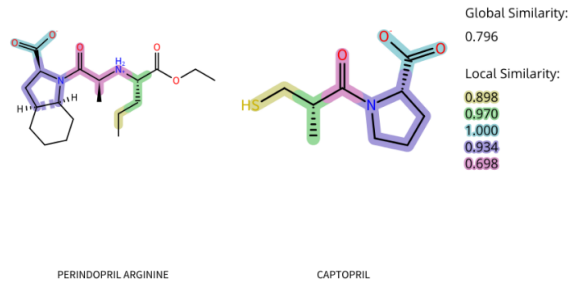
"We previously reported a new class of antibacterial agents, borinic acid quinoline esters. In this report, we describe a related class, borinic acid picolinate esters and the identification of a new antibacterial agent, 3-hydroxypyridine-2-carbonyloxy-bis(3-chloro-4-methylphenyl)borane, which has additional activity against pro-inflammatory cytokines. This combination of activities is ideal for the treatment of AD and also acne, where the inflammatory response is mediated by the anaerobic bacterium, *Propionobacterium acnes.* […]

In order to test for concomitant anti-inflammatory activity, compounds **2g**, **2s**, **2q**, and **2x** were evaluated for their ability to inhibit release of inflammatory cytokines from human peripheral blood mononuclear cells (PBMCs). Either lipopolysaccharide, Concanavalin A or phyto-hemagglutinin was used to induce the release of cytokines from the PBMCs(*656*)."

## PERINDOPRIL ARGININE

2015

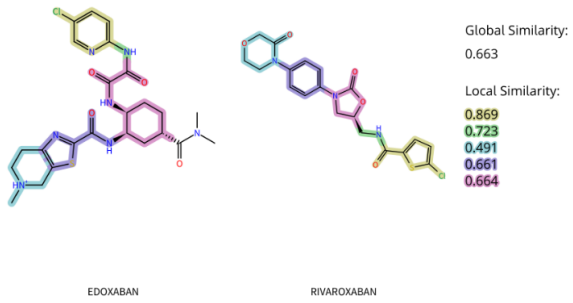
Analogue of captopril




## EDOXABAN

2015

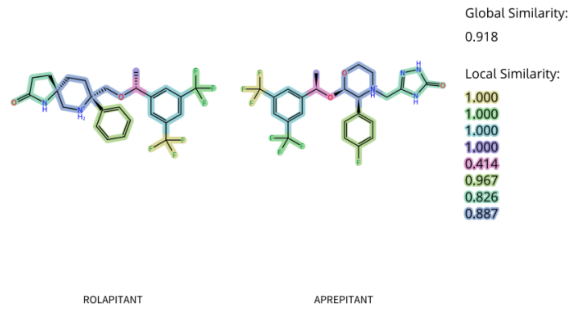
Analogue of rivaroxaban




## ROLAPITANT

2015

Analogue of aprepitant




## IDARUCIZUMAB

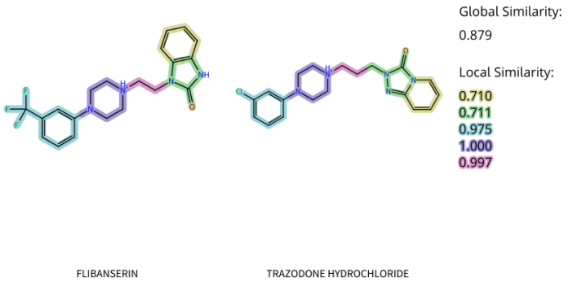
2015

Monoclonal Antibody

FLIBANSERIN

2015

Analogue of trazodone




"It was originally in development for treatment of depression but did not show efficacy greater than placebo in phase 2 trials. During those trials, it was noted that there was no associated sexual dysfunction and subsequently was found to show a positive effect on sexual desire using a validated measurement of sexual functioning, leading to the change in the targeted condition(*657*)."

ALECTINIB

2015

From the discovery paper:

"Since we consider that a high selectivity is ideal for targeted cancer therapies in terms of safety, our discovery research has focused on finding an inhibitor with high ALK selectivity.

In the previous study, we identified a potent and selective ALK inhibitor **15c**, which has 6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole scaffold, by chemical modification of HTS hit compound **1**. Conversion of 3-ethoxy group into cyano group and oxygen atom at 5-position into nitrogen atom resulted in drastically improved inhibitory activity against ALK enzyme. N-(Oxetan-3-yl)piperazine at 8-position contributed to the improved metabolic stability and its cationic nitrogen is crucial for potent antiproliferative activity against NPM-ALK-positive cell- line, KARPAS-299. Additionally, the substituent at 9-position of **15c**, which recognizes a particularly wide-open surface in the $E_0$ region of ALK protein, improved kinase selectivity. So far we have investigated the derivatives bearing side-chains with cationic nitrogen only at 8-position and their structural diversity was limited. Therefore, further exploration of side-chains is needed for the clinical candidate selection.

We report here the results of derivatization focused on side-chains at 8- and 9-positions. As a result, we identified the clinical candidate CH5424802 (**18a**), which has more potent anti-proliferative activity and a more suitable pharmacokinetic profile than those of **15c**. Pharmacokinetics data of 18a is also described in this paper(*658*)."

ALIROCUMAB

2015

Monoclonal Antibody

SELEXIPAG

2015

"The discovery strategy for a long-acting IP receptor agonist was based on the observation that the prototypical prostanoid structure is not necessary for activation of the IP receptor. Octimibate and **1** (BMY-42393), both partial agonists at the IP receptor, bear no structural resemblance to $PGI_2$ and its analogs, apart from a carboxylic acid moiety.

Compound **1**, which has a long duration of action in animal models of thrombosis, was chemically modified by replacing the oxazole ring with a pyrazine ring to obtain the lead compound, the 2-amino-5,6-diphenylpyrazine derivative **4c**. The potency of compounds at the human IP receptor was measured by their inhibition of adenosine diphosphate (ADP)-induced platelet aggregation. Compound **4c** inhibited platelet aggregation with a half maximal inhibitory concentration

($IC_{50}$) value of 1.5 μM(*659*)."

CHOLIC ACID

2015

Endogenous(*217*)

"Cholic acid is a primary bile acid synthesized from cholesterol in the liver. Endogenous bile acids including cholic acid enhance bile flow and provide the physiologic feedback inhibition of bile acid synthesis(*1*)."

From an early report of the use of bile acids in Zellweger syndrome:

"In light of the recent success of oral bile acid therapy in treating the liver disease associated with specific inborn errors in bile acid synthesis, we investigated the potential of this approach for the treatment of the liver disease associated with the Zellweger syndrome. We describe here the clinical and biochemical responses observed in a patient with Zellweger syndrome who was treated with primary bile acids(*660*)."

From the earlier articles on using bile acids in inborn disorders of bile acid synthesis:

"The unsaturated bile acids were present at high concentration in the urine in sulphated form. They did not seem to be able to promote bile acid dependent bile flow and the absorption of fat and fat soluble vitamins from the intestine. The infant had conjugated hyperbilirubinaemia from birth, steatorrhoea, and low plasma concentrations of vitamins A, D, and E. There was also evidence that either the production of abnormal bile acids or the failure to produce cholic and chenodeoxycholic acids was causing progressive liver damage. The patient had raised transaminase activities and liver biopsy specimens taken from his affected siblings showed a giant cell hepatitis that progressed to a micronodular cirrhosis.

We argued that if this patient were given chenodeoxycholic acid or cholic acid, or both, these bile acids would be retained within the enterohepatic circulation and could promote bile acid dependent bile flow and facilitate micellar solubilisation of fats and fat soluble vitamins. As cholesterol 7α-hydroxylase Is inhibited by cholic and chenodeoxycholic acids, we could also hope for a reduction in the synthesis of abnormal metabolites of 7α-hydroxycholesterol. This Report describes the progress of this patient who was not treated until the age of 4.3 years, at which time he was started on treatment with chenodeoxycholic acid(*661*)."

Regarding the use of bile acid analogues in cholangitis:

The first clues toward the anti-inflammatory activity of bile acids was observation of the alleviation of rheumatoid arthritis in patients with jaundice(*662*).

Also see the cortisone entry.

From an earlier paper of one of the discoverers, Philip Hench:

"When patients with rheumatoid (atrophic, chronic infectious) arthritis or with primary fibrositis become definitely jaundiced a notable event usually occurs: their rheumatic symptoms are rapidly, markedly, and generally completely alleviated for some weeks or months. My first observations on this phenomenon were reported in 1933 and later. This phenomenon was unmentioned in the modern literature on rheumatic diseases, but was casually noted by Still in 1897, by Wishart in 1903, and in three recent discussions, not on arthritis but on cinchophen toxicity. More recently further observations on the phenomenon were reported by Sidel and Abrams (1934), and by Borman (1936)(*91*)."

From the earliest article mentioning the relationship, published in 1896:

"Curiously enough, some accidental complications have been followed by marked improvement; thus I have known measles, scarlet fever, and catarrhal jaundice, to be each

followed by distinct improvement of the joint symptoms(*92*).”

From an early paper regarding the use of bile acids as anti-inflammatory therapeutics:

“[I]t is a clinically recognised fact that there occurs a rapid and striking remission of symptoms in cases of rheumatic and asthmatic patients upon the appearance of jaundice.

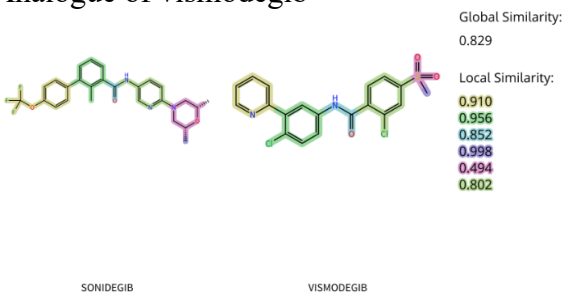
It thus naturally occurred as well to me to resort to fresh ox-bile percutaneously in the form of an ointment in the treatment of these and other inflammatory disorders. […]

In a survey of a series of over 596 cases of these various affections treated with the bile ointment, an assessment of the results has been made in the following table. The cases treated are of both sexes, and various ages, nationalities and walk of life including physicians and chemists. Therapeutic effectiveness was obtained in just over 95 per cent of the total number of cases, all belonged to infective inflammatory conditions, and was remarkably more rapid than with any other method of therapy(*663*).”

SONIDEGIB

2015

Analogue of vismodegib




EVOLOCUMAB

2015

Monoclonal Antibody

INSULIN DEGLUDEC

2015

Endogenous-based biopharmaceutical

SUGAMMADEX

2015

Chelating agent

ASFOTASE ALFA

2015

Bone-targeted recombinant human tissue-nonspecific alkaline phosphatase

ELOTUZUMAB

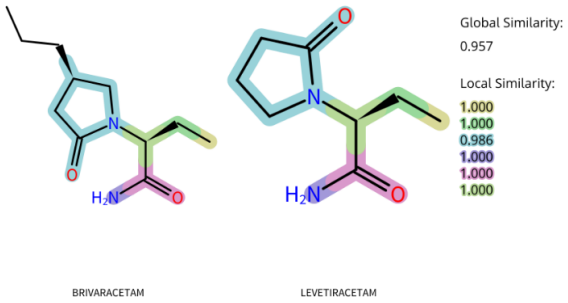
2015

Monoclonal Antibody

BRIVARACETAM

2016

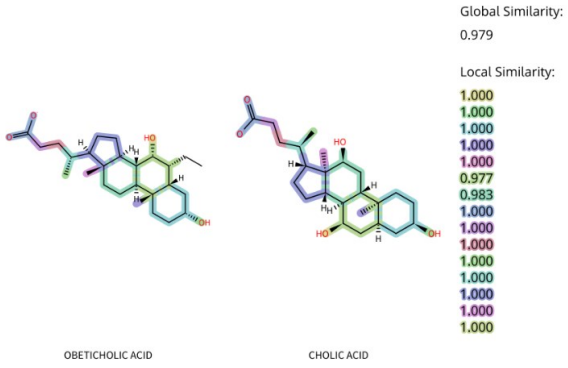
Analogue of levetiracetam(*2*)




OBETICHOLIC ACID

2016

Analogue of the endogenous cholic acid




IXEKIZUMAB

2016

Monoclonal Antibody

## PRASTERONE

2016

Analogue of estradiol(*1*)

From an early paper regarding the effects of prasterone (trans-dehydroandrosterone) on vaginal tissue:

"Butenandt and others (see Koch) have reported that some of the unsaturated androgens, notably androstane-dione and dehydroandrosterone, will induce estrus in the normal infantile rat. […]

The administration of testosterone, androsterone, dehydroandrosterone and androstanedione to groups of 2 to 4 spayed female rats for 30 days failed in every case to produce vaginal cornification (as determined by daily smears and histological section). In all cases castration changes were completely or almost completely prevented. […]

The above androgens, and in addition, androstene-dione, cis-androstene-diol and trans-androstene-diol have been administered to groups of 2 to 5 adult normal female rats for 16 to 30 days. Daily vaginal smears were made, in each instance, for at least 2 weeks prior to the initiation of and throughout the period of treatment. Normal 4 to 5 day cycles were present in all animals prior to treatment. […]

The tendency shown by cis-androstene-dione to induce continued estrus was even more apparent for dehydroandrosterone. The latter when injected at the 1.0 mg. daily level in normal rats resulted in estrous type smears for 16 of 18 days, 12 of 20 days, 19 of 22 days, and 21 of 22 days, respectively. The ovaries were small, the mammary glands were not stimulated, and the uteri were large.

The amazing effect of dehydroandrosterone in the adult normal female led us to administer this treatment to 4 hypophysectomized females. To our surprise, particularly in view of its failure to change the vaginal picture in the spayed rat, the hypophysectomized female reacted in a manner even more striking than the normal female. Estrous type smears were shown for 21 of 25 days, 22 of 22 days, 22 of 22 clays, and 12 of 14 days, respectively. The ovaries were only slightly decreased, the mammary glands were not stimulated, and the uteri were enlarged.

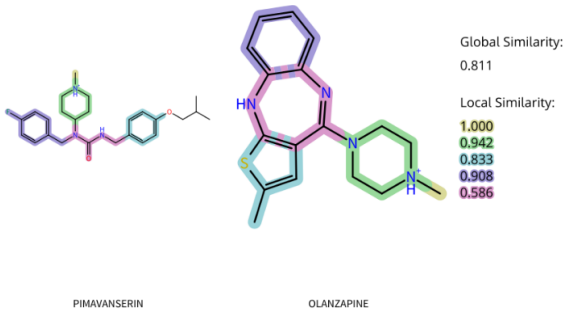
All animals showed a marked enlargement of the preputial glands and in many instances a striking enlargement of the clitoris(*664*)."

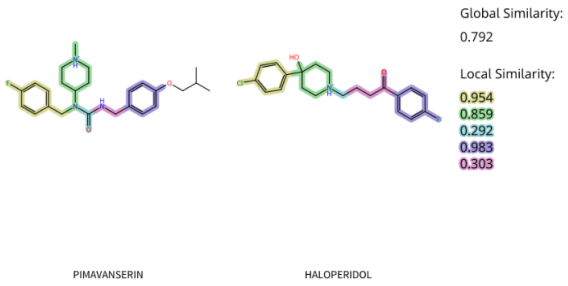
The article of Koch(*665*) which was cited in the previous quotation provides a good review regarding the path which had led to the observations of the previous quotation.

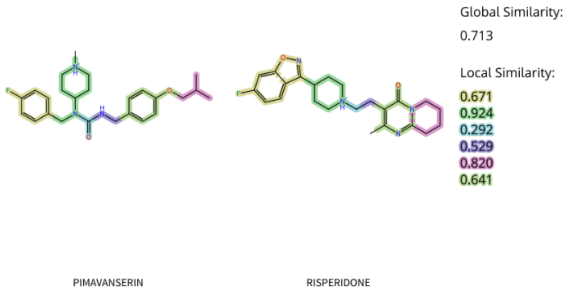
## PIMAVANSERIN

2016

Analogue of haloperidol



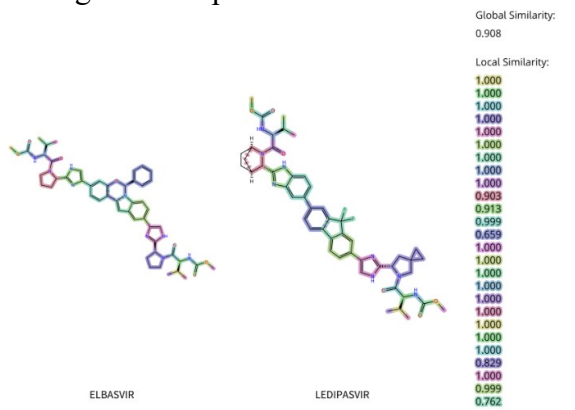



ELBASVIR

2016

Analogue of ledipasvir




From the discoverer(s):

"For nearly 30 years, HCV discovery research teams at Merck pursued multiple molecular targets in the search of a cure. The NS5A project took root at its IRBM site where the team discovered a series of piperazine-based small molecules that inhibited HCV replication but did not show activity in any of the typical HCV enzyme assays. The partial mode of action was subsequently characterized and linked to their ability to alter NS5A biogenesis which resulted in a reduction of p56–p58 conversion, and the resistance mutations identified were mapped to NS5A,

**Lead Identification**

With the IRBM compounds as a starting point, initial efforts focused on the synthesis and SAR development of these N-arylpiperazines. The incorporation of a cyclic constraint within these structures afforded indole **2**, which showed similar potency in the replicon assay (GT1b $EC_{50}$ ~150 nM) and was an attractive entry toward modulating this target. […]

Several heterocyclic scaffolds were synthesized and incorporated into the final inhibitor structures. The cellular activity of each new compound was determined using the replicon-system-expressing genotypes 1b, 2a, and 1a(*666*)."

GRAZOPREVIR

2016

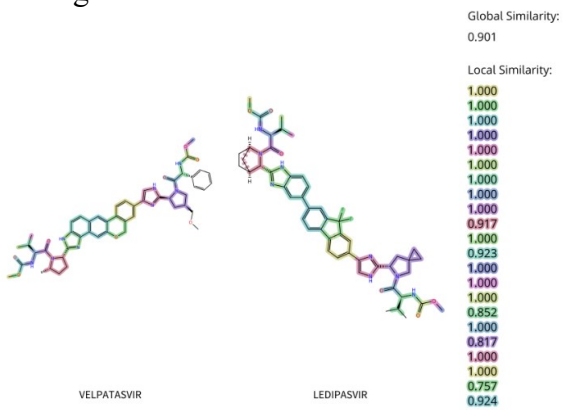
Analogue of paritaprevir

Error in similarity calculation by FTrees because of the unsupported macrocycle

VELPATASVIR

2016

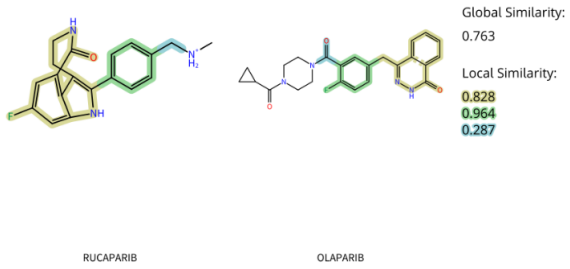
Analogue of elbasvir




RUCAPARIB

2016

Analogue of olaparib




DACLIZUMAB

2016

Monoclonal Antibody

OLARATUMAB

2016

Monoclonal Antibody

COPPER OXODOTREOTIDE CU-64

2016

Diagnostic

LIFITEGRAST

2016

From the discoverer(s):

"Lifitegrast, previously referred to as SAR 1118, is a member of the class of direct competitive LFA-1 antagonists that mimic the binding epitope of LFA-1's cognate ligand ICAM-1. As such, lifitegrast is 'purpose built' for the treatment of DED to bind LFA-1 on leukocytes and block their binding to ICAM-1 in the adhesion, extravasation, migration, activation, cytokine secretion, and proliferation of these leukocytes in inflammatory diseases. […]

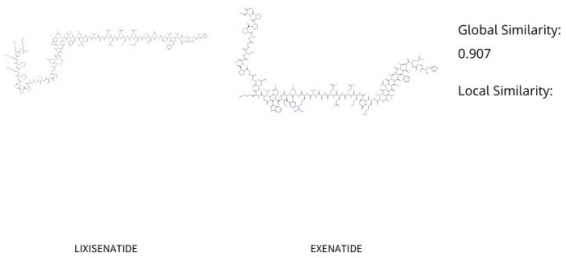
Lifitegrast was discovered in a rational design process that began with alanine point mutagenesis of the ICAM-1 protein to identify the amino acid side chains that were critical for LFA-1 epitope binding. Six key binding residues from the first immunoglobulin domain of ICAM-1 were identified: glutamic acid 34 (E34), lysine 39 (K39), methionine 64 (M64), tyrosine 66 (Y66), asparagine 68 (N68), and glutamine 73 (Q73).50 Although these residues are not directly linked together in the primary amino acid sequence of ICAM-1, they are presented in a spatially contiguous manner within the folded tertiary structure of native ICAM-1 that falls within the dimensions suitable for a novel small molecule. Using the dimensional coordinates obtained through X-ray crystallography and other structural techniques, work was initiated to create small molecule scaffolds that could mimic aspects of this epitope. […]

Each individual module was modified – while holding the remaining modules constant – resulting in the creation of a laborious combinatorial series of over 3,000 analogs. These analogs were further assessed based initially on the potency of LFA-1/ICAM-1 inhibition using an enzyme-linked immunosorbent assay followed by secondary testing using ex vivo cellular immune assays to assess potency of human T-cell inhibition (eg, Jurkat cell and mixed lymphocyte reaction assays). This exhaustive process led to the identification of SAR 1118 – lifitegrast(*667*)"

LIXISENATIDE

2016

Analogue of exenatide




DEFIBROTIDE SODIUM

2016

"Defibrotide was introduced as part of research programs begun in the 1950s for developing compounds derived from mammalian organs, which could be used for the treatment of coagulation and thrombotic disorders, and had a lower risk for hemorrhage than other contemporary anticoagulant therapies. Defibrotide was first identified in 1968 as a phosphorous-containing fraction derived from bovine lung, which was called 'fraction P' and later found to be a fragment of DNA(*668*)."

OBILTOXAXIMAB

2016

Monoclonal Antibody

RESLIZUMAB

2016

Monoclonal Antibody

BEZLOTOXUMAB

2016

Monoclonal antibody

VENETOCLAX

2016

From the discoverer(s):

“Initial efforts to generate a starting point for a BCL-2-selective small-molecule program involved high-throughput and fragment-based screening, along with detailed SAR and structural studies on the acylsulfonamide pharmacophore that is present in compounds such as ABT-737 and navitoclax. The structures of ABT-737 and related analogs in complex with BCL-$X_L$, as well as the structure of navitoclax in complex with BCL-2, revealed key interactions with two hydrophobic pockets, which had been identified previously through alanine scanning as BH3-peptide-binding ‘hot spots’ of BCL-$X_L$. […] This interaction was previously deemed critical for binding to BCL-$X_L$,– the primary protein target for the initial small-molecule inhibitor program. […]

In order to generate a starting point for a BCL-2-selective inhibitor program, compounds that lacked various elements of the dual BCL-$X_L$/BCL-2-binding pharmacophore were evaluated for binding to the two proteins(*669*).”

NUSINERSEN

2016

Antisense oligonucleotide

FLUCICLOVINE F-18

2016

Radiopharmaceutical

ETEPLIRSEN

2016

Antisense oligonucleotide

NALDEMEDINE TOSYLATE

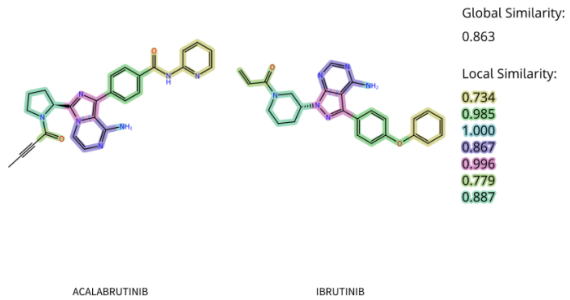
2017

Secondary

ACALABRUTINIB

2017

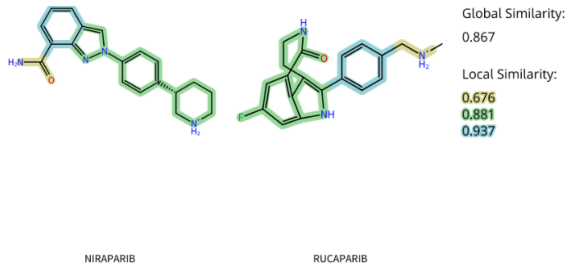
Analogue of ibrutinib




NIRAPARIB

2017

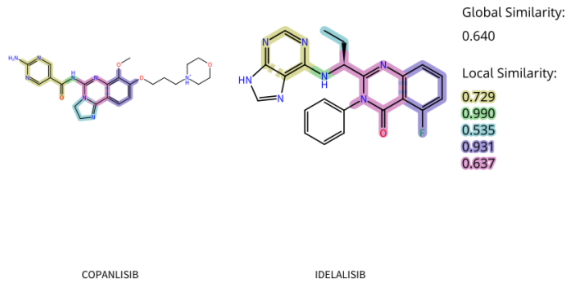
Analogue of olaparib




COPANLISIB

2017

Analogue of idelalisib




OCRELIZUMAB

2017

Monoclonal Antibody

DURVALUMAB

2017

Monoclonal Antibody

ANGIOTENSIN II

2017

Endogenous(*217*)

"Williams and Grossman found that a heat-stable pressor substance having certain qualities similar to epinephrine was formed in the kidney when this organ was perfused. They termed this substance perfusin. Kohlstaedt, Helmer, and Page and Friedman, Abramson, and Marx showed that renin itself is not a pressor substance, and Page and Helmet showed that renin incubated with plasma forms a heat-stable substance which they termed angiotonin. Braun Menendez *et al*. independently made similar observations and termed this substance hypertensin. […] It seems that hypertensin and angiotonin are the same substance and it is quite possible that perfusin is of identical character(*670*)."

From the discovery paper of Williams and Grossman cited in the previous quotation:

"Hypertension may be produced in animals by certain procedures which interfere with the renal blood flow or with the escape of urine. The rise in blood pressure so caused appears to be due to substances formed in the kidney, for it persist after renal denervation, after complete resection of the sympathetic nervous system and even after transplantation of the kidneys; but disappears when the affected kidneys are removed. It has been shown that kidney tissue contains a pressor substance and that the amount of this substance seems to be increased in certain types of renal hypertension. However, attempts to demonstrate a pressor action from blood obtained from the renal veins of animals with experimental renal hypertension have yielded negative results. Since the blood flow through the kidneys is very large in proportion to their size it seems possible that the failure to find pressor effects from renal vein blood may be due to dilution of a small amount of pressor substance with a large amount of blood. Such a difficulty might be overcome by perfusing kidneys removed from the body, using a small volume of perfusion fluid relative to the size of the kidneys. The purpose of this communication is to reports a study of the pressor properties of material obtained in this way.

Kidneys of hogs were obtained from the slaughter house, […] the outflow from the renal vein being collected by means of a funnel.

The pressor property of the perfusate was determined on rats anesthetized with sodium pentobarbital. Blood pressure was measured(*671*)"

From the paper of Friedman, Abramson, and Marx cited in the first quotation of this entry:

"Ever since it was found that persistent hypertension can uniformly be produced in the dog by partially obstructing the arterial blood flow to the kidneys, the mechanism Responsible for the elevation in blood pressure has aroused much interest and speculation. […] We have attempted to investigate further the nature, mode and site of action of this substance.

The pressor effect of the extracts was tested upon anesthetized dogs in which blood pressure was recorded directly from the femoral or the carotid artery with a mercury manometer. […]

The extracts were also tested upon the isolated dog's tail and the isolated dog's kidney, perfused with titrated blood or Tyrode solution(*672*)."

From the paper of Kohlstaedt, Helmer, and Page cited in the first quotation of this entry:

"The purpose of these experiments was to learn something of the nature of the pressor action of renin. Renin was prepared from pig's kidneys in such concentration that an amount containing less than 2 mg of nitrogen produced a sharp, sustained rise of blood pressure in an unanesthetized dog. Its

vasoconstrictor action was studied on perfused dogs' tails(*673*)"

From the discovery paper of Page and Helmer cited in the first quotation of this entry:

"Renin is a protein-like substance extractable from normal kidneys which, when injected intravenously into animals, causes prolonged rise in arterial blood pressure (Tigerstedt and Bergmann, 1898). When purified by the method of Helmer and Page (1939), it was found to be highly active when injected into intact animals, but produced no vasoconstriction when perfused with Ringer's solution through a dog's tail or rabbit's ear. Kohlstaedt, Page, and Helmet (1939) found that the pressor activity could be restored by addition of a protein-like substance contained in plasma and red blood cells. They designated this substance renin-activator to connote only that renin was inactive as a pressor substance without it. […] In short it was found that a pressor substance was produced which was heat-stable and which yielded crystalline derivatives. For this substance we suggest the name "angiotonin".

*Animal Assay* Cats were employed as test animals. […]

*Pressor Action*.-Angiotonin produces a sharp rise in blood pressure similar to that of adrenaline, but usually slightly more prolonged when injected intravenously in a single dose(*674*)."

From one of the co-authors of the article of Braun Menendez *et al* cited in the first quotation of this entry:

"[W]e found that dog kidneys, either grafted in the neck of recipient dogs or perfused with defibrinated blood with a Schuster-Dale pump, released a pressor substance within minutes after 80-90% reduction of the blood flow.10 The pressor activity of the venous blood was tested by intravenous injection of 20-40 ml of the venous blood of these kidneys into nephrectomized dogs. The blood pressure of the recipient dogs rose slowly, and the elevation persisted for more than 30 minutes, resembling the effect found by grafting of ischemic kidneys. The pressor activity persisted after bilateral vagotomy, atropine, cocaine, or injection of the sympathiolytic drug Fourneau 933. Nephectromized dogs were more sensitive to the pressor substance. At this point, we had developed a fairly abundant source of the pressor substance and a semiquantitative method to estimate the pressor activity of the blood.

We were now ready to proceed to the next step: The identification of the pressor substance. […]

After trying the toad preparation that had been previously used by Taquini to test for the activity of the various extracts, we decided to use dogs, a more expensive but a more reliable method of assay. […]

Extracts of the venous blood from the ischemic kidneys made by the addition of 3 volumes of acetone were found to increase arterial pressure of the dogs, whereas extracts made from venous blood of normal kidneys failed to raise pressure. The blood pressure rose abruptly, but the increase lasted for only a few minutes. We were puzzled, as we expected a long-lasting rise similar to that induced by grafting an ischemic kidney or by the injection of the venous blood from an ischemic kidney.

The pressor substance was thermostable, insoluble in ether, and had a vasoconstrictor action on the vascular bed of the toad. Its chemical and pharmacological properties were different from those of other pressor substances known at that time. We called it hypertensin because we believed it to be the humoral mediator of renal hypertension(*675*)."

SARILUMAB

2017

Monoclonal Antibody

LETERMOVIR

2017

From the discovery paper:

"In our attempt to discover novel anti-HCMV compounds that could potentially yield new therapeutic agents, we identified 3,4-dihydro-quinazoline-4-yl-acetic acid derivatives as a novel class of compounds with anti-HCMV activity by screening a compound library in a high-throughput manner. Hit-to-lead optimization activities, including extensive structure-activity relationship studies and pharmacological analyses (unpublished data), led to the discovery of AIC246(*676*)."

It is not determined if the discovery assay was a biochemical enzyme-based assay or a phenotypic cell-based assay. In the discovery paper, results of the following assays are reported, yet it is not known certainly whether the discovery assay was among these reported assays or not. However, as all the reported assays in the discovery paper are phenotypic, it sees that the discovery was also phenotype-based(*676*):

- ✓ HCMV cytopathic effect reduction assay
- ✓ HCMV plaque assay
- ✓ HCMV fluorescence reduction assay
- ✓ Cytotoxicity assay
- ✓ Focus expansion assay. "Briefly, late-stage-infected fibroblasts were cocultured with an excess of uninfected fibroblasts for 5 days in the presence or the absence of 50 nM AIC246"
- ✓ Kinetic block release assay. "NHDF cells grown in six-well plates were infected with AD169 at an MOI of 0.1."
- ✓ Time-of-addition assay. "NHDF cells were cultured in black 96-well plates and infected with AD169-GFP."
- ✓ Mouse xenograft model

PLECANATIDE

2017

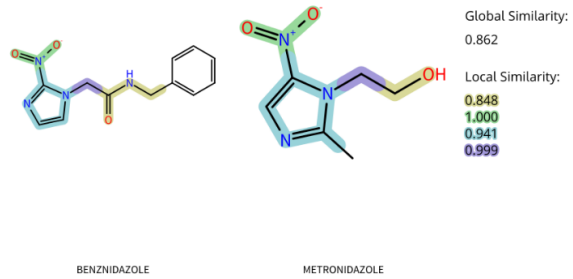
Analogue of the endogenous uroguanylin(*1*)

Error in similarity calculation by FTrees because of the unsupported macrocycle

BENZNIDAZOLE

2017

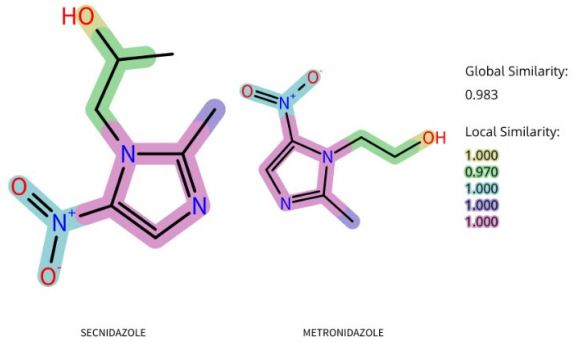
Analogue of metronidazole




SECNIDAZOLE

2017

Analogue of metronidazole




VOXILAPREVIR

2017

Analogue of paritaprevir

Error in similarity calculation by FTrees because of the unsupported macrocycle

GLECAPREVIR

2017

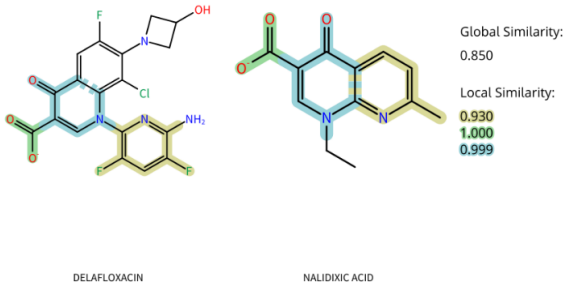
Analogue of paritaprevir

Error in similarity calculation by FTrees because of the unsupported macrocycle

## DELAFLOXACIN

2017

Analogue of nalidixic acid




## NETARSUDIL

2017

From the discoverer(s):

"Aerie's Rho kinase program previously identified the amino isoquinoline amide AR-12286 as a potent ROCK inhibitor ($K_i$ = 2.0 nM) that effectively lowered IOP in animal models and human subjects. The goal of the present study was to discover ROCK inhibitors with a more durable IOP-lowering effect to allow once-daily dosing in patients. We describe the discovery of novel amino-isoquinoline amide ROCK inhibitors that provide a longer duration of IOP-lowering effect in animal models than previous ROCK inhibitors. The most effective compounds were also found to have inhibitory activity against the norepinephrine transporter.

The α-aryl α-amino isoquinoline analog **2** displayed potent ROCK2 inhibition ($K_i$ = 1.5 nM) but was less effective at disrupting focal adhesions and actin stress fibers in cell-based assays conducted with SV-40 transformed human trabecular meshwork cells (HTM) and primary porcine trabecular meshwork cells (PTM), respectively. Analogs including α-aryl-β-amino isoquinoline **3** and α-aryl-β-amino isoquinoline **6**, with extended alkyl-amino arms, displayed a significant improvement in both HTM and PTM assays. The β-amino analog **3** was twice as potent against ROCK2 ($K_i$ = 0.8 nM) relative to the α- and γ amino analogs **2** and **6**, respectively ($K_i$ = 1.5 nM). Furthermore, the S-enantiomer **4** of the b-amino analog **3** was 42 times more potent against ROCK2 than the R-enantiomer **5**. […]

Analogs **2**, **3** and **6** were then compared to AR-12286 and SNJ-1656 for their ability to lower IOP in Dutch Belted rabbits. […]

The long duration of IOP lowering for **3** was a unique feature relative to the ROCK inhibitors AR-12286 and SNJ-1656, as well as other published ROCK inhibitors. To screen for potential activity against other targets, **3** was tested against a panel of 79 human proteins including transmembrane receptors, transporters, channels, and CYTP450s.

For comparison, AR-12286 was screened against the same panel. When assayed at a concentration of 10 μM, **3** produced ⩾70% inhibition against 5 proteins: norepinephrine transporter (NET), serotonin reuptake transporter (SERT), and CYP450 2C19, 2D6, and 3A4. AR-12286 had no activity against these proteins with the exception of CYP450 2D6 (67% inhibition). The inhibitory activity of **3** against NET and SERT was considered of interest since both adrenergic and serotonergic signaling are involved in IOP regulation, and the adrenergic agonists epinephrine and brimonidine are in clinical use as IOP-lowering drugs for glaucoma. Because of the potent and sustained efficacy of the α-aryl β-amino isoquinoline analog 3, a continued SAR effort was further explored […]

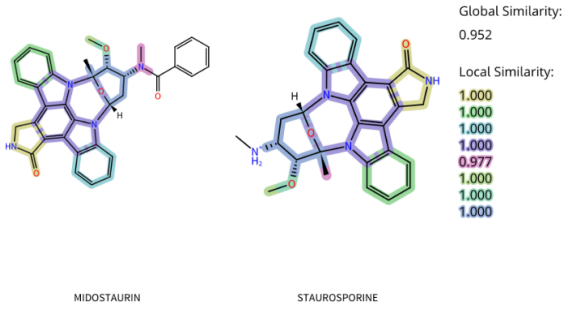
The esters in both classes maintained ROCK2 and HTM activity, though the activity was less that of the respective parent compounds. These compounds were tested for IOP lowering in Dutch Belted rabbits at 0.1% on day one and the dose was increased to 0.3% on day 2. IOP measurements were taken at 1, 2, 4, 8, 24 h after dosing each day. Irritation was scored according to the Draize scale at each time point. To identify the

optimal ester to carry forward, several criteria had to be met. The compound had to be dissolved and stable in a topical formulation. It also had to demonstrate a significant and sustained reduction in IOP with minimal hyperemia and no chemosis(*677*).”

## MIDOSTAURIN

2017

Analogue of staurosporine




Discovery of staurosporine:

From the discoverer(s):

“Staurosporine was discovered in the course of screening for microbial alkaloids in 1977, of which stucture was elucidated to be an indolo [2,3-a] carbazole derivative in the next year, and has been shown to possess various biological activities, including hypotensive activity and inhibitory activity of platelet aggregation other than antifugal activity soon after its discovery(*678*).”

## ENASIDENIB

2017

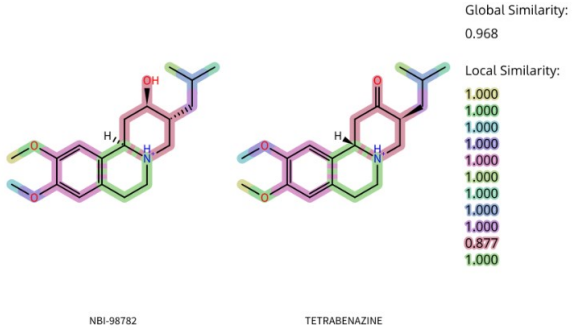
From the discoverer(s):

“In pursuit of drug candidates targeting recurrent oncogenic *IDH2* mutations, we initiated a high-throughput screen for inhibitors of the enzyme carrying the most prevalent *IDH2* mutation in AML, *IDH2*$^{R140Q}$. Several triazine compounds active against the IDH2$^{R140Q}$ homodimer emerged, and initial hit-to-lead chemistry led to compound 1, the first sub–100 nmol/L inhibitor of IDH2$^{R140Q}$(*679*).”

## (+)-ALPHA-DIHYDROTETRABENAZINE

2017

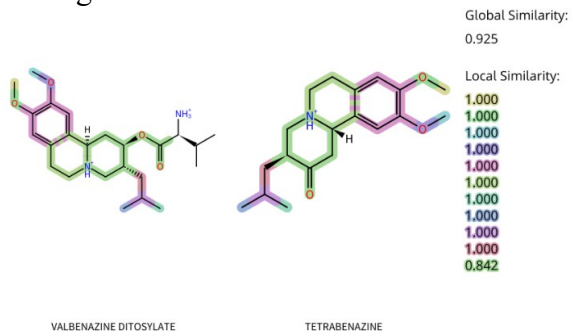
Analogue of tetrabenazine




## VALBENAZINE DITOSYLATE

2017

Analogue of tetrabenazine




## DEUTETRABENAZINE

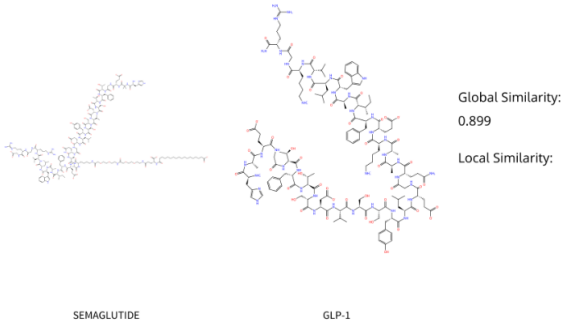
2017

Deuterated tetrabenazine

## SEMAGLUTIDE

2017

“Semaglutide is a glucagon-like peptide 1 (GLP-1) analog used to manage type 2 diabetes along with lifestyle changes, such as



dietary restrictions and increased physical activity. Other members of this drug class include Exenatide and Liraglutide(*2*).”

See the exenatide entry.

ETELCALCETIDE

2017

From the discoverer(s):

“The discovery and development of etelcalcetide started with the unexpected observation that intravenous administration of a cysteine-containing polycationic peptide resulted in a marked PTH reduction in both preclinical models and the clinical setting. This paved the way to the pursuit of peptide-based therapy for SHPT. Since serum PTH is an easy-to-measure pharmacodynamic biomarker that is tightly linked to CaSR activation, peptide optimization to decipher the structure–activity relationship (SAR) was primarily conducted by assessing the impact on serum PTH in rats(*680*).”

TELOTRISTAT

2017

“Lexicon used a high-throughput binding assay for TPH1 to identify compounds with high selectivity for this enzyme. They screened a library of 200,000 agents to choose a candidate for further drug development. They eventually selected telotristat(*681*).”

DUPILUMAB

2017

Monoclonal Antibody

GUSELKUMAB

2017

Monoclonal Antibody

BRODALUMAB

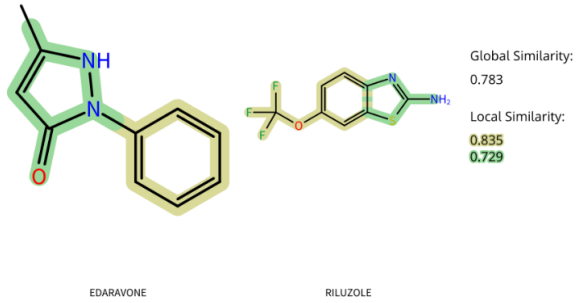
2017

Monoclonal Antibody

EDARAVONE

2017

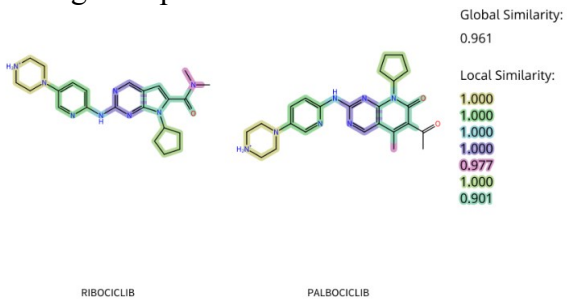
Analogue of riluzole




RIBOCICLIB

2017

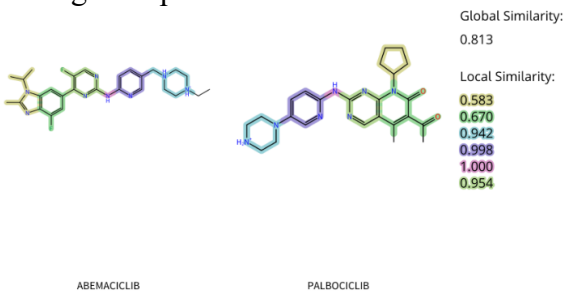
Analogue of palbociclib




ABEMACICLIB

2017

Analogue of palbociclib




MACIMORELIN ACETATE

2017

Diagnostic

CERLIPONASE ALFA

2017

Endogenous-based biopharmaceutical

## GEMTUZUMAB OZOGAMICIN

2017

"Gemtuzumab ozogamicin is a recombinant humanized IgG4 kappa antibody which is conjugated with calicheamicin derivative, a cytotoxic antitumor antibiotic isolated from fermentation of Micromonospora echinospora ssp. calichensis(*2*)."

From the discoverer(s) of calicheamicins, a class of antitumor chemicals which includes ozogamicin:

"The calicheamicins are produced by the fermentation of *Micromonospora echinospora* ssp *calichensis*, a bacterium isolated from a chalky, or caliche, soil sample collected in Texas. They were discovered in the mid-1980s in a fermentation products screening program through the use of the biochemical induction assay (BIA), which utilized a genetically engineered strain of *Escherichia coli* to detect DNA damaging agents. Crude preparations of the BIA positive fermentation broths were evaluated in murine tumor models P388 and B16. Only those demonstrating good efficacy were pursued further(*682*)."

## INOTUZUMAB OZOGAMICIN

2017

Antibody-drug conjugate

See the gemtuzumab ozogamicin entry for ozogamicin.

## ABALOPARATIDE

2017

Endogenous-based biopharmaceutical

Analogue of the endogenous parathyroid hormone-related protein (PTHrP)(*2*)

## EMICIZUMAB

2017

Monoclonal Antibody

## VESTRONIDASE ALFA

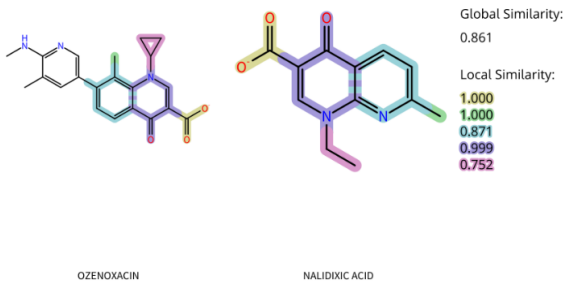
2017

Recombinant lysosomal beta glucuronidase with the same amino acid sequence(*2*).

## OZENOXACIN

2017

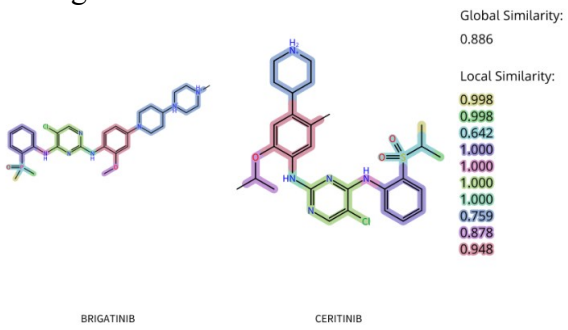
Analogue of nalidixic acid




## BRIGATINIB

2017

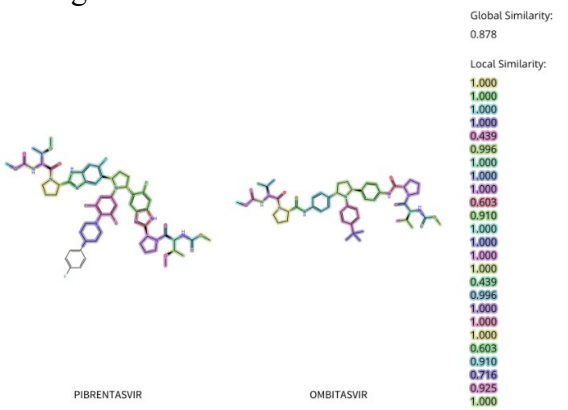
Analogue of ceritinib




## PIBRENTASVIR

2017

Analogue of ombitasvir




## BENRALIZUMAB

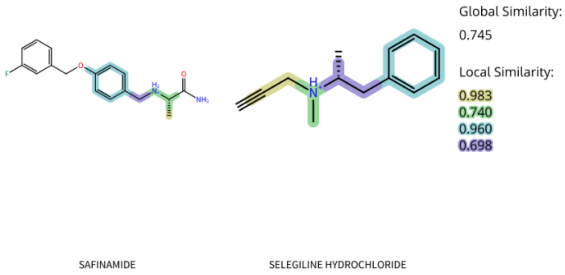
2017

Monoclonal Antibody

SAFINAMIDE

2017

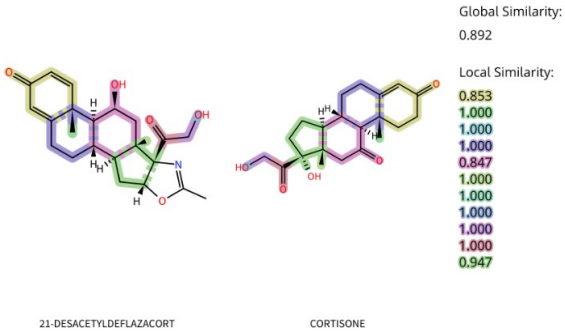
Analogue of selegiline




21-DESACETYLDEFLAZACORT

2017

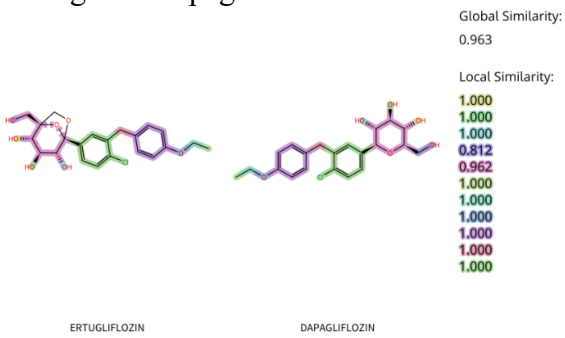
Analogue of cortisone




ERTUGLIFLOZIN

2017

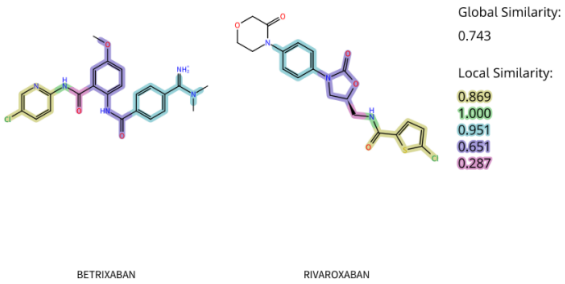
Analogue of dapagliflozin




BETRIXABAN

2017

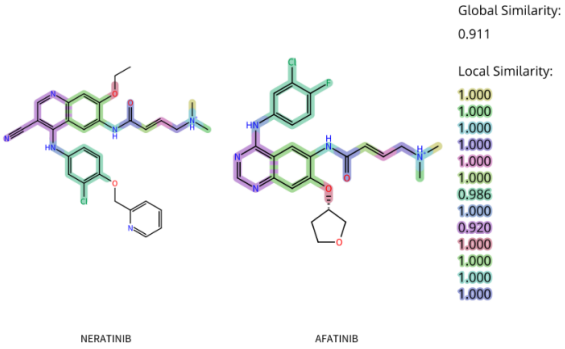
Analogue of rivaroxaban




NERATINIB

2017

Analogue of afatinib




STIRIPENTOL

2018

"Stiripentol (l-[3,4-methylenedioxyphenyl]-4,4-dimethyl-1-penten-3-ol) is a new antiepileptic drug currently undergoing clinical trial. It was selected from a series of aromatic allylic alcohols which demonstrated anticonvulsant and hypnotic activities in rodent screens(*683*)."

I was unable to find the abstract or full-text of the discovery paper cited in the previous quotation:

Astoin J, Marivain A, Riveron A, Crucifix M, Lapotre M, Torrens Y (1978) Action de nouveaux alcools - éthyléniques sur le système nerveux central. Eur J Med Chem 13:41-47

MOXIDECTIN

2018

Analogue of ivermectin

Error in similarity calculation by FTrees because of the unsupported macrocycle

AMIFAMPRIDINE

2018

"4-aminopyridine has been tested, but its usefulness is limited by central nervous system stimulant effects sometimes causing seizures. We have tried another aminopyridine, 3,4-diamino- pyridine (3,4-DAP), in three patients with Eaton-Lambert syndrome. This drug is known from animal experiments to be more potent in improving neuromuscular transmission and less convulsant than 4-aminopyridine(*684*)."

From the discovery paper of 4-aminopyridine cited in the previous quotation:

"Guanidine is a potent drug in this condition but serious adverse reactions have been reported. We have treated a patient suffering from this syndrome with a new drug, 4-aminopyridine. This drug powerfully increases neurally evoked transmitter release from motor nerves possibly by acting directly on the calcium channels in the nerve terminal membrane, allowing the inward calcium current during depolarisation of the nerve terminal to become regenerative. The drug has recently been shown to restore neuromuscular transmission in paralysis produced by botulinum toxin in the rat(*685*)."

From the discovery paper of guanidine cited in the previous quotation:

"Recently, I have studied a patient who had a defect of neuromuscular transmission different from those just described. In some respects the defect resembled that which occurs with bronchogenic carcinoma. In the rested muscle, there was a marked depression of the response to a single nerve stimulus. However, facilitation of the response occurred during repetitive stimulation at all rates from 1 per second to 200 per second. There was no depression of successive responses to stimulation at slow rates as is characteristic of myasthenia gravis and the myasthenic syndrome SCCa. Although this defect may prove to be but a variant of that seen in the myasthenic syndrome SCCa, it is sufficiently unique to warrant a detailed study of its characteristics. Some results of electrophysiologic and pharmacologic tests of the defect will be described. […]

The electrophysiologic methods used in this study were described in the last symposium on myasthenia gravis. The muscle action potentials evoked by stimulation of nerves were recorded with electrodes at standard positions on the skin surface over the belly and tendon of the muscle. When responses were to be compared over a period of days, the electrode positions were marked with indelible pencil, so that the position would remain the same in successive tests. The amplitude of the action potentials was measured from the baseline to the peak of the negative spike.

A biopsy of the vastus medialis muscle revealed no abnormality in specimens stained with haematoxylin and eosin, with Masson's trichrome stain and for phosphorylase. […]

Biopsy of the skin was performed by Peter Dyck. The pad of the right fifth digit which had a normal threshold for touch and a 'low-normal' 2-point discrimination had 6.2 Meissner corpuscles per sq. mm., a value low in the normal range. The pad of the right first toe which had an abnormally high threshold for touch and 2-point discrimination had only 0.4 Meissner's corpuscle per sq. mm., a value on the lower border of normal for healthy persons of the same age. Together with the studies of terminal motor innervation, these observations suggest that there is a low grade abnormality of nerve endings. […]

*Tensilon*. […]

*Prostigmin*. […]

*Epinephrine*. […]

*Calcium gluconate*. […]

*Guanidine*. Another drug which increases the amount of acetycholine released from motor

nerve endings by a nerve impulse is guanidine. It proved to be more effective than anticholinesterases in treatment of Patient W. Guanidine increased the response of the rested muscle to a single maximal nerve stimulus and greatly reduced the time required to reach maximal facilitation during repetitive stimulation of the nerve.

A single test dose of the drug was not as effective as prolonged administration. On three occasions, when no drugs had been administered for several days, a single oral dose of 8 to 10 mg. per kg. of body weight was given. The amplitude of the action potentials evoked from the rested hypothenar or thenar muscles by a single maximal stimulus to the ulnar or median nerves increased from 38 to 120 per cent above initial values. The effect reached its peak 45 to 60 minutes after ingestion of the drug and subsided over the next 1 to 2 hours. The twitch response of the muscle increased in a parallel fashion. Paresthesia of the lips, tongue and occasionally of the fingers appeared 30 minutes after the ingestion of the drug and persisted for about 2 hours. This was not disturbing to the patient. Only moderate improvement in performance occurred after the test dose. Walking was a little more brisk and steady. Rising from a chair with arms folded was easier.

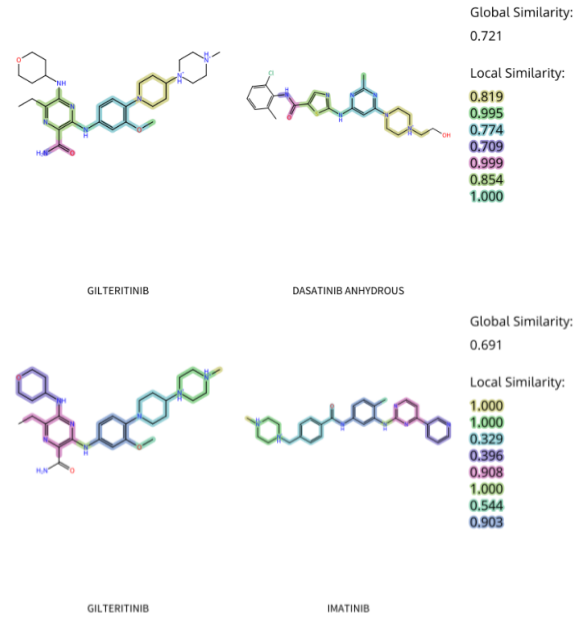
Maximal benefit from guanidine was not obtained until the drug had been taken for several days. The patient felt that he continued to improve for about a week after he began taking the drug. For prolonged use guanidine hydrochloride in capsule or tablet form was taken by mouth in daily amounts of 20 to 30 mg. per kg. divided into four doses. After 30 mgm. of guanidine hydrochloride per kg. of body weight was taken daily for seven days, the muscle action potential evoked by a single maximal stimulus was, on the average, 5.9 times its initial value. Addition of Mestinon to the regimen caused a slight further increase in the response to 6.5 times the initial value. In contrast, Mestinon alone in a dose that was tolerated provided only a fraction of the improvement obtained with guanidine.

After the study illustrated in TABLE 2, the patient continued taking a combination of guanidine and Mestinon. However, he observed that omitting the Mestinon did not appreciably decrease his performance, and since that time he has taken guanidine alone in a dose of 30 mgm./kg. daily. He has discarded his cane, been able to walk briskly and steadily and resumed a number of activities he had not undertaken for several years. He can throw a ball and cast much more accurately(*686*).”

GILTERITINIB

2018

Not found




TAGRAXOFUSP

2018

“Tagraxofusp is an IL-3 conjugated truncated diphtheria toxin. It is composed by the catalytic and translocation domains of diphtheria toxin fused via Met-His linker to a full-length human IL-3(*2*).”

EMAPALUMAB

2018

Monoclonal Antibody

CANNABIDIOL

2018

"Records of the medicinal use of cannabis appear in the Egyptian Ebers papyrus of the sixteenth century BC. Much later, the plant is mentioned in Assyrian texts as a medicinal agent, and in Greek and Roman sources as a minor drug […] We found the skeletal remains of a girl aged about 14 at death in an undisturbed family burial tomb in Beit Shemesh, near Jerusalem. Three bronze coins found in the tomb dating to AD 315-392 indicate that the tomb was in use during the fourth century AD. We found the skeletal remains of a full-term (40-week) fetus in the pelvic area of the girl, who was lying on her back in an extended position, apparently in the last stages of pregnancy or giving birth at the time of her death. […]

Thin-layer chromatography revealed one main spot with an $R_f$ value (0.72) identical with that of $\Delta^6$-tetrahydrocannabinol ($\Delta^6$-THC), a component of cannabis. We confirmed our conclusion using gas chromatography, mass spectrometry and NMR spectroscopy, all of which gave spectra identical with those obtained from authentic $\Delta^6$-THC.

$\Delta^6$-THC is a minor, highly stable constituent of cannabis; its presence presumably indicates conversion of the major components, $\Delta^1$-THC and cannabidiol, into $\Delta^6$-THC, a process known to occur after acid catalysis, apparently during the burning process.

We assume that the ashes found in the tomb were cannabis, burned in a vessel and administered to the young girl as an inhalant to facilitate the birth process. […]

As mentioned above, scattered literary references indicate that cannabis was used for a wide variety of medical conditions well into the twentieth century. In the nineteenth century, its use in obstetrics is cited in several medical publications, one of which indicates that *C. sativa* had the remarkable power to increase the force of uterine contractions, concomitant with a significant reduction of labour pain(*687*)."

"Exact mechanism of action of cannabidiol is not known(*1*)"

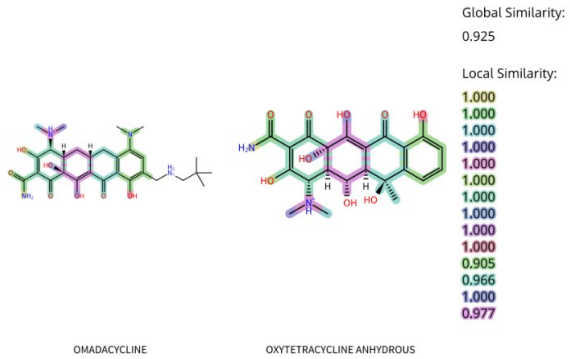
"Cannabis is one of the first plants to have been used as a medicine, for religious ceremonies and recreationally, the first accounts of its use for these purposes stretching back 5000 years

Another finding made at this time, that sleep induced in mice by an unnamed barbiturate can be prolonged by CBD, although not by higher doses of CBN or THC, is also attributable to Loewe (1944)(*688*)."

OMADACYCLINE

2018

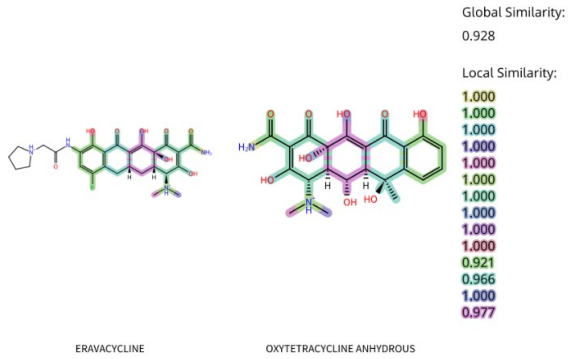
Analogue of oxytetracycline




ERAVACYCLINE

2018

Analogue of oxytetracycline



## TECOVIRIMAT

2018

From the discoverer(s):

"ST-246 was identified in a high-throughput screen of 356,240 compounds in a chemically diverse library. A total of 759 compounds were found to be capable of inhibiting the poxvirus cytopathic effect on tissue culture cells *in vitro*. The effective concentration capable of inhibiting 50% of the cytopathic effect seen in untreated infected cells ($EC_{50}$) was calculated for all 'hits'. They were grouped into nine distinct chemical series based upon the structure of their parent scaffolds. Several chemical series were optimized further based on nascent structure–activity relationships of related analogs. Among these were the tricyclononene carboxamides with $EC_{50}$ values that ranged from 20 nM to the upper limit of measurement (>20 μM). The 4-trifluoromethyl-phenol derivative (ST-246) was selected for further characterization from a group of analogs based on a low $EC_{50}$ and relative metabolic stability(*689*)."

From the discovery paper cited in the previous quotation:

"A high-throughput screening (HTS) format was used to evaluate compounds for their ability to inhibit vaccinia virus-induced cytopathic effect (CPE). The HTS consisted of Vero cell monolayers seeded in 96-well plates (104 cells per well) that were infected with vaccinia virus at approximately 0.1 PFU per cell. At 3 days postinfection, the cultures were fixed with 5% glutaraldehyde and stained with 0.1% crystal violet in 5% methanol. Virus-induced CPE was quantified spectrophotometrically by absorbance at 570 nm(*690*)."

## RAVULIZUMAB

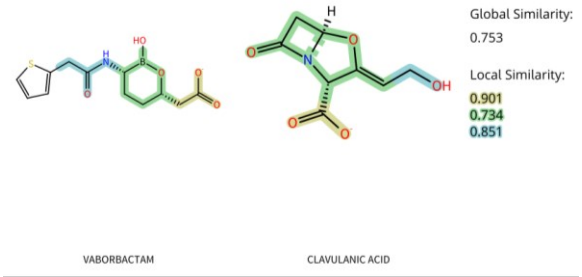
2018

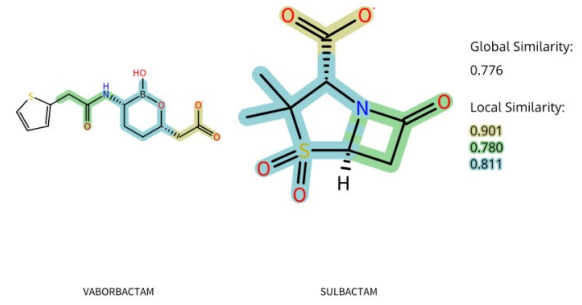
Monoclonal Antibody

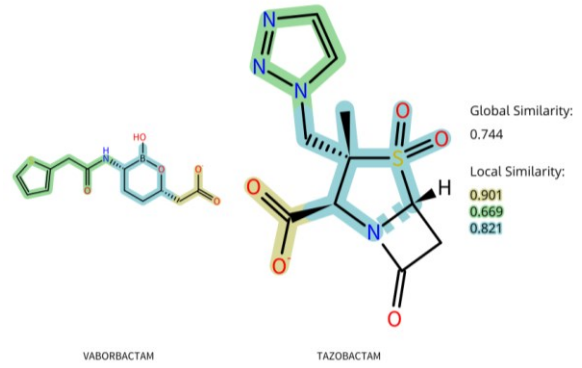
## VABORBACTAM

2017

Analogue of sulbactam



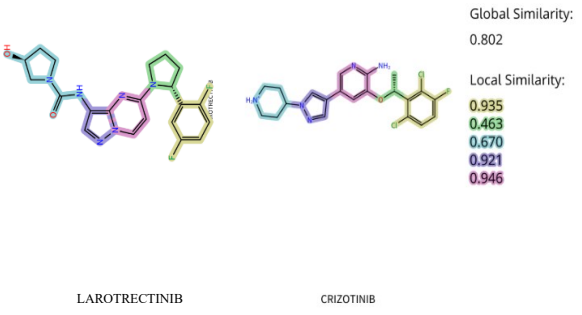




## LAROTRECTINIB

2018

Analogue of crizotinib



## LORLATINIB

2018

Analogue of crizotinib(*691*)

Error in similarity calculation by FTrees because of the unsupported macrocycle

From the discovery paper:

"Compound 1 (PF-02341066, crizotinib), a MET, ALK, and ROS1 kinase inhibitor at clinically relevant drug exposures, was in early clinical trials when the EML4−ALK translocation was identified. The marked efficacies from two clinical trials led to U.S. Food and Drug Administration (FDA) approval in 2011 based on an objective response rate of approximately 60% and progression-free survival (PFS) times of approximately 10 months. Xalkori was the first ALK inhibitor approved by the U.S. FDA as a first-line treatment for ALK-positive lung cancer patients.

Although compound 1 demonstrates initial robust efficacy in ALK-positive tumors, patients eventually develop resistance. […]

Optimization to address emerging resistance to compound 1 was previously described. Table 1 highlights some key compounds from the first- and second-generation ALK inhibitor programs. […]

Structure-based, property-based, and efficiency-focused drug design efforts culminated in broadly potent, permeable, and metabolically stable second-generation ALK inhibitors, highlighted by compound 6a (PF-06439015). […]

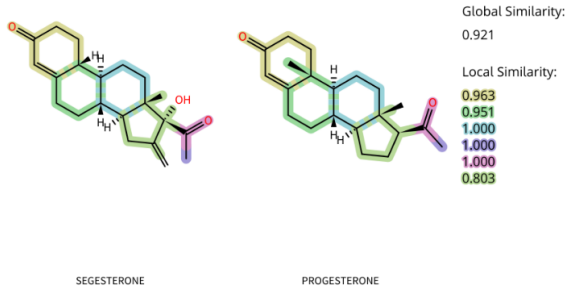
To evaluate the macrocycle design concept, a variety of 12−14-membered ether-linked macrocycles were prepared on the basis of the cocrystal structure analysis of acyclic methyl ether 6b, and the data are summarized in Table 2. According to matched molecular pairs, the smaller ring sizes consistently provided the most lipophilic efficient macrocycles. For example, cyclic ethers 7a, 7c, and 7e had higher LipE than their corresponding larger ring matched molecular pairs 7b, 7d, and 7f. The 12-membered macrocycle 7e displayed the highest LipE (4.4) with picomolar binding affinities and good cellular potencies (ALK IC50 = 1.0 nM; ALK-L1196M IC50 = 20 nM). […]

On the basis of outstanding potency, low in vitro clearance, good selectivity, and low efflux potential, macrocycle 8k emerged as a candidate for further profiling. As revealed in Table 5, 8k demonstrated significantly improved cell activity against ALK and a large set of ALK clinical mutations compared to compound 1(*691*)."

## SEGESTERONE

2018

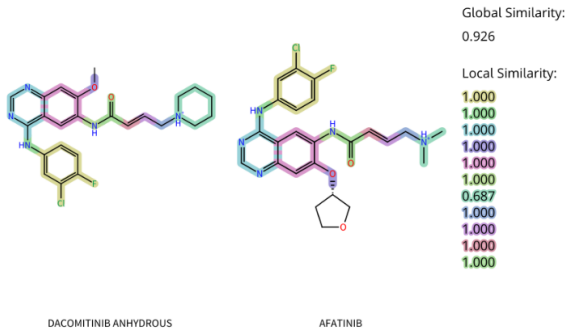
Analogue of progesterone




## DACOMITINIB

2018

Analogue of afatinib




## LUTETIUM OXODOTREOTIDE LU-177

2018

Chelated complex of the radioisotope $^{177}$Lu as a radiotherapeutic

## FOSTAMATINIB

2018

From the discoverer(s):

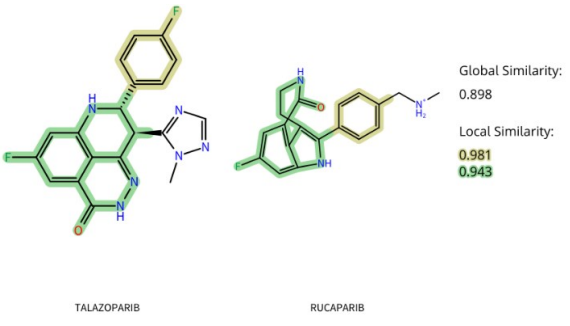
"We used a cultured human mast cell (CHMC) assay to identify small molecules that inhibited IgE-mediated activation through the FcεR1 receptor cross linking with anti-IgE antibodies and hence downstream inhibition of mast cell degranulation, and therefore inhibition of generation and release of inflammatory lipid mediators and cytokines. Control of production and release of leukotriene $LTC_4$, and cytokines and chemokines, for example, TNFα, IL-8, and GM-CSF could be functionally useful mechanism for treatment of inflammatory and autoimmune diseases.

We pursued SAR on compound **1** to improve the upstream anti-IgE mediated CHMC degranulation inhibition as measured by tryptase release. 1a Analog **1** resulted from SAR studies during lead optimization towards intranasal clinical lead R112 for the treatment of allergic rhintis. Gratifyingly compound **1** displays desirable CHMC degranulation inhibition with $EC_{50}$ = 0.540 μM, with approximately 10-fold selectivity over downstream ionomycin mediated tryptase release(*692*)."

## TALAZOPARIB

2018

Analogue of rucaparib



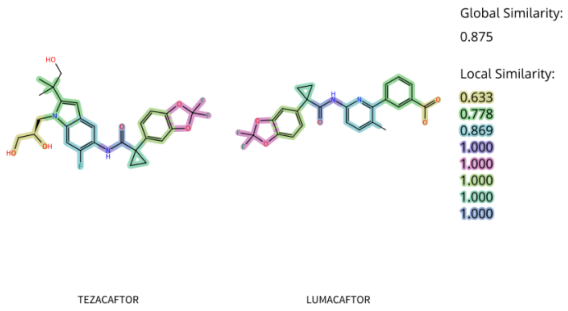

## SODIUM ZIRCONIUM CYCLOSILICATE

2018

## TEZACAFTOR

2018

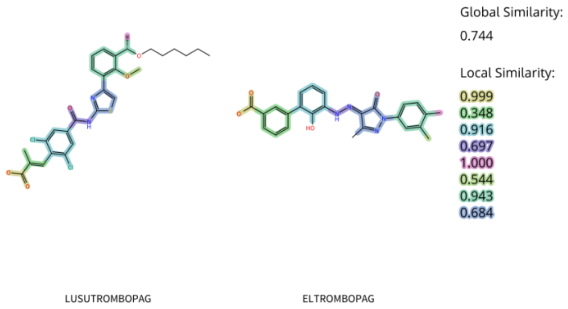
Analogue of lumacaftor




## LUSUTROMBOPAG

2018

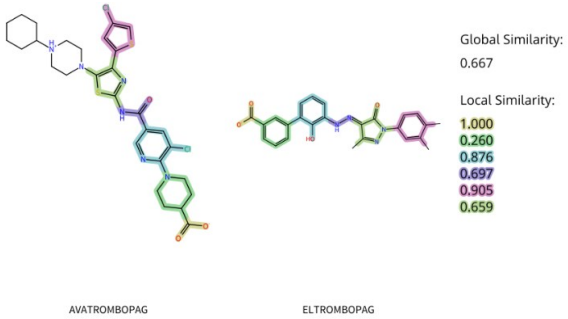
Analogue of eltrombopag




## AVATROMBOPAG

2018

Analogue of eltrombopag




## LANADELUMAB

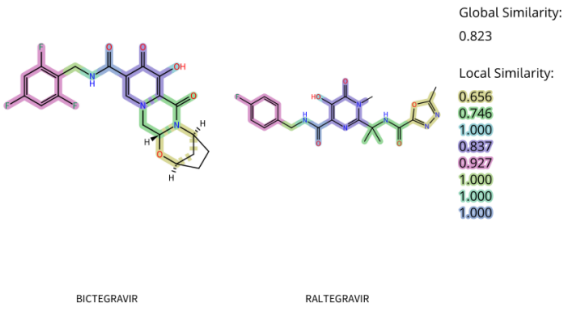
2018

Monoclonal Antibody

## BICTEGRAVIR

2018

Analogue of raltegravir




## ELAGOLIX

2018

From the discovery paper:

"We have previously reported 3-[(2R)-amino-2-phenylethyl]-1-(2,6-difluorobenzyl)-5-(2-fluoro-3-methoxyphenyl)-6-methylpyrimidin-2,4-dione, 4a (NBI-42902), as a potent and orally active antagonist of the human gonadotropin-releasing hormone receptor (hGnRH-R). […]

As a primary assay for establishing structure-activity relationships, synthesized compounds were tested for their ability to compete for binding of the radiolabeled peptide [$^{125}$I-Tyr$^{5}$,DLeu$^{6}$ ,NMeLeu$^{7}$,Pro$^{9}$-NEt]GnRH to hGnRH-R as previously reported. Compounds were also screened for their ability to inhibit a ligand binding to the CYP3A4 enzyme in an *in Vitro* assay.

Although there was no significant difference in binding affinity among the three butyric acids **10a-c** ($K_i$ = 0.9-2.1 nM) in the peptide competition binding assay, their functional activities varied. Compound **10b** had an $IC_{50}$ value of 1.5 nM in the IP accumulation assay, while **10a** ($IC_{50}$ = 27 nM) was 18-fold less potent(*693*)."

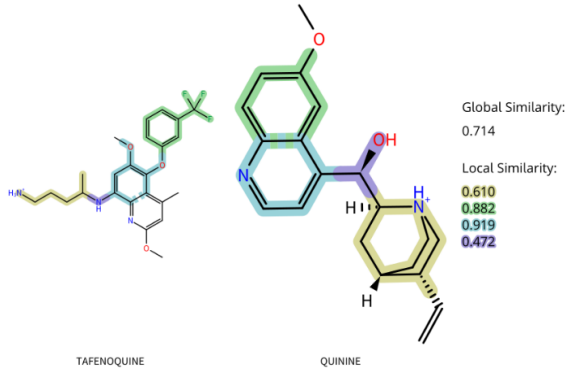
From the discovery paper of NBI-42902:

"The compounds herein synthesized were evaluated for their ability to inhibit [$^{125}$I-Tyr$^{5}$,DLeu$^{6}$ ,NMeLeu$^{7}$,Pro$^{9}$-NEt]GnRH agonist binding to the cloned human, monkey, and rat GnRH-Rs as previously described, and the data are summarized in Tables 1-3. Selected compounds were tested in the inhibition of GnRH-stimulated calcium flux in RBL cells stably expressing the hGnRH-R to determine functional antagonism(*694*)."

## TAFENOQUINE

2018

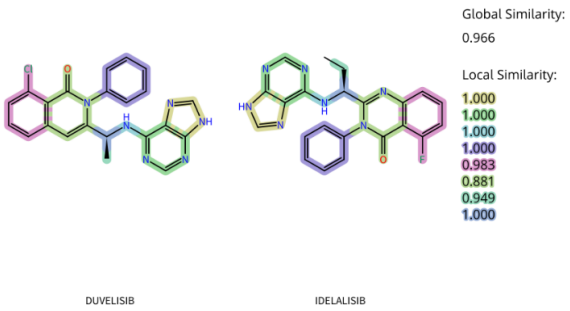
Analogue of quinine




## IVOSIDENIB

2018

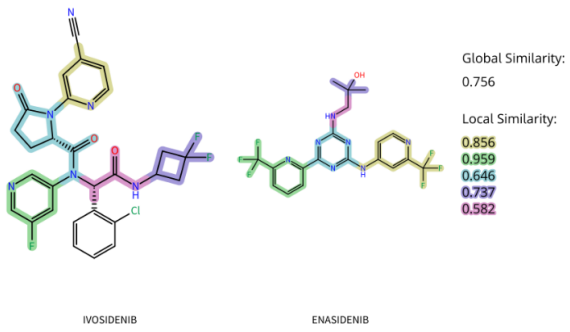
Analogue of enasidenib




## DUVELISIB

2018

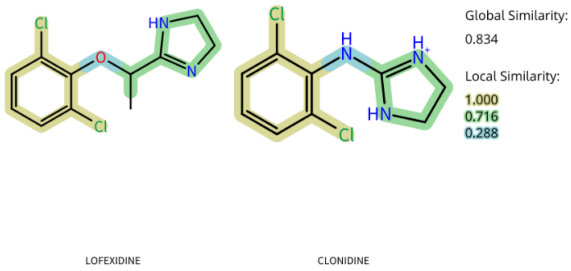
Analogue of idelalisib(*1*)



## LOFEXIDINE

2018

Synthesized as an analogue of clonidine and tested for management of the symptoms of opioid withdrawal for which clonidine had been used off-label(*695*)




"To my knowledge, there was no existing preclinical work in any form detailing the effects of lofexidine on opiate withdrawal prior to the report by a well-rounded team led by Herbert Kleber in 1981 describing the superiority or, at least, the equivalency of lofexidine over clonidine in easing symptomology in opiate-dependent patients(*695*)."

From the discovery paper of the effectiveness of clonidine in managing the symptoms of opioid withdrawal:

"We have given clonidine 5 µg/kg to five male opiate addicts after withdrawal of 15-50 mg chronic methadone treatment. […]

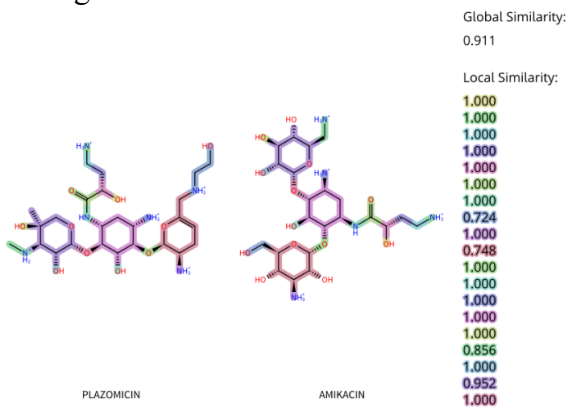
We tried clonidine because of the possibility of a noradrenergic mechanism being responsible for opiate withdrawal, as suggested by studies on a major brain noradrenergic nucleus, the locus coeruleus, in monkeys. The effects of electrical or pharmacological activation of this nucleusl-4 were strikingly similar to those noted after opiate withdrawal. Both morphine and clonidine blocked the effects of activation of the locus coeruleus in primates, correlating with the time course of decreased neuronal activity in the locus coeruleus and decreased noradrenaline release. While clonidine and the opiates have similar effects on the locus coeruleus, clonidine appears to exert specific effects through non-opiate, alpha-2 adrenergic receptors. These data suggested that the opiate-withdrawal syndrome is due to increased noradrenergic neuronal activity in areas such as the locus coeruleus which are regulated both by alpha-2 adrenergic and opiate receptors.

Our preliminary results in man support a noradrenergic system mediation of opiate withdrawal and suggest that clonidine may be a more definitive treatment for opiate withdrawal than others now available(*696*)."

## PLAZOMICIN

2018

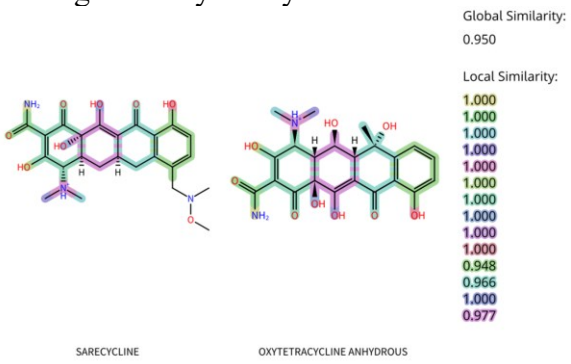
Analogue of amikacin




## SARECYCLINE

2018

Analogue of oxytetracycline




## INOTERSEN

2018

Antisense oligonucleotide

## MOXETUMOMAB PASUDOTOX

2018

Monoclonal Antibody

RIFAMYCIN

2018

It was first discovered in 1963(*220*) (see the rifampin entry). But it was not developed in the US and was optimized to rifampin which was approved by FDA in 1971.

From the discoverer(s):

"An intensive strategy for chemical modification of the basic rifamycin structure was planned, with the aim of obtaining a compound with the following improvements over rifamycin SV in chemotherapeutic properties: better oral absorption; more prolonged antibacterial levels in blood; and greater activity against mycobacterial infections and infections due to gram-negative bacteria […]

Many of these derivatives were extremely active, both in vitro and in vivo, against *M. tuberculosis* and other gram-positive bacteria and were moderately active against gram-negative bacteria. The in vivo activity of some of these derivatives in infected animals was of the same order whether the products were administered orally or parenterally; this observation suggested good absorption from the gastrointestinal tract. In various experimental infections, the hydrazone of 3-formylrifamycin SV with N-amino-N'-methylpiperazine, designated rifampicin or rifampin, was the most active after oral administration and was also the least toxic. Rifampin was therefore selected for clinical studies(*220*)."

GALCANEZUMAB

2018

Monoclonal Antibody

CEMIPLIMAB

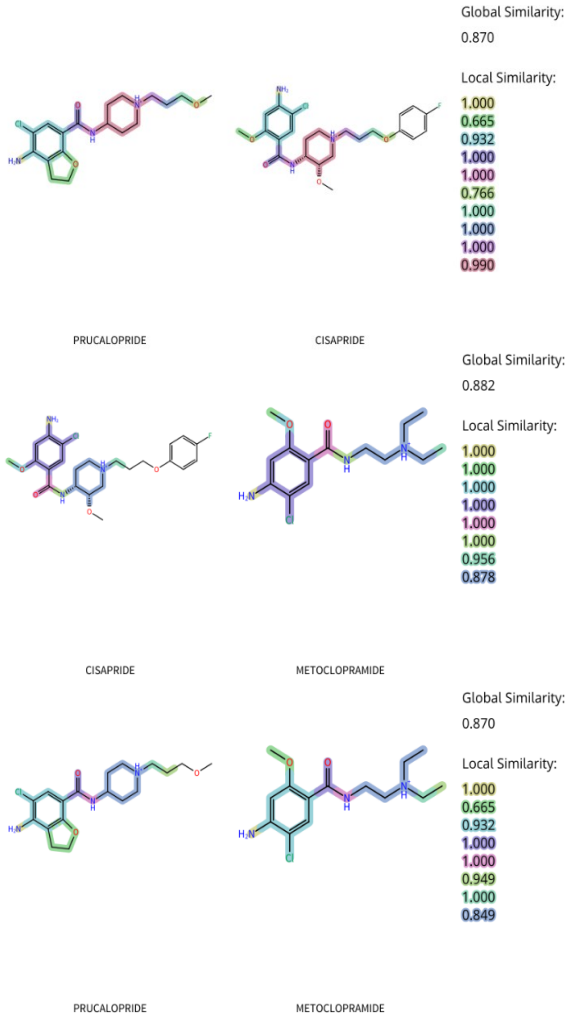
2018

Monoclonal Antibody

PRUCALOPRIDE

2018

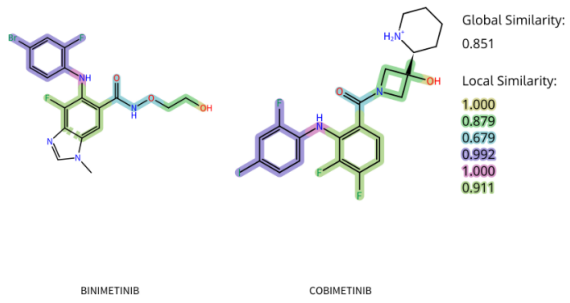
Analogue of cisapride which itself is an analogue of metoclopramide(*697*)




BINIMETINIB

2018

Analogue of cobimetinib

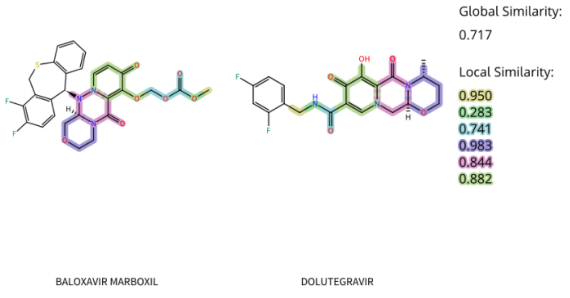


## BALOXAVIR MARBOXIL

2018

“It was not until 2009 that the structure of PA was determined by crystallography, and it was discovered that the viral endonuclease function resides in the N-terminus of the PA subunit. Further study with residues 1–209 revealed highly conserved residues for metal ion binding (H41, E80, D108, and E119) and catalytic activity (K134) typical of type II endonucleases. Mutation of any of these residues results in loss of PA endonuclease activity.

These studies laid the groundwork for rational design of successful inhibitors targeting the active site of the PA endonuclease. Knowing the preferential binding of manganese ions that are essential for its activity, many groups used this to computationally design inhibitors with a metal ion binding structure that could specifically fit within the endonuclease site. The most successful of these groups to date is Shionogi Inc., which designed baloxavir marboxil based off of a metal ion binding integrase inhibitor for human immunodeficiency virus, dolutegravir. Baloxavir acid, the active form of baloxavir marboxil, was designed to be specific for the PA endonuclease. From co-crystal structural data of baloxavir acid bound to PA, it can be seen that stable binding to the active site requires an interaction with two manganese ions and van der Waals interactions with residues-specific to the pocket(*698*).”




## PATISIRAN SODIUM

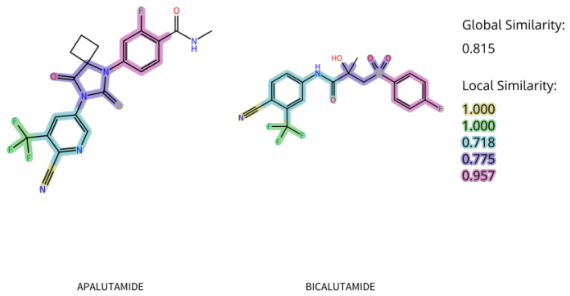
2018

Double-stranded short interfering RNA (siRNA) targeting mRNA

## APALUTAMIDE

2018

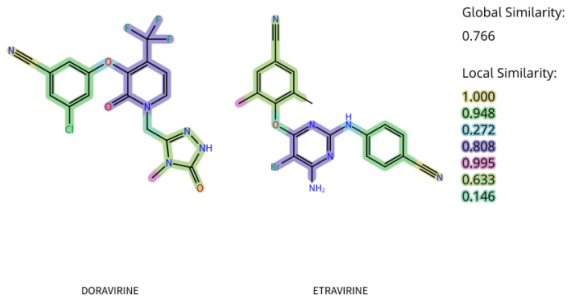
Analogue of bicalutamide




## DORAVIRINE

2018

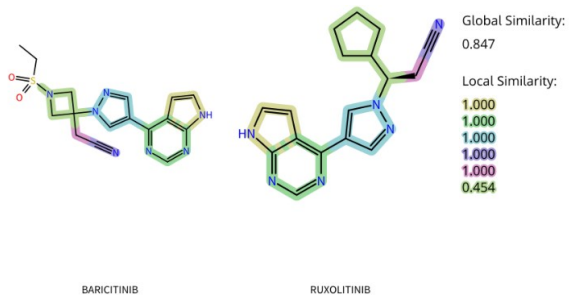
Analogue of etravirine




## BARICITINIB

2018

Analogue of ruxolitinib




## FREMANEZUMAB

2018

Monoclonal Antibody

## MIGALASTAT

2018

"Although it might appear counterintuitive, substrate analogues (glycomimetics) behaving as competitive glycosidase inhibitors are good candidates to perform PC tasks. […]

In 1995, Okumiya et al. reported that galactose restores FD-associated mutant acid α-galactosidase (α-Gal A) activity. Subsequently, Fan et al. discovered that the iminosugar glycomimetic 1-deoxygalactonojirimycin, a potent inhibitor of α-Gal A, restores the intracellular activity of mutant α-Gal A in cultured lymphoblasts from human hemizygous Fabry patients with the R301Q or Q279E mutations(*699*)."

## CALASPARGASE PEGOL

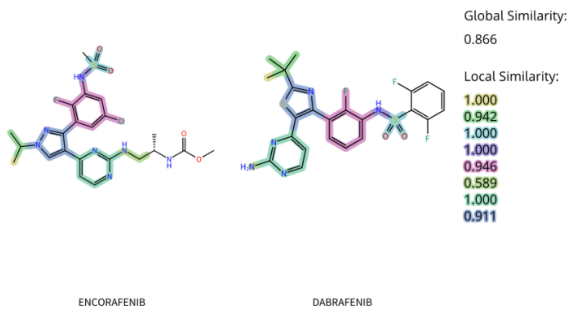
2018

"conjugate of L-asparaginase (L-asparagine amidohydrolase) and monomethoxypolyethylene glycol (mPEG) with a succinimidyl carbonate (SC) linker to create a stable molecule which increases the half-life and decreases the dosing frequency(*2*)"

## ENCORAFENIB

2018

Analogue of dabrafenib




## ELAPEGADEMASE

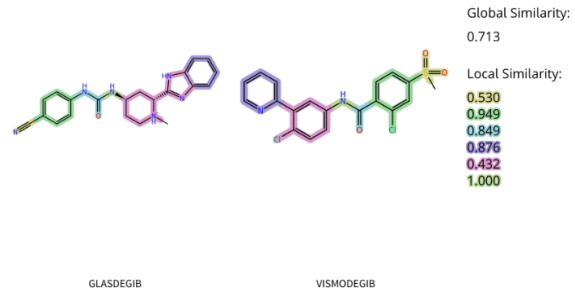
2018

"Elapegademase is a PEGylated recombinant adenosine deaminase. It can be defined molecularly as a genetically modified bovine adenosine deaminase with a modification in cysteine 74 for serine and with about 13 methoxy polyethylene glycol chains bound via carbonyl group in alanine and lysine residues(*2*)."

## GLASDEGIB

2018

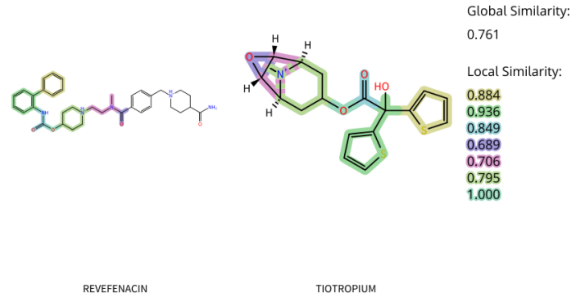
Analogue of vismodegib




## REVEFENACIN

2018

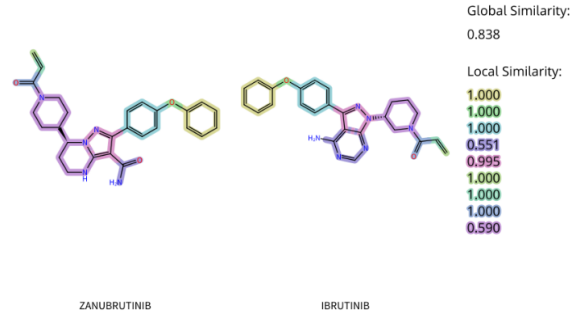
Analogue of tiotropium(*700*)




## ZANUBRUTINIB

2019

Analogue of ibrutinib




## CAPLACIZUMAB

2019

Monoclonal Antibody

BREMELANOTIDE

2019

From the discoverer(s):

"There was for several decades a knowledge that a MC probably regulated some aspect of sexual function in animals, but not humans. There never was any evidence that MSH or ACTH (corticotropin) played a role in reproductive physiology when administered systemically in animals. But

when delivered directly into the third ventricle of the brain of animals, sexual behaviors were elicited suggesting that a MC might act within the central nervous system (CNS) to control sexual function. A role for a MC in human reproductive function provides an interesting story which emphasizes the old adage that 'Chance favors the prepared mind' […]

Around 1984, in collaboration with Victor Hruby and his students, we synthesized and biologically characterized some super potent melanotropic peptides. One of these [Nle$^4$, DPhe$^7$]-substituted MCs, referred to as Melanotan I (MTI), was licensed for commercialization as a tanning agent. This MC is well on its way toward development for use as a potential 'therapeutic tan,' a 'tan from inside-out,' with minimal need for prolonged sun exposure

During the development of MTI, I served as a proverbial 'human pincushion' (a.k.a., guinea pig), that is, I tested the efficacy of the peptide to produce a tan on myself. Therein lies a very interesting story. Our group of University investigators prepared and characterized some fragment [Nle$^4$, DPhe$^7$]-substituted MC analogs that proved to be as potent as MTI, even though structurally only half the size (seven amino acids) of the parent analog. In addition, the melanotropin,MTII,Ac-Nle-c[Asp,HisDPhe,Arg,Trp,Lys]-NH 2 , was conformationally restrained by a lactam bridge to provide a cyclic structure of increased lipophilicity. The smaller molecule is just as active as the larger MTI; it is cheaper to synthesize and might gain access more readily into the body. Based upon these and other considerations, a sterile preparation was provided for injection to determine its tanning potential.

One mistake in my deliberations was made, however. MTI had previously been administered at a dose as high as 10mg without physiological consequences (other than tanning). I forgot, however, that MTII was only about half the molecular weight of MTI. Therefore, when I took an equivalent (10mg) dose of MTII, I inadvertently received about twice the number of molecules of the peptide. Unlike MTI, however, MTII caused a rather immediate, unexpected response: nausea and, to my great surprise, an erection (no figure provided). While I lay in bed with an emesis pan close by, I had an unrelenting erection (about 8h duration) which could not be subdued even with a cold pack. When my wife came upon the scene, she proclaimed that I 'must be crazy.' In response, I raised my arm feebly into the air and answered, 'I think we may become rich.'

Realizing the importance of the observation, I was determined to find out what a lower dose of MTII might do. So several days later, I used half (5mg) of the previous dose. This again elicited an immediate erection which, however, only lasted about 5h with somewhat less nausea. Again, at a later date, I cut the dose in half (2.5mg), and this resulted in an erection of only 2–3h duration, with only minimal nausea. I now knew I was on the right track. So when I administered about half the previous dose (1.25mg) there was no nausea

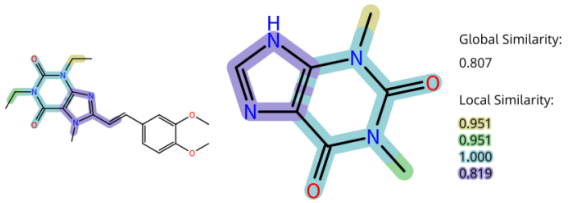
and only a feeble wobble, a response which, however, could be rather easily coaxed to a full erectile response following a few erotic

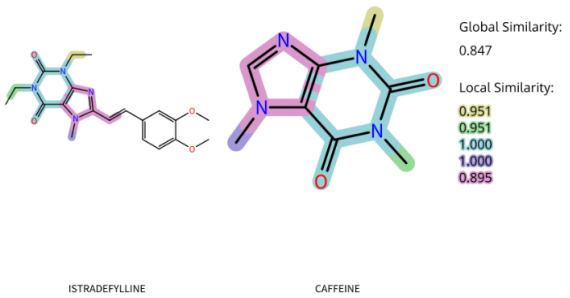
reflections. Further experimentation demonstrated that a dose of about 1.5–2.0mg of MTII invariably induced a full erection without much conscious effort in myself and other volunteers(*701*).”

## ISTRADEFYLLINE

2019

From the discovery paper:




“Methylxanthines such as theophylline and caffeine have been well-known to enhance locomotor activity and the stimulant effects are related, at least in part, to their ability to block adenosine receptors. […]

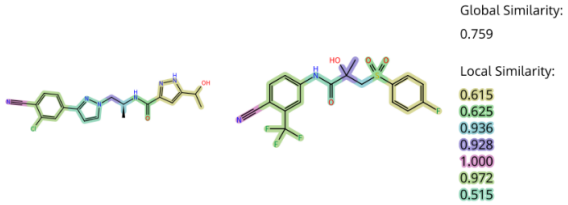
We have reported that 1,3,7-trialkylxanthine derivatives substituted with (E)-styryl groups at the 8-position act as selective $A_{2A}$ antagonists *in vitro*. Oral administration of KF17837, a highly selective $A_{2A}$ antagonist, ameliorated the cataleptic response induced by dopamine $D_1/D_2$ antagonist (haloperidol). In this study, structure-activity relationships of 8-styrylxanthines were explored by varying substituents on the phenyl ring and the 1- and 3-positions of the xanthine moiety to optimize *in vivo* efficacy. […]

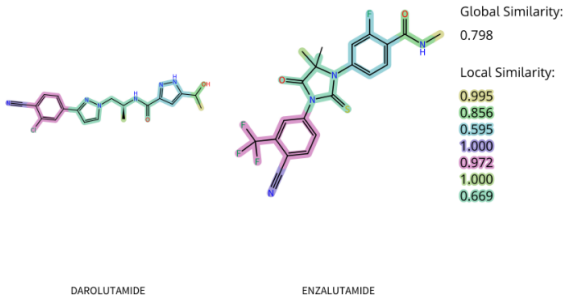
The $ED_{50}$ values of inhibitory activity on haloperidol-induced catalepsy are also presented in the Table. Two or three substitution of the phenyl moiety with methoxy or methyl at 2,3,4-, 3,4,5- and 3,4-position was found to be favored for in vivo activity. Surprisingly, diethyl substitution at the 1- and 3-position dramatically potentiated the anti-cataleptic activity without exception(*702*).”

## DAROLUTAMIDE

2019

Analogue of bicalutamide

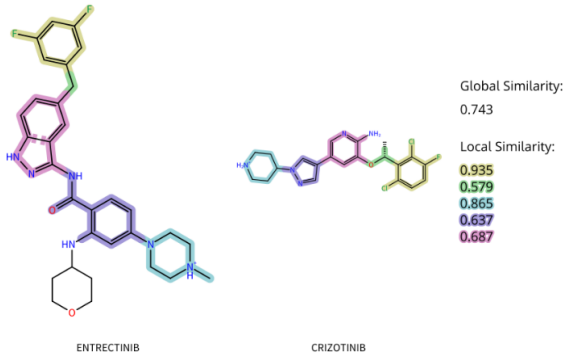



## ENTRECTINIB

2019

Analogue of crizotinib




## ROMOSOZUMAB

2019

Monoclonal Antibody

SELINEXOR

2019

= KPT-330

From the discovery paper:

"Novel selective inhibitors of nuclear export (SINE) targeting XPO1 are being explored as potential therapeutic approaches for treatment of malignancy. Indeed, XPO1 levels are often elevated in tumors when compared with non-malignant cells of the same lineage, including pancreatic cancer, glioma, and cervical cancer. Importantly, elevated XPO1 expression is generally correlated with poor prognosis in these cancers, as well as in osterosarcoma and ovarian cancer. It is thought that XPO1 may support the malignant phenotype by promoting the export of TSP and GRP out of the nucleus. The non-drug-like, natural product leptomycin B (LMB) has been used to potently inhibit XPO1 function and induce anti-proliferative activity in a range of tumor cell lines, including melanoma. This compound is a potent, fully irreversible inhibitor of XPO1 with a novel mechanism of action. However, due to a very poor therapeutic window in animals and dose-limiting emesis, diarrhea and asthenia with lack of therapeutic efficacy observed in a phase I clinical trial of intravenous LMB, no further trials were conducted using this toxic agent. […]

In the present study, we demonstrated that XPO1 expression was elevated in patient primary and metastatic melanomas as compared to nevi. Therefore we hypothesized that inhibition of XPO1 in human melanoma cells would induce nuclear retention of key proteins that promote tumor suppressive pathways and inhibit melanoma cell viability. Treatment of the cells was associated with increased nuclear retention of TP53 and pMAPK, cell cycle arrest, and apoptosis. We utilized a novel platform of SINE compounds that demonstrated significant anti-tumor activity both *in vitro* and using *in vivo* xenograft models of melanoma. […]

Selective Inhibitor of Nuclear Export (SINE) compounds, a family of small drug-like molecules, were provided by Karyopharm Therapeutics, Inc. (Natick, MA). SINE compounds show extremely high selectivity for blocking XPO1 without any significant effects in standard protein screens (including other cysteine-active kinases, caspases and other enzymes), cytochrome P450s, or the hERG ion channel (personal communication, Karyopharm Therapeutics, Inc.). KPT-185 or the 10-100X less active (as an XPO1 inhibitor) trans-isomer (KPT-185-trans) were resuspended in DMSO at stock concentrations of 15.48 mM and 12.66 mM respectively. KPT-276 and KPT-330 were resuspended in DMSO at stock concentrations of 18.77 mM or 18.05 mM respectively(*703*)."

The assays used in the discovery paper(*703*):

- ✓ Growth inhibition and apoptosis in a panel of human melanoma cell lines (A375, Hs294t, FO-1, Wm1366, CHL-1) and three normal human melanocyte cell lines (HEM-l, HEMn-MP, HEMn-DP).
- ✓ Cell cycle assay
- ✓ Subcellular fractionation assay
- ✓ Melanoma murine tumor model

Discovery of leptomycin B, mentioned in the previous quotation:

"In the course of a screening program for substances which cause abnormal morphology on the growth of various fungi, *Streptomyces* sp. ATS1287 was found to produce substances which caused cell elongation of the fission yeast, *Schizosaccharomyces pombe* and hyphal swelling or curling of *Mucor racemosus* and *Mucor rouxianus*.

This strain was found to produce two active substances, named leptomycin A and B (formerly called ATS1287 A and B). […]

The leptomycin-producing strain was isolated from a soil sample collected in Japan(*704*).”

PRETOMANID

2019

From the discovery paper:

“A series of bicyclic nitroimidazofurans, originally investigated as radiosensitizers for use in cancer chemotherapy, were found to possess activity against cultured replicating *M. tuberculosis* (MTB) and had significant *in vivo* activity in a murine infection model. The lead compound in this series, CGI-17341 was mutagenic, discouraging further investigation of the antibacterial activity of the compound series. These studies suggested, however, that the bicyclic nitroimidazoles might be potential antitubercular agents. A series of 328 3-substituted nitroimidazopyrans (NAPs) were synthesized on the basis of the structure of CGI-17341. Over 100 of these compounds possessed substantial antitubercular activity, matching or exceeding that of CGI-17341. The active compounds lacked the mutagenicity previously associated with bicyclic nitroimidazoles. Structure activity relationship studies focusing on antitubercular activity revealed substantial variety in the tolerated substituents at C3, but optimal activity was achieved with lipophilic groups. The stereochemistry at C3 was important for activity, as the *S* enantiomers were generally at least 10-fold more active than the *R* enantiomers. NAP activity was found to be highly specific for the MTB complex, and showed only modest or no activity against mycobacteria outside the MTB complex (*M. avium*, *M. smegmatis*, *M. chelonae* and *M. fortuitum*)(*705*).”

CRIZANLIZUMAB

2019

Monoclonal Antibody

ESKETAMINE HYDROCHLORIDE

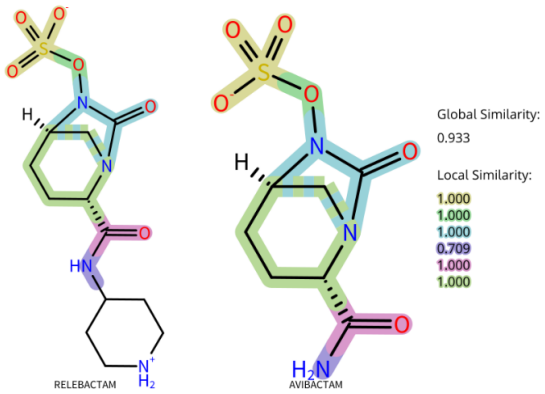
2019

Enantiopure ketamine

RELEBACTAM MONOHYDRATE

2019

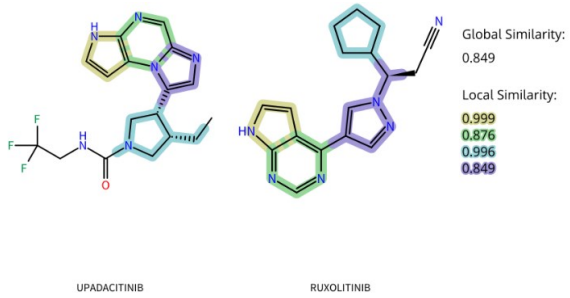
Analogue of avibactam(*2*)




UPADACITINIB

2019

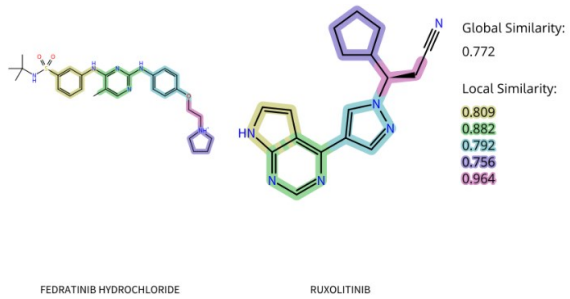
Analogue of ruxolitinib




FEDRATINIB HYDROCHLORIDE

2019

Analogue of ruxolitinib




GIVOSIRAN SODIUM

2019

Antisense oligonucleotide

UBROGEPANT

2019

“The experiments that clearly showed the relationship between the trigeminovascular system and CGRP were performed in cats and humans. The former received electrical stimulation of the trigeminal ganglion, whereas thermocoagulation to treat trigeminal neuralgia was studied in humans. In both cases, CGRP levels, measured in the external jugular vein, were elevated. The first studies that confirmed the importance of CGRP in migraine date from the early 1990s. Similarly, blood from the external jugular vein was obtained during the occurrence of a migraine attack showing increased CGRP. Interestingly, treatment of migraine attacks with migraine-specific acute medications, sumatriptan or dihydroergotamine, was capable of antagonizing this effect. The role of CGRP in migraine was reinforced in a placebo-controlled study in migraineurs. The infusion of CGRP, 2 mg/min for 20 minutes, led to headache in all participants and the headache onset was immediate in the majority (8/9). Initially, only C-terminal fragments of the peptide, such as CGRP(8–37), were available to act as antagonists and were not suitable for in vivo investigations. In 2000, the first CGRP receptor antagonist was developed.

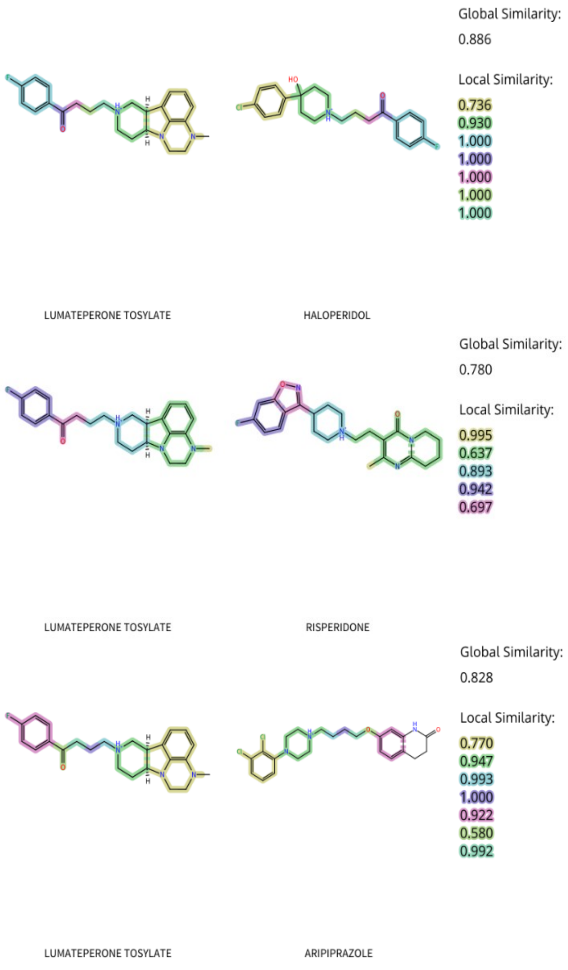
The only CGRP receptor monoclonal antibody, erenumab, has shown efficacy in the preventive treatment of episodic and chronic migraine. Erenumab has also shown efficacy in patients who were refractory to up to four headache preventives and in patients with medication overuse. […]

Ubrogepant is (3’S)-N-((3S,5S,6R)-6-methyl-2-oxo-5-phenyl-1-(2,2,2- trifluoroethyl)piperidin-3-yl)-2’-oxo-1’,2’,5,7-tetrahydrospiro[cyclopenta[b]pyridine-6,3’-pyrrolo[2,3- b]pyridine]-3-carboxamide. It was developed to avoid the hepatotoxicity of its predecessors, telcagepant and MK-3207. Ubrogepant is highly selective and its affinity at the human CGRP receptor showed a mean Ki of 0.067 ± 0.04nM in SK-N-MC cells. The $IC_{50}$ was 0.08 nM and the pKi was 10.2(*706*).”

LUMATEPERONE TOSYLATE

2019

Analogue of haloperidol




RISANKIZUMAB

2019

Monoclonal Antibody

GOLODIRSEN

2019

Antisense oligonucleotide

VOXELOTOR

2019

From the discovery paper:

"Sickle cell disease (SCD) is caused by a single mutation in the $\beta$ chain of hemoglobin (Hb) where a hydrophilic $\beta$Glu6 has been exchanged for a hydrophobic $\beta$Val6. Under low oxygen conditions the mutant hemoglobin (HbS) polymerizes via the mutated $\beta$Val6 from one Hb tetramer and a hydrophobic cavity formed by $\beta$1Ala70, $\beta$1Phe85, and $\beta$1Leu88 from a laterally located Hb tetramer. These polymers result in the red blood cell (RBC) losing its deformability properties and taking on a sickle-like shape. […]

An approach to therapy would be to maintain the HbS in the oxygenated state, as polymerization occurs only in the deoxygenated state under hypoxic conditions. The natural product, 5-hydroxymethylfurfural (5HMF), was shown to bind to HbS via a reversible Schiff-base linkage to the N-terminal valine of the α chain, and thereby prevent polymerization by inducing an allosteric conformational change that increases the oxygen affinity of the HbS. More potent synthetic aldehyde analogues of 5HMF such as BW12C79 and Tucaresol were developed earlier and shown clinically to reduce hemolysis when 20−30% of the HbS is modified. Neither BW12C79 nor Tucaresol was developed further although 5HMF is reported to be in a clinical trial. […]

we elected to study further analogues bearing a bicyclicaromatic B-ring. […]

As our hypothesis was that compounds that improved the affinity of HbS for oxygen should prevent polymerization when HbS is subjected to hypoxic conditions, we developed a polymerization assay to confirm activity of the most potent compounds identified in the whole blood assay(*707*)."

From the paper cited in the previous quotation regarding the discovery of the natural lead structure, 5HMF:

"This hypothesis has proven to be viable, as two Compounds-vanillin and 12C79 that shift the allosteric equilibrium to the high-affinity Hb-have shown antisickling properties. […]

In the current studies, we combined the use of aldehydic covalent modifiers of Hb with our knowledge of the molecular regulation of the allosteric equilibrium to produce potent antisickling compounds that should be clinically safe. Specifically, we examined 5-hydoxy-methyl-2-furfural (5HMF) and several of its analogues, including furfural (FUF), 5-methyl-2-furfural (5MF), and 5-ethyl-2-furfural (5EF) for their anti-sickling potencies. These compounds significantly shift the allosteric equilibrium to the high-affinity Hb and also act as potent inhibitors of SS cells sickling. In fact, one of the compounds, 5HMF, was about 3.5 times more potent than vanillin in inhibiting the sickling of SS cells. […]

Vanillin is clinically tested for SCD therapy and was studied with the examined heterocyclic aldehydes, also referred to as furanic compounds. We have also previously published detailed functional and antisickling properties of vanillin(*708*)."

Used assays(*708*):

- ✓ Oxygen Equilibrium Studies with Normal Whole Blood
- ✓ Oxygen Equilibrium Studies with Homozygous Sickle Red Blood Cells
- ✓ Transport through Homozygous Sickle Red Blood Cells Membrane and Reaction with HbS
- ✓ Antisickling Studies with Homozygous Sickle Red Blood Cells
- ✓ The Effect of Compounds on Homozygous Sickle Red Blood Cells Size

## ERDAFITINIB

2019

From the discoverer(s):

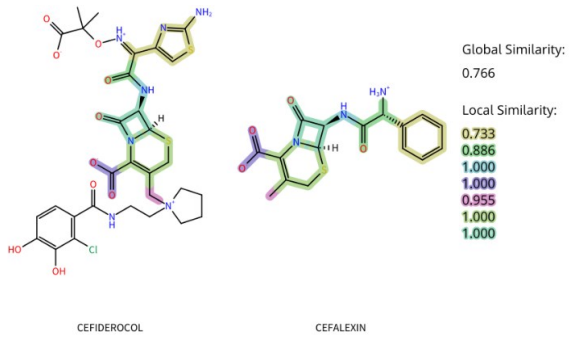
"In 2006, at the time of the collaboration initiation between NICR and Astex, most FGFR inhibitors in clinical development also inhibited VEGFR2, and VEGFR2 inhibition was believed to be linked to hypertension, limiting the ability to reach the exposure required for therapeutic inhibition of the FGFR pathway during dose escalation. Based on this hypothesis, a fragment-based drug discovery screen was initiated with the goal of identifying novel and selective FGFR inhibitors. In early 2008, a fragment-based screening approach followed by combined exploratory chemistry had led to the identification of highly potent and selective FGFR inhibitors from an imidazopyridine series. The compounds from this imidazopyridine series showed promising oral, *in vivo* efficacy against a range of FGFR-dependent human xenograft tumour models and unlike non-selective inhibitors, showed absence of activity against FGFR-independent xenografts models, demonstrating the FGFR selectivity of these compounds. In June 2008, Astex initiated a collaboration with Janssen Pharmaceutica and while extensive lead optimisation efforts were applied to this series, it was also decided to investigate other chemical series.

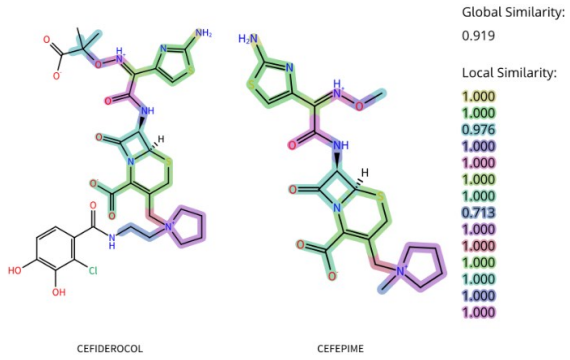
Fortunately, quinoxaline fragments were previously identified and through virtual screening efforts based on their crystal structures with FGFR1, a related analogue, compound 3, was identified. Compound 3 showed FGFR activity and selectivity against VEGFR2. Replacement of the benzyl group in compound 3 by an aniline led to a 30-fold improvement in potency. Superposition of the crystal structure of compound 4 and that of the earlier imidazopyridine series inspired further substitutions of the aniline which led to increased affinity and favourable physicochemical and pharmacokinetic properties. Collaborative lead optimisation culminated in the synthesis of compound 5 (erdafitinib) which was extensively characterized by both teams and advanced by Janssen into clinical development(*709*)."

## CEFIDEROCOL

2019

Analogue of cefalexin

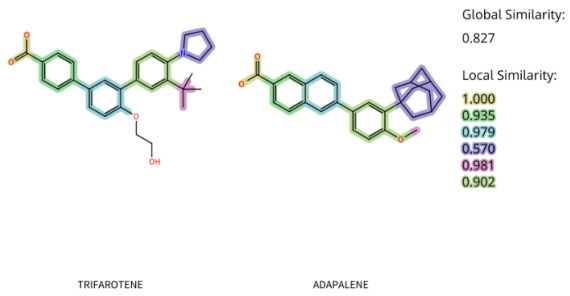



## TRIFAROTENE

2019

Analogue of adapalene




## BROLUCIZUMAB

2019

Monoclonal Antibody

## TAFAMIDIS

2019

From the discoverer(s):

"Transthyretin (TTR) is one of the many proteins that are known to misfold and aggregate (i.e., undergo amyloidogenesis) […]

The TTR amyloidoses associated with point mutations in the TTR gene include familial amyloid polyneuropathy (FAP)

We envisioned that small molecule binding to one or both of the $T_4$ binding sites should stabilize the AB/CD dimer-dimer interface in the dissociative transition state by simultaneously interacting with the A and C and/or B and D subunits across the weaker dimer–dimer interface of the tetramer, analogous to the hydrophobic bridging interactions enabled the T119M mutation. The human genetic data mentioned above along with the corresponding biochemistry strengthened our resolve to discover small molecules that could bind to the normally unoccupied TTR $T_4$ binding sites in blood and prevent amyloidogenesis through kinetic stabilization of the TTR tetramer. This pharmacologic principle was first demonstrated with $T_4$, a natural TTR ligand, and 2,4,6-triiodophenol, when it was found that they inhibited TTR amyloidogenesis. This proof-of-principle experiment justified a robust screening and structure-based drug design program to find small molecule TTR ligands that bind tightly and selectively to TTR, kinetically stabilizing the native, non-amyloidogenic quaternary structure(*710*)."

From the discovery paper:

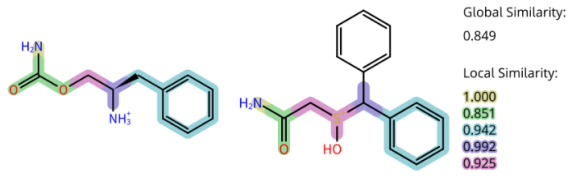
"A previously developed fibril-formation assay was used as the first screen. wtTTR was incubated for 30 min with a test compound. Since at least one molecule of the test compound must bind to each molecule of TTR tetramer to be able to stabilize it, a test compound concentration of 7.2 mm is only twice the minimum effective concentration. […]

The 11 most-active compounds were then evaluated for their ability to bind selectively to TTR over all other proteins in the blood. Human blood plasma was incubated for 24 h with the test compound at 37ºC. The TTR and any bound inhibitor were immunoprecipitated using a sepharose-bound polyclonal TTR antibody. The TTR with or without bound inhibitor was liberated from the resin at high pH value, and the inhibitor:TTR stoichiometry was ascertained by HPLC analysis. Benzoxazoles with carboxylic acids in the 5- or 6-position, and 2,6-dichlorophenyl or 2-trifluoromethylphenyl substituents at the 2-position displayed the highest binding stoichiometries. In particular, exhibited excellent inhibitory activity and binding selectivity(*711*)."

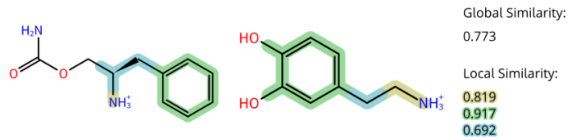
## SOLRIAMFETOL HYDROCHLORIDE

2019

Analogue of epinephrine, dopamine and modafinil




SOLRIAMFETOL HYDROCHLORIDE ARMODAFINIL




SOLRIAMFETOL HYDROCHLORIDE DOPAMINE

## LEVAMLODIPINE

2019

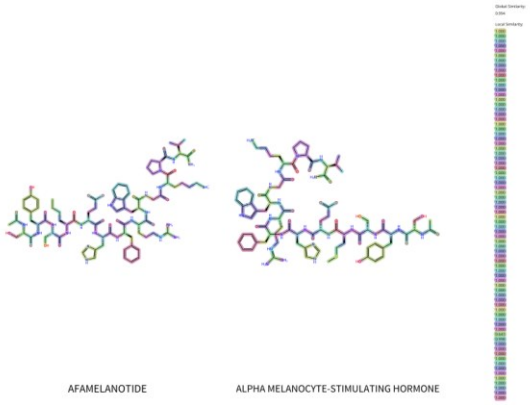
Enantiopure amlodipine

## AFAMELANOTIDE

2019

Analogue of the endogenous alpha melanocyte-stimulating hormone(*2*)

Global Similarity: 0.994




From the discovery paper:

"We report here the synthesis of [Nle$^4$, D-Phe$^7$]-α-MSH and present data demonstrating its unique biological properties. […]

**Frog-Skin Bioassay.** The α-MSH analogues were compared with respect to their ability to stimulate melanosome dispersion *in vitro* using the frog (*Rana pipiens*) skin bioassay

**Tyrosinase Activity.** Cloudman S-91 NCTC 3960 melanoma cells were obtained […] the tyrosinase activity of the melanoma cells was determined by assaying for the $^3H_20$ released from the [$^3$H]tyrosine by the action of tyrosinase.

**Adenylate Cyclase Activity.** Adenylate cyclase activity of the particulate membrane fraction isolated from Cloudin S-91 mouse melanoma tumors was determined by assaying [α-$^{32}$P]ATP conversion to [$^{32}$P]cAMP(*712*)."

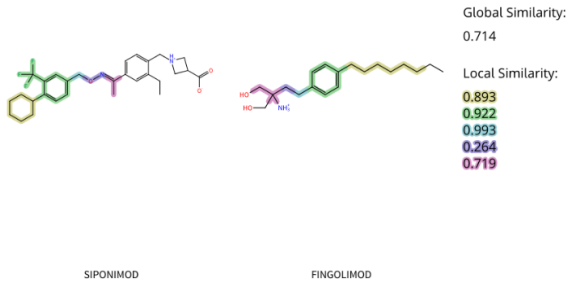
From the discoverer(s):

"The amino acid residues that are important to the biological activity of α-melanottopin have been elucidated by systematic structure-function studies of α-MSH, α-MSH fragments, and related analogs on amphibian melanophores and, more recently, on mammalian melanoma cells(*713*)."

## SIPONIMOD

2019

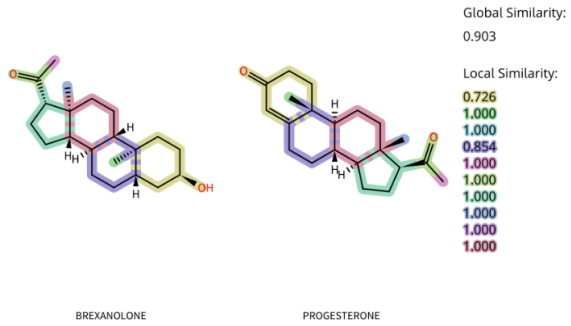
Analogue of fingolimod




## BREXANOLONE

2019

Analogue and one of the metabolites of progesterone




"In 1985 Dalton surveyed the effects of progesterone in 100 women who had previously suffered postnatal depression. A further survey of 181 women was conducted in 1989. The recurrence rate in both surveys was less than 10%. This compares with a postnatal depression recurrence rate of 68% in a historic control group of 221 women with a history of postnatal depression(*714*)."

## LUSPATERCEPT

2019

"Luspatercept is a recombinant fusion protein comprised of a modified extracellular domain of activin receptor type IIB fused to the FC domain of human IgG1(*2*)."

## BRILLIANT BLUE G

2019

Dye

PITOLISANT

2019

From the discoverer(s):

"The third histamine receptor was discovered in 1983 by a traditional pharmacological approach, consisting of assessing the inhibitory effect of histamine on its own release from depolarized rat brain slices. The same *in vitro* test was used to design, in 1987, the first highly selective and potent H3-autoreceptor ligands, the antagonist thioperamide and the agonist (R)alphamethylhistamine which enhances and inhibits, respectively, the activity of histaminergic neurons in brain(*715*)."

"Initially the compounds were tested *in vitro* and *in vivo*. The *in vitro* procedure measured the release of tritiated histamine from synaptosomes prepared from rat cerebral cortex. The synaptosomes were first incubated with [$^3$H]L-histidine at 37ºC and then washed extensively before being resuspended in fresh $K^+$ Krebs–Ringer medium in the presence of the test drug. […]

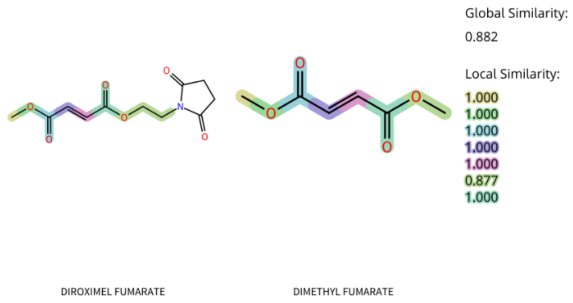
For the *in vivo* test, the compounds were given orally to male Swiss mice as described in. Brain histaminergic neuronal activity was assessed by determination of the main metabolite of histamine, *N-tele*-methylhistamine. After being fasted for 24h, mice were given the test compound orally and were sacrificed 90min later. The brain was then isolated and homogenized. The N-tele-methylhistamine level was determined by radioimmunoassay. The $ED_{50}$ value is expressed as mean ± SEM and is related to the maximal increase given by 3mgkg$^{-1}$ of ciproxifan. […]

The research leading to the discovery of pitolisant was conducted in the era using classical pharmacology and *in vivo* screening of compounds, before the availability of the human or rat recombinant receptor. However in 1999, the human $H_3$ receptor was cloned by Lovenberg and colleagues in Johnson & Johnson Laboratories, San Diego, California. Later, the disclosure of the sequence of the human $H_3$ receptor allowed many pharmaceutical companies to enter the field, and they set up high throughput screens using compound libraries to seek other non-imidazole $H_3$-receptor antagonists. Many such leads were obtained and have generated several compounds in development. At the time of writing, however, no compound is yet on the market(*716*)."

DIROXIMEL FUMARATE

2019

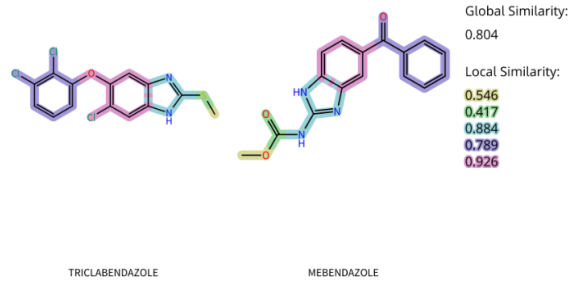
Analogue of dimethyl fumarate(*2*)




TRICLABENDAZOLE

2019

Analogue of mebendazole




ENFORTUMAB VEDOTIN

2019

"Enfortumab vedotin is an antibody-drug conjugate comprised of multiple components. It contains a fully human monoclonal antibody directed against Nectin-4, an

extracellular adhesion protein which is highly expressed in urothelial cancers, attached to a chemotherapeutic microtubule-disrupting agent, monomethyl auristatin E (MMAE). These two components are joined via a protease-cleavable linker(*2*)."

See the discovery of monomethyl auristatin E in the polatuzumab vedotin entry.

## LEFAMULIN ACETATE

2019

"In 1951, the first reference to the antibacterial substance pleuromutilin was made in a paper published in the Proceedings of the National Academy of Sciences. Researchers had identified several species of the mold genus Pleurotus that inhibited the growth of *Staphylococcus aureus*. […]

In the early 1960s, the research groups of Arigoni

and Birch had elucidated the structure and provided first insights into the biosynthesis. Around this time, Brandl and Knauseder from Biochemie, Kundl, Austria, reisolated pleuromutilin from a culture of *Clitopilus passeckeranius* and found that the substance was not only active against penicillin and streptomycin-resistant staphylococci, but also highly active against *Mycoplasma* spp. […] In an attempt to further improve the antimicrobial activity, a series of new derivatives was synthesized between 1963 and 1966, with a strong focus on variations in the C(14) side chain. Already at that time, it was recognized that the number of functional groups was small, which led to the consideration that an 'activation' of the molecule via sulfonic acid esters at the C(14) atom would give the best opportunities for numerous exchange reactions. Of the derivatives generated, the mutilin esters of substituted thioglycolic acids demonstrated superior minimum inhibitory concentration (MIC) values. Further alterations within this group led to the development of the first veterinary pleuromutilin, tiamulin (81.723 hfu), which was approved in 1979(*717*)."

From the 1951 discovery paper of pleuromutilin cited in the previous quotation:

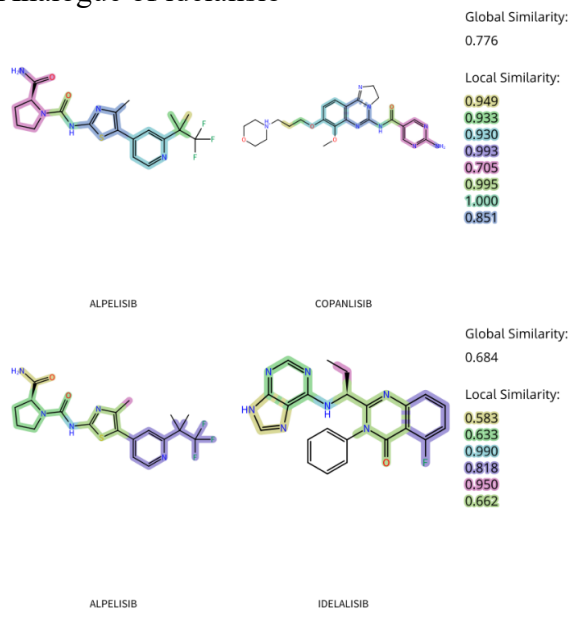
"Several species of the genus *Pleurotus* have been found in this laboratory to form substances inhibitory for *Staphylococcus aureus*. Among these were two species, *Pleurotus mutilus* (Fr.) Sacc. and *P. Passeckerianus* Pilat, obtained from the Centraalbureau voor Schimmelcultures at Baarn. An antibacterial substance formed by these fungi was isolated in crystalline form from culture liquids; it was named pleuromutilin.

*P. mutilus* grown on corn-steep, thiamine-peptone, or potato-dextrose agars for two days and tested by the streak-method, markedly inhibited Staphylococcus *aureus*, inhibited incompletely *Mycobacterium smegma*, and had no effect on *Escherichia coli*. Agar disks cut from colonies 10 days old formed inhibition zones 20 mm. in diameter with *S. aureus* and a small zone of incomplete inhibition with *M. smegma. P. Passeckerianus* produced similar zones of inhibition(*554*)."

## ALPELISIB

2019

Analogue of idelalisib



## CENOBAMATE

2019

From the patent:

"The present invention is directed to neurotherapeutic azole compounds containing a carbamoyl group which are useful as anticonvulsant agents.

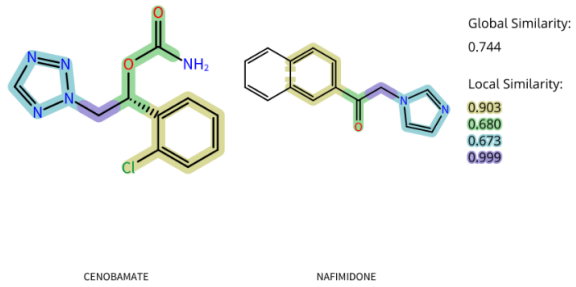
**Background Art**

Many reports have disclosed that arylalkyl azole compounds are effectively used as anticonvulsant, antimicrobial and hypoglycemic agents. One of the structurally distinct classes of antiepileptic drugs is the (arylalkyl) imidazoles.

J. Med. Chem., 24, 67 (1981) and J. Med. Chem., 24, 727 (1981) disclose Nafimidone (2-(lH-imidazole-l-yl)-l-(2-naphthalenyl)ethanone) and denzimol (α-(4-(2-phenylethyl)phenyl)-lH-imidazole-l-ethanol) are two independently discovered representatives of this group and protect mice and rats against maximal electroshock- or pentylenetetrazole-induced tonic seizures but do not antagonize clonic seizures induced by pentylenetetrazole, strychnine, bicuculline, or picrotoxin. These indicated that denzimol and nafimidone possess a profile of activity similar to that of phenytoin or carbamazepine but distinct from those of barbiturates or valproic acid(*718*)."

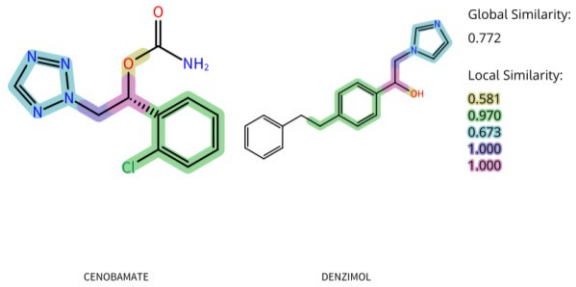
From the discovery paper of nafimidone, cited in the previous quotation:

"The new naphthalene compound **42**, prepared in connection with our interest in imidazole-containing antifungal agents, was submitted to pharmacological screening in the mouse based on its structural resemblance to phenethylamines. Following the finding of anticonvulsant activity, and in view of the clearly expressed need for more selective and less toxic anticonvulsant drugs, we initiated a synthetic program based on this lead. A series of analogues of **42** was prepared and evaluated for anticonvulsant activity in the maximal electroshock assay, with the goal of identifying a compound with an enhanced therapeutic index relative to currently available drugs(*719*)."




From the discovery paper of denzimol cited in the first quotation of this entry:

"A novel series of *N*-(benzoylalkyl)imidazoles and *N*-(ω-phenyl-ω-hydroxyalkyl)imidazoles was synthesized and evaluated for anticonvulsant activity in mice against maximal electroshock induced seizures. Some of the compounds showed an activity comparable to or better than phenytoin and phenobarbital(*720*)."



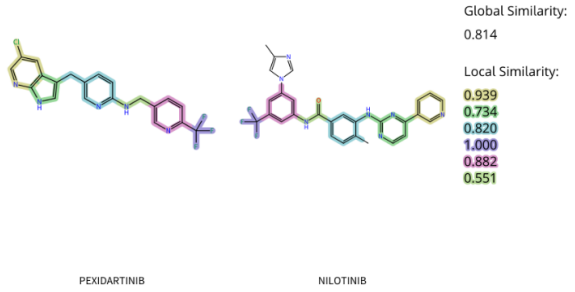

## PEXIDARTINIB

2019

Analogue of nilotinib

"Pexidartinib or PLX3397 was first discovered by Plexxikon Inc., the small molecule structure-guided research and development center of Daiichi Sankyo. Pexidartinib (brand name Turalio) is an orally bioavailable small-molecule tyrosine kinase inhibitor that inhibits CSF-1R and gained Food and Drug Administration (FDA) approval for the treatment of TGCT in August 2019. Pexidartinib

was designed to stabilize CSF-1R in the auto-inhibited state by interacting with the CSF-1R juxtamembrane region, resulting in inactivation of the kinase domain and prevention of CSF-1 and adeno-sine triphosphate (ATP) binding(*721*).”




## POLATUZUMAB VEDOTIN

2019

“Polatuzumab vedotin is a CD79b specific antibody conjugated to the antineoplastic agent monomethyl auristatin E(*2*).”

Discovery of monomethyl auristatin E:

Analogue of dolastatin 10

From the discoverer(s) of dolastatin:

“Certain marine animals were known to the ancients for their potent biological constituents and presumed use in primitive medicine. […]

In 1965-66, we began the first systematic study of marine invertebrates, vertebrates, and plants as a vast untapped resource for discovery of promising new anticancer drugs with the presumed unprecedented structures


necessary to improve human cancer treatment. During the next four years, we evaluated components from many such marine organisms from a broad geographic area that included the Atlantic and Pacific coasts of North and South America and the coasts of Asia. Antineoplastic activity was assessed by use of the Walker 256 carcinoma (intramuscular) and both a lymphoid (L1210) and lymphocytic leukemia (PS) as developed at the U.S. National Cancer Institute. […]

The great Roman natural scientist Pliny the Elder in his comprehensive study of about 60 A.D. first described a most potent Indian Ocean sea hare of the genus *Dolabella*. Extracts from this animal and two related *Aplysia* species from the Mediterranean were well known for their toxic properties during the reign of Nero. […]

By 150 A.D. Nicander recognized the possibility of using such extracts for treatment of certain diseases. In 1568 the French scholar Grevin described in vivid details the potency of extracts prepared from a sea hare presumed to be *Dolabella auricularia.* […]

By October, 1972 our broad geographic exploratory survey of marine organisms for antineoplastic constituents had been extended to the Western Indian Ocean and concentrated in the region from Mauritius to South Africa. With the capable assistance of my marine zoologist colleague, Claude Michel, we were able to evaluate Mauritius specimens of the olive green *Dolabella auricularia*. Against the U. S. National Cancer Institute’s P388 lymphocytic leukemia (PS system), ethanol extracts of *D. auricularia* gave 67 to 135% life extension at doses of 176 to 600 mg/kg. In short, it was a very high priority lead and was pursued on that basis. […]

Because of the complexity of the bioassay-guided (PS *in vivo* cell line) isolation of dolastatins 10-15, a summary has been outlined(*722*)”

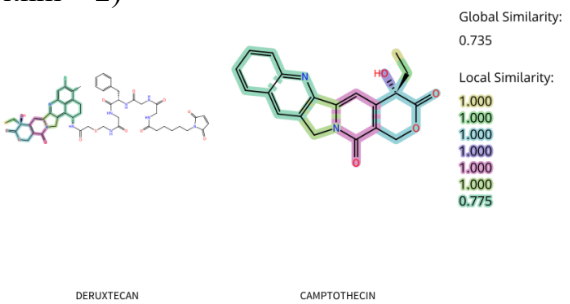
## TRASTUZUMAB DERUXTECAN

2019

“Trastuzumab deruxtecan is a HER-2 directed antibody attached to a topoisomerase inhibitor that is approved for use in certain types of metastatic, unresectable breast cancer. It is classified as an antibody-drug conjugate. The cleavable peptide linker used to bind the antibody and drug in this product distinguishes it from other members of its class. Trastuzumab deruxtecan has been granted FDA approval for specific patients with HER-2 positive breast cancer who have failed other treatments(*2*).”

The discovery of deruxtecan:

Analogue of irinotecan (Comparison Algorithm = 2)




## PRALSETINIB

2020

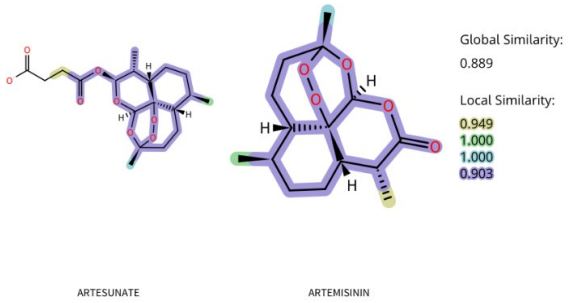
From the discovery paper:

“A library of over 10,000 agnostically designed kinase inhibitors with greater than 60 chemical scaffolds and annotated versus the human kinome was interrogated to identify compounds with inhibitory activity against wild-type (WT) RET and oncogenic RET variants, while maintaining selectivity against other human kinases. Iterative medicinal chemistry optimization was performed with these initial compounds to improve RET potency, selectivity, and pharmaceutical properties, leading to the generation of BLU-667. In biochemical assays, BLU-667 inhibited the kinase activity of WT RET with subnanomolar potency(*723*).”

## ARTESUNATE

2020

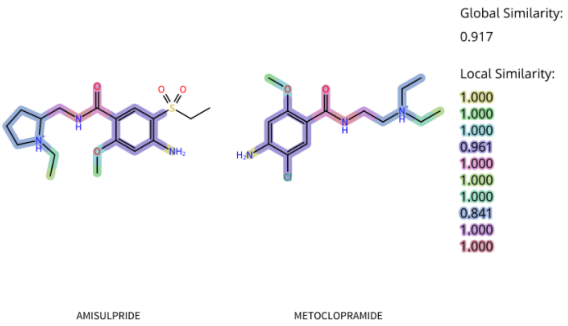
Analogue of artemisinin




## AMISULPRIDE

2020

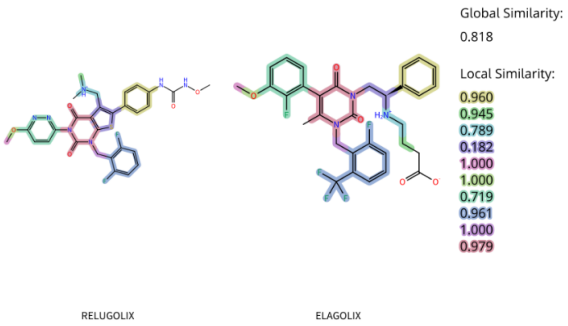
Analogue of metoclopramide




## RELUGOLIX

2020

Analogue of elagolix




## LACTITOL

2020

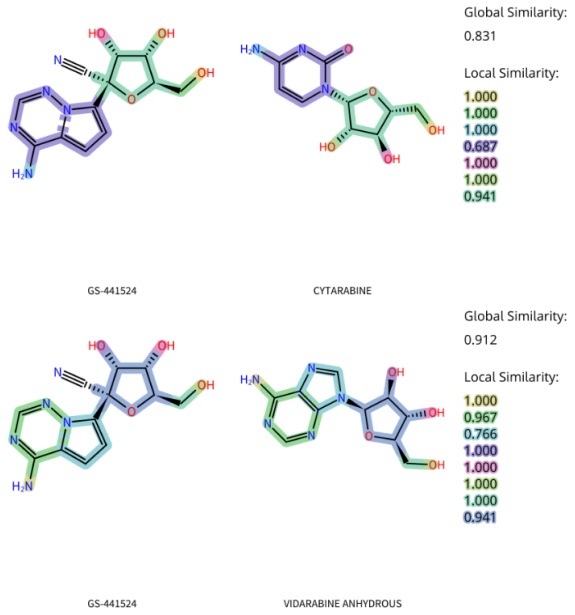
“As a laxative agent, lactitol is minimally absorbed in the small intestine, and when it reaches the large intestine, it creates an osmotic gradient that increases the water

retention in the stool, enhancing its passage(*724*).”

REMDESIVIR

2020

Analogue of cytarabine

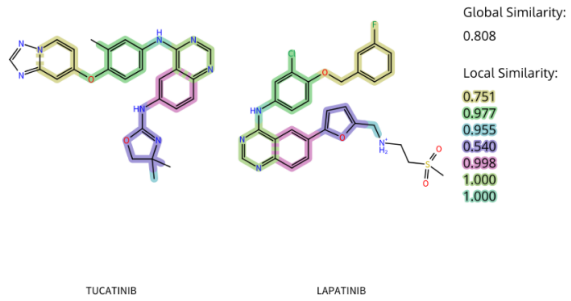



“As a starting point for discovery, a library of ~1000 small molecules focused around nucleoside analogues was compiled, based on prior knowledge of effective antiviral compounds targeting RNA viruses. Nucleosides are poorly cell-permeable (and therefore can have a low hit rate in cell-based screens such as antiviral screens), so modified nucleosides such as monophosphate, ester, and phosphoramidate prodrugs composed a significant portion of the library. Such prodrugs are typically more permeable and metabolized to liberate the nucleoside or phosphorylated nucleoside within cells. While the data from the original full screen does not appear to have been disclosed, a 1′-CN modified adenosine C-nucleoside hit (GS-441524), along with a prodrug form of the monophosphate of GS-441524 (GS-5734, later renamed as remdesivir), was found to be highly potent. GS-441524 and its S-acyl-2-thioethyl monophosphate prodrug had previously been reported in 2012 as potent leads from a series of 10-substituted 4-aza-7,9-dideazaadenosine C-nucleosides, with broad activity against a panel of RNA viruses: yellow fever virus (YFV), Dengue virus type 2 (DENV-2), influenza A, parainfluenza 3, and SARS. The primary assay used was the cytoprotection effect (CPE) assay, in which live virus is incubated with a target cell line and the antiviral activity is inferred by the ability of a test agent to rescue cell death, measured using a standard cell viability reagent(*725*).”

TUCATINIB

2020

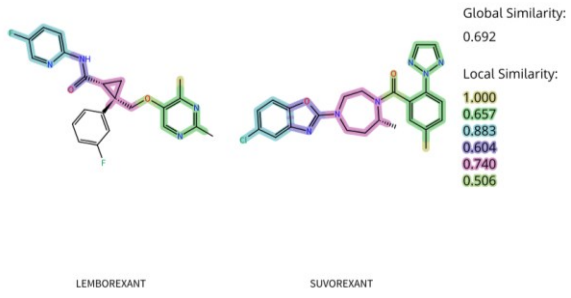
Analogue of lapatinib




LEMBOREXANT

2020

Analogue of suvorexant




TRIHEPTANOIN

2020

“Triheptanoin is a medium chain triglyceride indicated to provide calories and fatty acids to treat long chain fatty acid oxidation disorders (lc-FAODs)(*2*).”

TAFASITAMAB

2020

Monoclonal Antibody

BEMPEDOIC ACID

2020

From the discovery paper:

"Systematic chemical modification of long-chain hydrocarbons is one approach to identify novel lipid-regulating compounds for the treatment of human dyslipidemias. Over the last 30 years, a variety of compound classes have been identified that demonstrate activity in animal models of dyslipidemia. For example, Parker and coworkers and McCune and Harris have described a series of alkyloxyarylcarboxylic acids, one of which, 5-(tetradecyloxy)-2-furancarboxylic acid (TOFA), has been well studied. TOFA showed marked hypolipidemic activity in both rats and monkeys. Another series termed MEDICA (β,β′-methyl-α,ω-dicarboxylic acids) has been developed and extensively studied by Bar-Tana and coworkers. In particular, MEDICA 16 has been shown to possess hypolipidemic, anti-diabetic, and anti-atherosclerotic activity in relevant animal models. In work spanning many years, Berge, Bremer, and colleagues have described a series of 3-thia fatty acids that possess properties similar to those of MEDICA compounds when administered to animal models of dyslipidemia. In addition, Pill and coworkers described a series of ω-substituted alkyl carboxylic acids that showed insulin-sensitizing activity and lipid-regulating properties in rodents. Finally, Bisgaier and coworkers described a series of carboxyalkylethers with lipid-regulating activity, including HDL-cholesterol (HDL-C) increase, in rats. One of the carboxyalkylethers, PD-72953, also known as CI-1027 or gemcabene, has been administered to humans and shown to have effects on serum lipid levels. Currently, no consensus exists on the primary mechanism of action of long-chain hydrocarbon derivatives that eventually leads to the favorable lipid changes in humans or to the amelioration of metabolic derangements in animal models of dyslipidemia, diabetes, and obesity. Proposed primary mechanisms of action include alterations in enzyme activities through allosteric or redox state changes and modulation of gene expression through the activation or inhibition of nuclear hormone receptors.

Here, we describe a novel ω-hydroxy-alkanedicarboxylic acid, ESP 55016, that favorably alters serum lipid profiles in the Zucker rat, an animal model of diabetic dyslipidemia. Data from those studies led us to hypothesize that fatty acid oxidation was enhanced by ESP 55016. We have used both in vitro and in vivo models to test this hypothesis while focusing our efforts on identifying the short-term (minutes to hours) metabolic changes induced by ESP 55016 with the goal of identifying the initial primary mechanism(s) of action(*726*)."

Reported assays(*726*):

- ✓ Effect of ESP 55016 on fasting glucose, fasting insulin, and weight gain in the obese female Zucker rat
- ✓ Effect of ESP 55016 on fatty acid oxidation in primary rat hepatocytes
- ✓ Effect of ESP 55016 on lipid synthesis in primary rat hepatocytes
- ✓ Effect of ESP 55016 on lipid synthesis in vivo with [$^{14}$C]acetate
- ✓ Effect of ESP 55016 on [$^{14}$C]mevalonolactone incorporation into sterols in vitro

  To further define the step(s) in the cholesterol biosynthetic pathway that may be inhibited by ESP 55016, we measured sterol synthesis in primary rat hepatocytes with the radiolabeled metabolic tracer [$^{14}$C]mevalonolactone.
- ✓ Effect of ESP 55016 on [$^{14}$C]mevalonolactone incorporation into sterols in vivo

- ✓ Effect of ESP 55016 on the AMP-activated protein kinase (AMPK) pathway in primary rat hepatocytes

  ESP 55016 did not affect the phosphorylation states of either ACC or AMPK in treated hepatocytes

- ✓ Conversion of ESP 55016 to its CoA derivative

  Because phosphorylation of ACC did not appear to be responsible for reduced fatty acid synthesis in vitro, we tested whether ESP 55016 or intracellular metabolites of ESP 55016 might inhibit ACC directly. Some naturally occurring fatty acid-CoA molecules inhibit ACC. Therefore, our initial aim was to determine whether ESP 55016 could be converted to a xenobiotic-CoA derivative using rat microsomes.

- ✓ Effect of ESP 55016-CoA on ACC and HMG-CoA reductase activity in a cell-free assay

Mechanism of action is investigated after observation of the effect(*726*).

From the study of Parker and coworkers, the oldest study cited in the first paragraph of the first quotation in this entry:

"During our continued search for novel hypolipidemic agents, we discovered that methyl *p*-dodecylbenzoyl-acetate (**3**) effectively lowered serum cholesterol and triglycerides in rats (cf. Table I). We also noted, however, that **3** caused an elevation of liver fat, particularly liver cholesterol, as well as liver weight. Further studies indicated that **3** and the corresponding benzoic acid **34** were incorporated to an appreciable degree into liver lipids of rats (triglycerides and cholesterol ester). We subsequently prepared and evaluated a number of analogues to find an effective compound without these side effects. These compounds and their activities are listed in Tables I-V.

Systematic exploration of the structure-activity relationships of these fatty acid-like alkyloxyarylcarboxylic acids led to the preparation and selection of 5-(tetradecyloxy)-2-furancarboxylic acid (**91**, RMI 14 514) for extended biological studies.

**Experimental Section**

**Biological Methods.** […] At the end of the treatment period, the rats were bled by cardiac puncture. Plasma cholesterol and triglyceride levels were determined on the Technicon Auto Analizer.

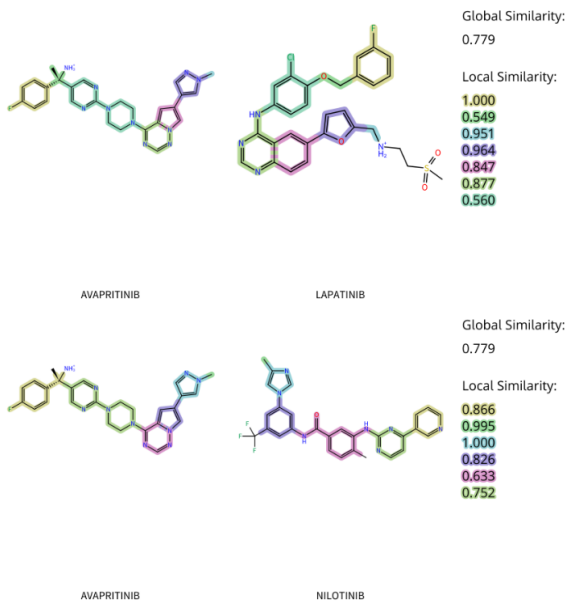
Livers were rapidly excised, blotted, and weighed at the end of the treatment period. […]

The data are expressed as percent reduction from control levels. Liver weight is expressed in g/100 g of final body weight, and liver cholesterol concentration is expressed as mg/g of wet tissue(*727*)."

AVAPRITINIB

2020

Analogue of lapatinib and nilotinib




MARGETUXIMAB

2020

Monoclonal Antibody

FOSTEMSAVIR TROMETHAMINE

2020

From the discovery paper:

"The discovery of **1** from a cell-based phenotypic screen as the initial member of a class of indole 3-glyoxamide derivatives that interfered with the attachment of HIV-1 gp120 to the CD4 protein expressed on human T-cells has been described previously. […] Initial structure−activity relationship (SAR) studies were focused on optimizing indole-based AIs, but as the challenges of developing this class of molecule became apparent, these studies evolved to encompass molecules with azaindole and diazaindole core heterocycles. The SARs associated with 1 and the optimization process that led to the identification of the 6-azaindole derivative BMS-488043 (**2**) have been described in detail. […]

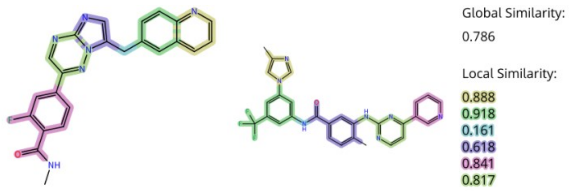
While **2** was advancing into clinical trials, the search for inhibitors with superior profiles had continued uninterrupted […] In this report, we describe the optimization and preclinical profiling of the 4-methoxy-6-azaindole series which provided a path to the most promising analogs, leading to the synthesis and selection of **3** (BMS-626529, temasavir) as a clinical candidate and its ultimate formulation as the phosphonooxymethyl prodrug **4** (BMS-663068, fostemsavir).

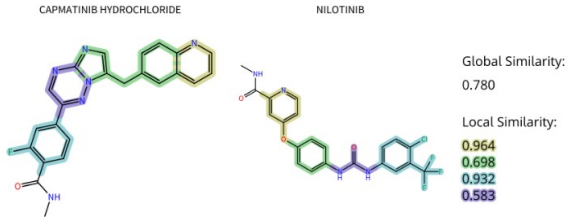
The HIV-1 inhibitory activity of test compounds was determined using a pseudotype assay that relied upon an engineered virus in which the env gene was replaced with a firefly luciferase gene to provide a convenient readout of the extent of virus infection, measured by luciferase activity 3 days after virus inoculation. To allow infection of host cells, either a JRFL (M-tropic, CCR5-specific) or LAI (T-tropic, CXCR-4-specific) virus envelope was provided to the pseudovirus by transfection. […] The concentration of drug inhibiting 50% of virus infectivity ($EC_{50}$ value) was determined while the therapeutic index was assessed by determining the concentration at which the test drug was half-maximally cytotoxic toward MT-2 cells ($CC_{50}$ value) after 3 days of incubation, with 2,3-bis(2-methoxy-4-nitro-5-sulfophenyl)-2H-tetrazolium-5-carboxanilide (XTT) used as an indicator of cell respiration and viability(*728*)."

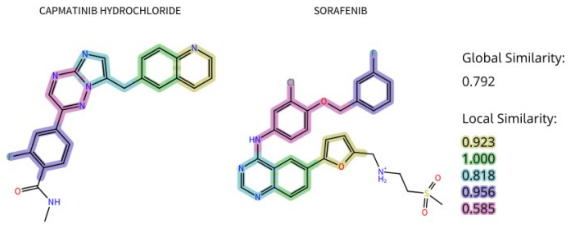
CAPMATINIB

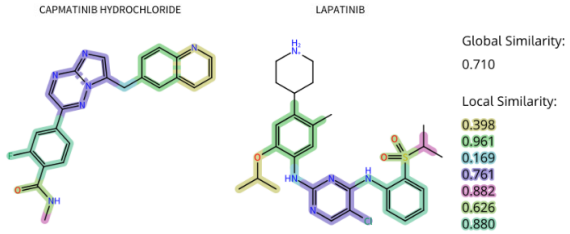
2020

Analogue of ceritinib



RISDIPLAM

2020

From the discovery paper:

"Spinal muscular atrophy (SMA) 1 is an autosomal recessive neuromuscular disorder characterized by the progressive loss of spinal motor neurons leading to muscle weakness. […]

SMA is caused by a homozygous deletion or mutation of the survival of motor neuron 1 (SMN1) gene on chromosome 5q (locus 5q13) which encodes survival motor neuron protein (SMN), an essential protein for normal development and functional homeostasis in all species, expressed in both neuronal and non-neuronal cells. […]

Our strategy to treat SMA has focused on the discovery and development of orally bioavailable and brain penetrant small molecules that shift the outcome of SMN2 alternative splicing toward the production of full length SMN2 mRNA increasing functional SMN protein levels. […]

In this paper, we describe the path from compound **2** (RG7800, RO6885247), the first molecule which entered human clinical trials in SMA, to the discovery of compound **1** (risdiplam, RG7916, RO7034067, 7-(4,7-diazaspiro[2.5]octan-7-yl)-2-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)pyrido[1,2-a]pyrimidin-4-one) currently undergoing pivotal clinical studies in SMA patients. […]

Next, to establish a structure−activity relationship (SAR) for *FOXM1* splicing in order to further increase selectivity in favour of *SMN2* splicing, we tested an already existing pool of 210 derivatives from the pyridopyrimidinone series for their activity in *FOXM1* splicing assay. A clear correlation was observed between the in vitro splicing activity of *SMN2* ($EC_{1.5\times}$ FL mRNA in-HEK293H) and *FOXM1* ($IC_{50}$ ΔA2 in fibroblast). […]

We therefore adapted our optimization strategy and focused on an increase of the in vivo selectivity between *SMN2* and *FOXM1* splicing as an improvement versus compound **2**(*729*)."

From the discovery paper of RG7800 cited the previous quotation:

"We have reported the discovery of highly specific, orally available small molecules (coumarin **1**, isocoumarin **2**, and pyridopyrimidinone derivatives) that specifically modify *SMN2* splicing in SMA patient-derived cells and in two SMA mouse models, resulting in a clear therapeutic benefit in mice that model a severe SMA form. However, the clinical development of the coumarin and isocoumarin compounds **1** and **2** was mainly hampered by an in vitro flag in the Ames assay indicative of genotoxicity, phototoxicity, and chemical instability in plasma or aqueous buffers. These findings shifted our focus to the pyridopyimidinone series.

We describe here the initial optimization attempts on the coumarin and isocoumarin series. Then we report the lead optimization strategy for the pyridopyrimidinone series, addressing multiple issues that led to the discovery of orally active compounds **3**−**5**. Compound **3** was selected as our clinical candidate. It became the first orally active small molecule *SMN2* splicing modulator to enter human trials for the potential treatment of spinal muscular atrophy.

**SMN HTRF Assay.** The levels of SMN protein in lysates of compound-treated cells were quantified as described previously(*730*)."

EPTINEZUMAB

2020

Monoclonal Antibody

CEDAZURIDINE

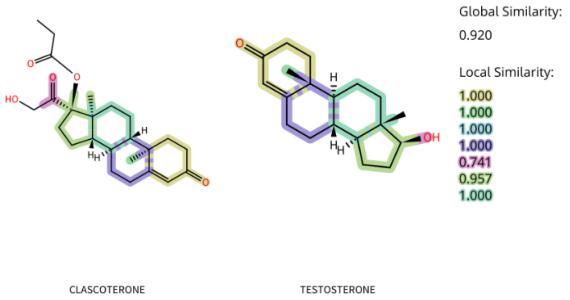
2020

Secondary

CLASCOTERONE

2020

Analogue of progesterone and testosterone




From the discovery paper:

"In this paper, we report the preliminary experimental results obtained with a new steroid androgen antagonist belonging to the family of ester derivatives of cortexolone (11-desoxycortisone, CAS 152-58-9). This family, which was found to express unexpected antiandrogenic properties, was screened and the 17α-propionate ester of cortexolone (CB-03-01, CAS 19608-29-8) was selected for its optimum topical antiandrogenic profile. CB-03-01 was assayed in the following tests: local antiandrogenic activity in hamster's flank organ, systemic antiandrogenic, antianabolic and glucocorticoid activity in the immature male castrated rat, effect on gonadotropins hypersecretion in the parabiotic rat, and effect on plasma corticosterone in rat. Preliminary information about the potential systemic toxicity of CB-03-01 in rat has been also collected.

The importance of this work lies in the fact that cortexolone 17α-propionate, considered here, shows unexpected pharmacological properties which cannot be demonstrated for the corresponding parent cortexolone. These properties are also of particular interest if compared to ones of the currently available androgen antagonists. When assayed as topical antiandrogen, CB-03-01 resulted highly effective and, when compared to well known androgen antagonists, it was significantly more active than progesterone, finasteride, and even more potent than the pure antiandrogen flutamide(*731*)."

TEPROTUMUMAB

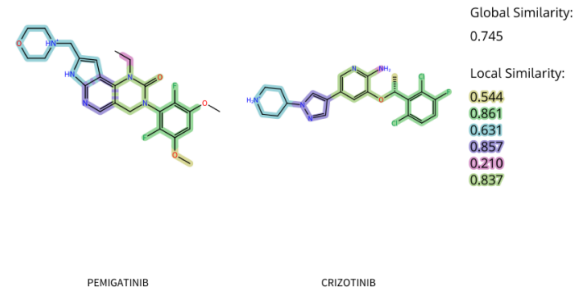
2020

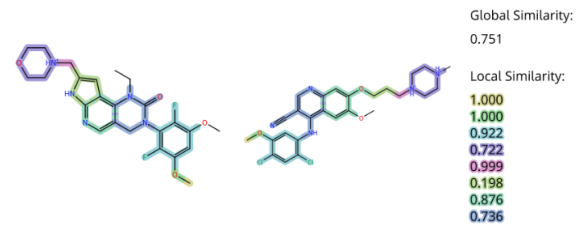
Monoclonal Antibody

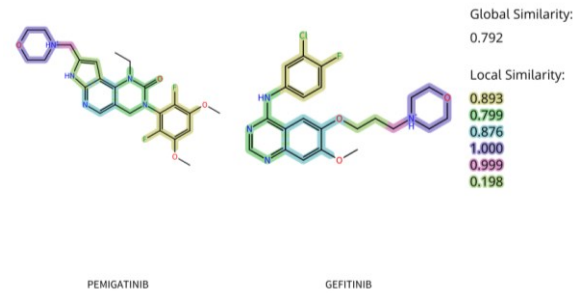
PEMIGATINIB

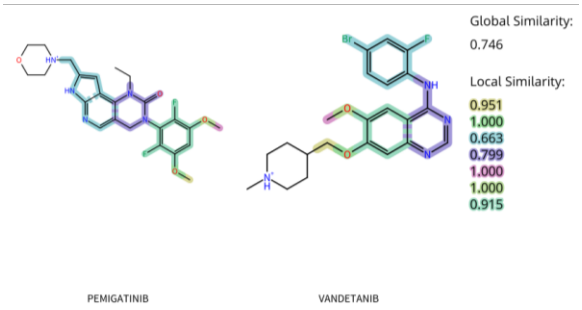
2020

The selection of the compound is not mentioned in the discovery paper(*732*).



ABAMETAPIR

2020

From the discoverer(s):

"In order to investigate the potential for improving ovicidal efficacy, an alternate approach to investigate the biochemistry associated with egg hatching in lice was adopted. These studies focused on the hatching process and involved collecting water washings from recently hatched body louse eggs. Once collected, these egg shell washings were analyzed by gelatin zymography for the presence of proteases. A number of proteases were identified with further characterization identifying them to be of the metalloprotease class. In addition, their presence in the washings from newly hatched louse eggs indicated that they may play a role in egg hatching in body lice. Data were subsequently obtained showing that when particular metalloproteinase inhibitors were incubated with body louse eggs, the treated eggs failed to hatch. This key finding provided an opportunity to investigate the role of metalloproteinases as novel ovicidal targets in lice. In an extension of this research, we used the model insect, *Drosophila melanogaster*, as a means to better understand the ovicidal effects of the compound 5,5′-dimethyl-2,2′-bipyridyl (formerly termed Ha44, now referred to as abametapir; Van Hiel et al. 2012). Abametapir is a heterocyclic organic molecule that is capable of chelating heavy metal ions, including iron, copper, and zinc, and is therefore able to interact with a range of targets within the insect that require metal co-factors for function, including metalloproteinases. These experiments demonstrated that abametapir was able to arrest *D. melanogaster* embryo development at the blastoderm stage, during the germ band stage, and at a very late stage near the point of hatching, providing further evidence for the ovicidal efficacy of this compound in insects(*733*)."

Form the 2012 discovery paper cited in the previous quotation:

"Metalloproteases required for egg hatching in lice have been suggested as potential new targets. Subsequent research led to the discovery of a series of compounds that prevented egg hatching as well as killing adult lice (unpublished data). Further research identifying the mode of action and the potential for resistance development may be useful in assessing the predicted efficacy of this insecticide in the longer term.

5,5′-dimethyl-2,2′-bipyridyl (termed Ha44) is a heterocyclic organic molecule predicted to chelate heavy metal ions and thereby interact with a range of targets that require heavy metal ions as co-factors within the insect. Ha44 has recently completed a Phase 2 b clinical trial in subjects with head lice, which demonstrated safety and efficacy (unpublished data). This paper analyses the biological activity and mode of action of this compound.

Using both feeding and contact assays in the *D. melanogaster* model system, we demonstrate that Ha44 is lethal to embryos, larvae and adults. We show the ability of Ha44 to inhibit a zinc dependent metalloprotease *in vitro* and provide evidence indicating that Ha44 chelates heavy metals *in vivo*. We show that the lethal effects of the insecticide can be reversed following exposure to the metal ions iron, zinc and copper(*734*)."

NAXITAMAB

2020

Monoclonal Antibody

INEBILIZUMAB

2020

Monoclonal Antibody

LUMASIRAN

2020

Antisense oligonucleotide

## SETMELANOTIDE

2020

Analogue of α-melanocyte stimulating hormone

Error in similarity calculation by FTrees because of the unsupported macrocycle

Discovery of the effect of α-melanocyte-stimulating hormone on body weight:

"It has been known for nearly a century that the obesity and the yellow coat color are associated. In 1972, Geschwind et al. demonstrated that the defect in these animals was not in the melanocyte itself since injection of alpha-MSH produced black pigmented hair in these animals. We have subsequently confirmed Geschwind's observation, and found in addition that the percentage of alpha-MSH is significantly reduced in the pituitary of the viable yellow obese mouse. This finding suggested the hypothesis that some of the metabolic abnormalities of the genetic syndrome in the yellow obese mouse might result from the altered ratio of desacetylated to acetylated MSH. If true, then the biological potency of these two peptides on food intake, body weight gain and pigmentation of hair should be different. The present experiments were designed to compare the dose-response relationships on pigmentation between the acetylated and desacetylated forms of MSH, and to examine the effects of these peptides on food intake, body weight and organ weights in both lean black (a/a) and viable yellow obese ($A^{vy}$/a) mice(*735*)."

## ATOLTIVIMAB;ODESIVIMAB;AFTIVIMAB

2020

Monoclonal Antibody

## OPICAPONE

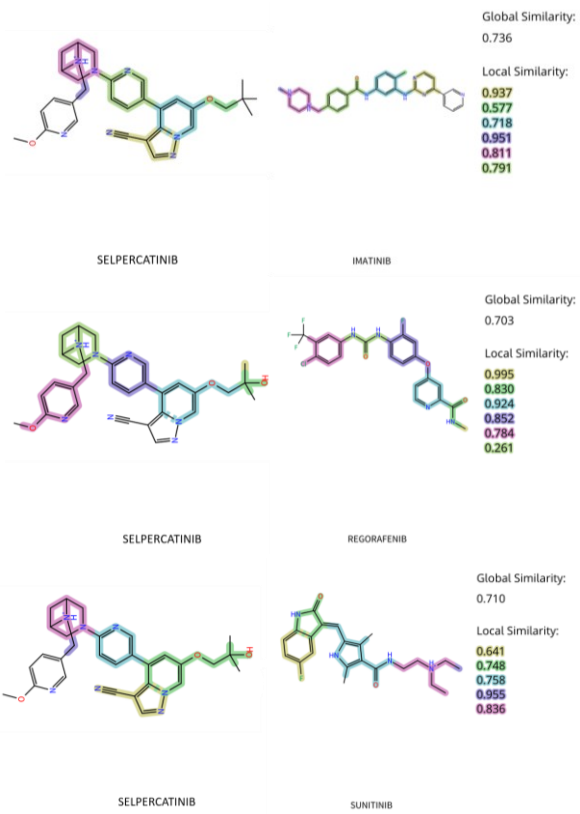
2020

Secondary, analogue of entacapone

## SELPERCATINIB

2020

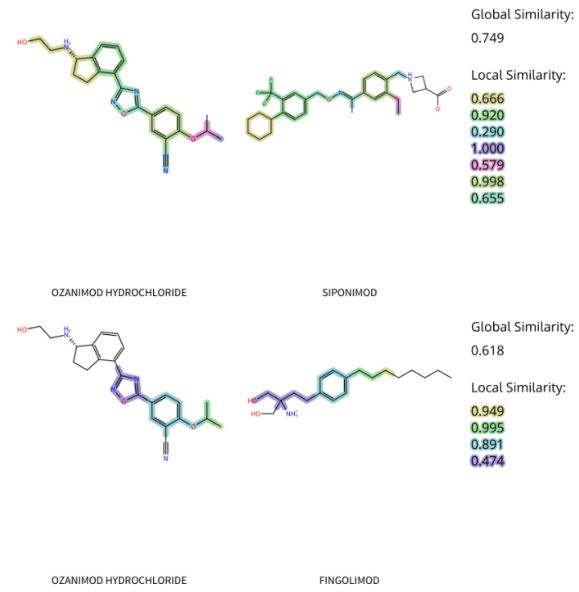
Analogue of imatinib




## OZANIMOD

2020

Analogue of fingolimod



## NIFURTIMOX

2020

"Until the publication of the Manual de Doenças Tropicaes e Infectuosas in 1935 by Carlos Chagas and Evandro Chagas (Manual of Tropical and Infectious Diseases), there was no pharmacological treatment available for trypanosomiasis. Drugs with trypanocidal activity have been investigated by a number of researchers; however, without success. In 1936, quinolinic compounds were successfully used to treat an acute case of trypanosomiasis. In the following years, nitrofurazone was administered to treat trypanosomiasis in mice and achieve efficacy rates between 20 and 100%, depending on the therapeutic schedule. These results motivated the experimental trials in humans, in which nitrofurazone demonstrated to be effective against trypanosomes in the circulating blood, cerebrospinal fluids as well as other promising clinical results.

Nifurtimox (NFX) belongs to the class of nitrofuran compounds. Her-Linger, Mayer, Petersen and Bock from Bayer™ synthesized it in 1962 in Germany. This was the first drug designed to treat trypanosomiasis, such as sleeping sickness and Chagas diseases. Its production was interrupted in 1980s due to the reduction on world demand. In 2009, the WHO Expert Committee on the Selection and Use of Essential Medicines recommends the inclusion of NFX in the model list of essential medicines and Bayer resumed the production of NFX(*736*)."

## TIRBANIBULIN

2020

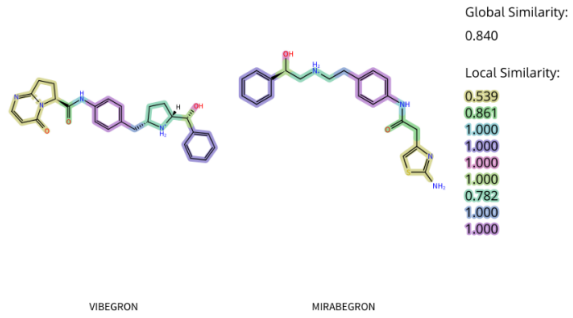
From the discoverer(s):

"KX-01 was designed as a peptidomimetic that targets the very specific peptide binding site of Src resulting in high specificity for Src kinase without significant cross reactivity to other tyrosine kinases(*737*)."

## VIBEGRON

2020

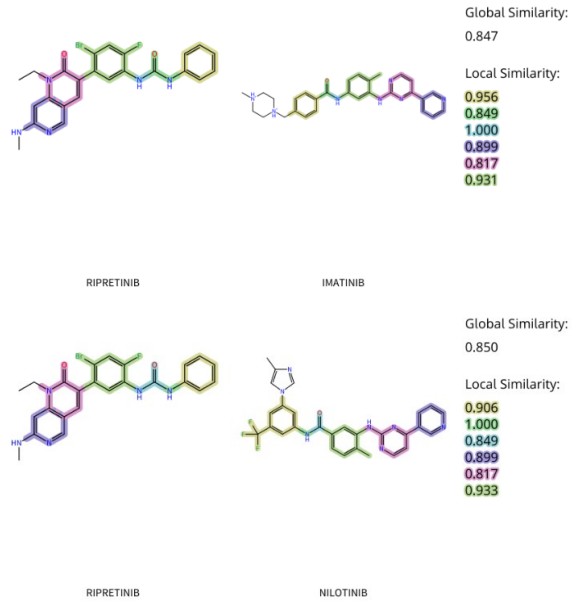
Analogue of mirabegron




## RIPRETINIB

2020

Analogue of imatinib




## SATRALIZUMAB

2020

Monoclonal Antibody

## ISATUXIMAB

2020

Monoclonal Antibody

## FLUOROESTRADIOL F-18

2020

Diagnostic

BEROTRALSTAT HYDROCHLORIDE

2020

= BCX7353

"Next-generation oral agents, targeting the essential steps of the contact cascade, are already underway. In May 2014, BioCryst Company, based in the USA, announced preliminary successful results of a proof-of-concept, phase 2a clinical trial (OPuS-1) with a specific plasma kallikrein inhibitor (Avoralstat, BCX4161), orally administered three times daily, for patients with HAE with frequent attacks. In December 2014, the company initiated enrollment in OPuS-2, a blinded, randomized, clinical trial evaluating the efficacy and safety of two different doses of avoralstat compared with placebo.

The same company has recently (October 2015) launched a randomized, placebo-controlled, phase 1 clinical trial with once-a-day orally administered kallikrein inhibitor (BCX7353)(*738*)."

From the Phase 1 Trial paper of avoralstat:

"The synthetic small molecule avoralstat (RN: 918407-35-9) is a potent inhibitor of plasma kallikrein that suppresses HK/kallikrein-dependent bradykinin production on human endothelial cells. The effect of avoralstat on kallikrein activity in human plasma has been demonstrated using a novel assay developed by the authors, in which contact activation is stimulated by ellagic acid and enzyme activity is measured with a specific fluorogenic substrate. In an ex vivo study of plasma samples from 51 healthy human subjects, the $EC_{50}$ values for avoralstat in this assay were 1.14 nM to 11.1 nM(*739*)."

From the discovery paper cited in the previous quotation:

"In the present study we report a group of newly developed anti-inflammatory compounds, primarily designed for tissue factor (TF) / factor VIIa (FVIIa), also potently inhibit kallikrein activity. Using structure-based drug design a series of potent small molecule inhibitors toward TF/FVIIa were designed and synthesized at BioCryst Pharmaceuticals (BCX) The inhibitory actions of these compounds towards FVIIa have been thoroughly characterized using a purified enzyme assay and relevant clotting-based assays. In addition to FVIIa the inhibitory effects of these compounds against various serum proteases, including C1s, thrombin, plasmin, FXa, activated Protein C (APC), tissue plasminogen activator (tPA) and kallikrein, were also studied. The data from these assays indicate that kallikrein is the only enzyme that was also potently inhibited by some of these compounds. In order to understand their inhibitory mechanism towards kallikrein, binding properties were extensively explored in an enzyme model. The data from binding kinetics studies demonstrate that all five compounds reported in this article are potent kallikrein inhibitors, and some of them showed exceptional binding affinity toward kallikrein with binding constants (*Ki* final) less than a nanomolar, comparable to P8720, which is a peptide based-kallikrein inhibitor. Further studies using on-site dissociation and *Ki* determination in extending binding conditions suggest that these compounds belong to slow binding inhibitors, which takes two steps to form stable inhibitor/enzyme complexes. One of the most important indications of contact activation is massive production of BK, a cleavage product of HK by proteolytic action of kallikrein. Thus the ability of selected compounds to inhibit BK generation was examined using a plasma based-assay. The data of BK release assays are consistent with the findings observed in enzyme kinetic assays. […]

**Plasma BK Release Studies**

***Bacteria***

A strain of bacteria *Staphylococcus aureus* (strain 5120) was originally derived from a

blood culture from a patient with septic shock. […]

***Bradykinin Release Inhibition Assay***

To assess inhibitory properties of BCX compounds toward kallikrein in plasma as well as kallikrein that assemble on the surface of bacteria, the assays were conducted under three different reaction conditions. […]

To confirm that the inhibition not only occurs in a reconstituted enzyme system but also takes place in kallikrein-containing plasma, the bacterial mediated-plasma BK release assay was performed in the presence or absence of inhibitors at early or late incubation steps, and the content of BK present in plasma or washed bacteria suspension was examined(*740*).”

LURBINECTEDIN

2020

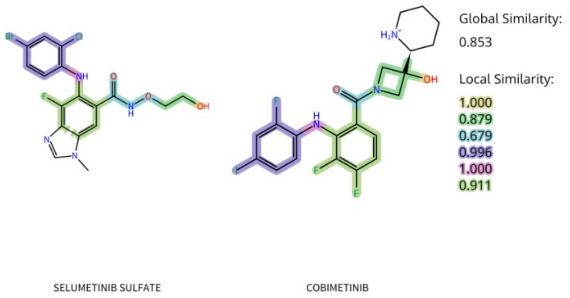
Analogue of trabectedin(*2*)

Error in similarity calculation by FTrees because of the unsupported macrocycle

SELUMETINIB SULFATE

2020

Analogue of cobimetinib




SOMAPACITAN

2020

Endogenous-based biopharmaceutical

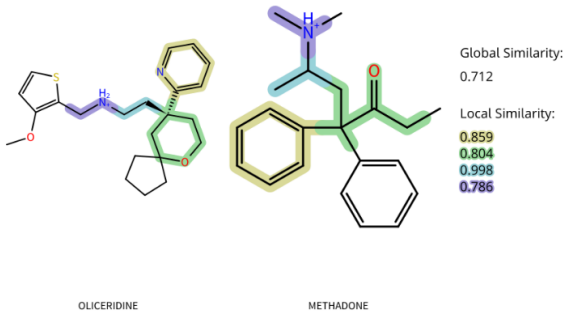
Analogue of the endogenous growth hormone

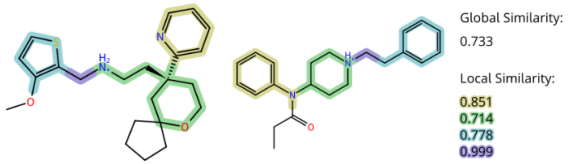
OLICERIDINE

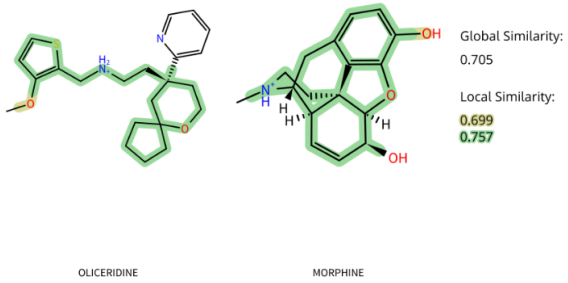
2020

Analogue of morphine

Also see the fentanyl entry and refer to Paul Janssen’s article cited there.



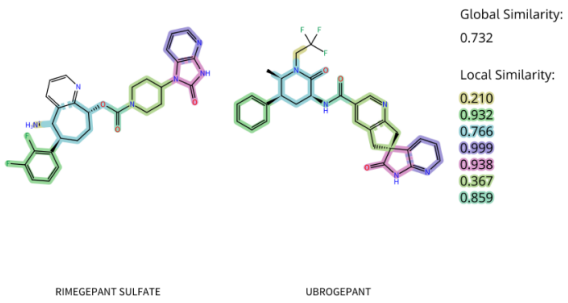




RIMEGEPANT SULFATE

2020

Analogue of ubrogepant




VILTOLARSEN

2020

Antisense oligonucleotide

TAZEMETOSTAT HYDROBROMIDE

2020

From the discovery papers:

"To find inhibitors of EZH2, high-throughput diversity screens were performed. The four component PRC2 complex containing EZH2, EED, SUZ12, and RbAp48 was used with chicken oligonucleosome as the substrate. The reaction was run under balanced conditions (at the $K_m$ for both SAM and nucleosome) to allow for discovery of inhibitors of all modes of inhibition such as competitive with S-adenosylmethionine (SAM) or with nucleosome(*741*)."

"**High throughput proliferation assay**

For the assessment of the effect of compounds on the proliferation of the WSU-DLCL2 cell line, exponentially growing cells were plated in 384-well white opaque plates at a density of 1,250 cells/mL in a final volume of 50 mL of assay medium(*742*)."

LONAFARNIB

2020

From the discovery paper:

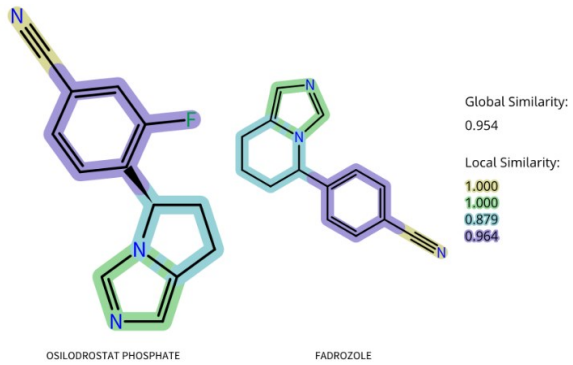
"Compounds prepared in this study were tested both for their ability to inhibit the transfer of [$^3$ H]farnesyl from farnesyl pyrophosphate to H-Ras-CVLS, a process that is mediated by FPT, and for their inhibitory activity toward the closely related enzyme GGPT-1 that catalyzes the transfer of [ 3 H]geranylgeranyl moiety from geranylgeranyl pyrophosphate to H-Ras-CVLL using conditions previously described. These compounds were also evaluated in a cellular ras-processing assay (COS cell assay) and a colony-forming assay (soft agar assay) as previously described(*743*)."

OSILODROSTAT

2020

Analogue of fadrozole

See the letrozole entry.




From the discovery paper of the aldosterone biosynthesis inhibitory activity of fadrozole:

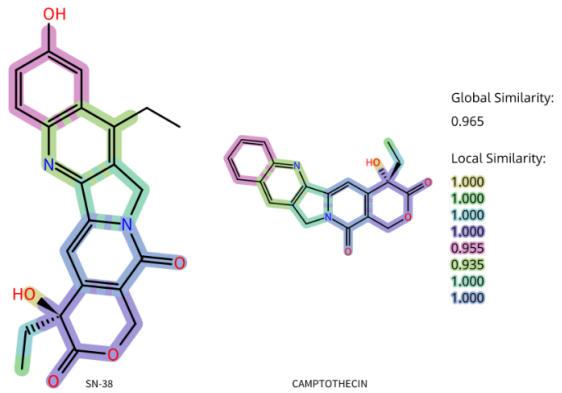
"CGS 16949A is a potent inhibitor of aromatase *in vitro* with an $IC_{50}$ of 0.03 µM for the inhibition of LH-stimulated estrogen biosynthesis in hamster ovaries. *In vivo*, CGS 16949A leads to sequelae of estrogen deprivation (e.g. regression of DMBA-induced mammary tumors) without causing adrenal hypertrophy in adult rats. To complement these *in vitro* and *in vivo* findings, the effect of CGS 16949A on adrenal steroid biosynthesis in rats was investigated in vitro and in vivo. The surprising finding *in vitro* was that CGS 16949A inhibited aldosterone biosynthesis ($IC_{50}$ = 1 µM) at concentrations 100 times lower than those for inhibition of corticosterone biosynthesis ($IC_{50}$ = 100 µM)(*744*)."

SACITUZUMAB GOVITECAN

2020

"Sacituzumab govitecan is an antibody-drug conjugate (ADC) targeting TROP-2-expressing cancer cells to induce DNA-damage-mediated cell death. The conjugate comprises a humanized anti-TROP-2 monoclonal antibody (RS7-3G11, also known as RS7) chemically linked by a hydrolyzable CL2A linker to the cytotoxic drug SN-38(*2*)."

SN-38: Analogue of camptothecin




[FLORTAUCIPIR F-18]

2020

Diagnostic

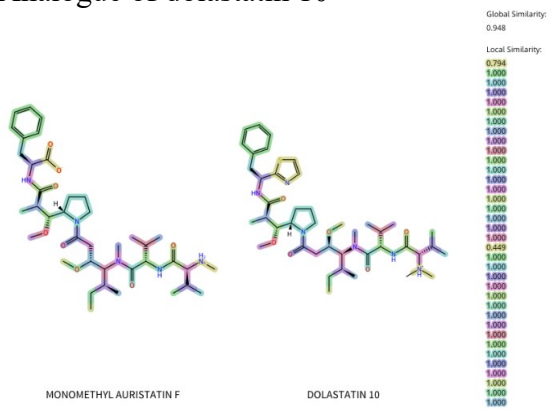
[BELANTAMAB MAFODOTIN]

2020

“Belantamab mafodotin, or GSK2857916, is an afucosylated monoclonal antibody that targets B cell maturation antigen conjugated to the microtubule distrupter monomethyl auristatin-F (MMAF)(*2*).”

Discovery of monomethyl auristatin-F:

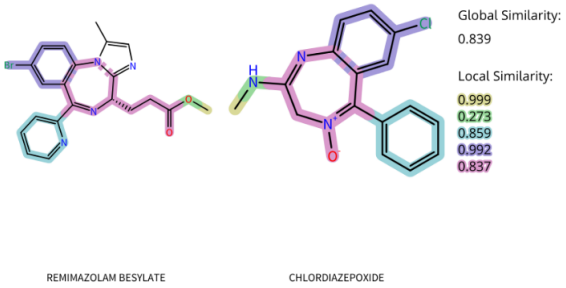
Analogue of dolastatin 10




[REMIMAZOLAM]

2020

Analogue of chlordiazepoxide



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