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Alkaloids as Important Scaffolds in Therapeutic Drugs for the Treatments of Cancer, Tuberculosis, and Smoking Cessation

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Abstract: Alkaloid molecules can act, depending on a type of amine functionality present in alkalods, as either hydrogen-acceptor or hydrogen-donor for hydrogen bonding that is critically important for the interaction (binding) between targets (enzymes, proteins and receptors) and drugs (ligands). Because of this unique property, alkaloid scaffolds are therefore present in several drugs and lead compounds. This review highlights alkaloid scaffolds in drugs, particularly those recently approved in 2012; it also covers the scaffolds in leads and drug candidates which are in clinical trials and preclinical pipeline. The review focuses on three therapeutic areas including treatments of cancer, tuberculosis, and tobacco cessation. Alkaloid scaffolds in drugs and leads are inspired by those of naturally occurring alkaloids, and these scaffolds include pyridine, piperidine, quinoline, quinolinone, quinazoline, isoquinoline, indole, indolinone, isoindole, isoxazole, imidazole, indazole, thiazole, pyrazole, oxazolidinone, oxadiazole, and benzazepine. In addition to medicinal chemistry aspects, natural products possessing an individual alkaloid scaffold, as well as the mechanism of action of drugs and leads, are also discussed in this review.

Keywords: Alkaloids, natural products, drugs, lead compounds, cancer, anticancer drugs, cytotoxic activity, antitubercular activity, antimycobacterial activity, tuberculosis, smoking cessation.

INTRODUCTION

In 2012, the US Food and Drug Administration (FDA) approved 39 new drugs including 33 organic molecules and 6 biological drugs [1]. Among 33 small molecule drugs, there are at least16 drugs whose structures are alkaloids or related to alkaloid molecules, and this underscores the importance of alkaloid structural features in drug discovery. While natural alkaloids isolated from various living sources provide many new leads with different drug targets, many synthetic alkaloids generated from medicinal chemistry research, through rational drug design (both computer-aided and structure-based drug designs) and lead optimization, prove to be potential drug candidates. The "-omics" technologies have accelerated drug discovery process; genomics and proteomics have revealed new potential drug targets [2-4]. Chemical proteomics enabling the direct analysis of protein activities, or proteins binding the drug, prove to be useful for the elucidation of drug targets as well as lead verification [5,6]. Computer-based docking and chemoinformatic screens are widely used to discover new ligands for targets of known structure, and to predict new substrates for enzymes of unknown function [7]. *In silico* prediction of drug-target interactions from heterogeneous biological data (chemical, genomic, and pharmacological data) [8], translational bioinformatics [9], and network-based relating pharmacological and genomic spaces for drug target identification [10] have also accelerated the drug discovery processes. Upon the recent technologies mentioned above, it is anticipated that drug leads would be rapidly identified, and thus speeding the drug development processes. Therefore, these advanced technologies would consequently increase number of drugs approved in the future. Among the new small molecule drugs approved in the future, the numbers of molecules decorated with alkaloid scaffolds will also increase.

Alkaloids are generally known as compounds that contain nitrogen and heterocyclic rings, and they are relatively basic. Natural alkaloids are widely found in plants, animals, and microorganisms. Since alkaloids contain nitrogen atom(s) in their molecules, the most common functional groups in alkaloids are primary, secondary, and tertiary amines. The nitrogen atom(s) in alkaloids significantly contributes to the drug properties; a lone pair of electrons on the nitrogen usually accepts the protons (H-acceptor), while hydrogen(s) in primary and secondary amines act as a proton donor (H-donor) necessary for hydrogen bonding. It should be noted that the target-ligand interaction (or protein-ligand binding) heavily employs such hydrogen bonding. These H-acceptor and donor properties of nitrogen and hydrogen mentioned above, together with H-acceptor and donor of other functional groups (i.e. phenolic hydroxyl and polycyclic moieties), enable alkaloids to be ideal bioactive molecules which have perfect ability to bind (or interact) with drug targets (proteins, enzymes, and receptors); accordingly most natural alkaloids usually exhibit biological activities

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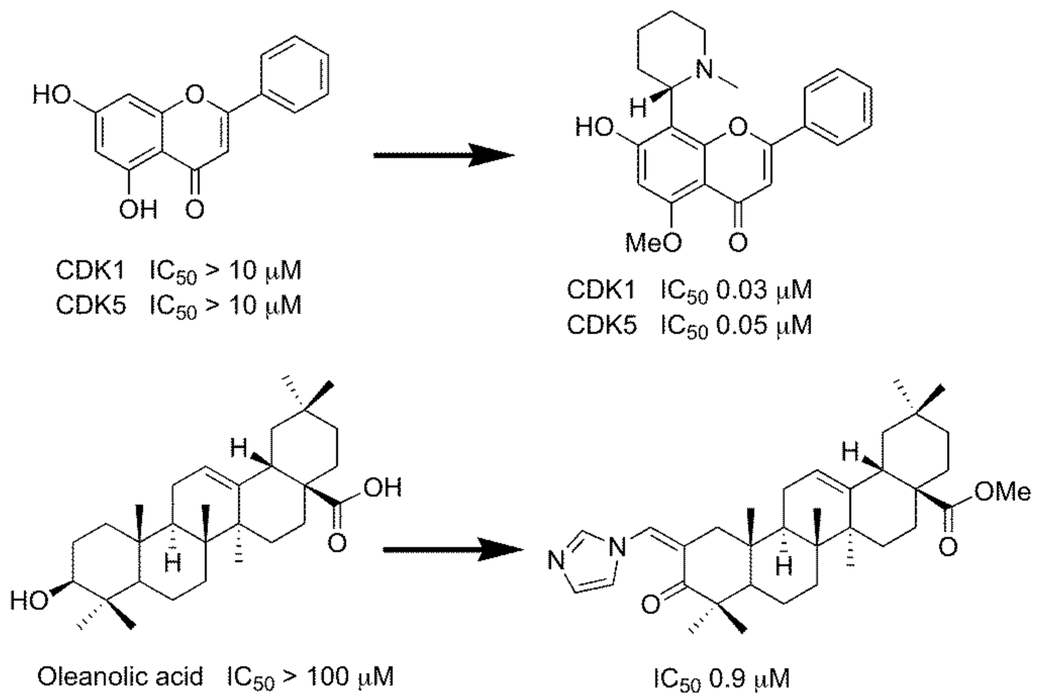
which are of pharmaceutical interest. Therefore, it is not surprised that in some cases, the installation of alkaloid scaffolds into non-alkaloid molecules could lead to the increase of biological activities. Two recent studies have demonstrated that the transformation of non-alkaloids into alkaloidal compounds leads to dramatic increase of biological activities (Scheme 1). The installation of an alkaloid scaffold (a piperidine derivative) into flavonoids to furnish flavonoidal alkaloids led to the markedly increase in cyclin-dependent kinases (CDKs) inhibitory activity (at least 333 folds for CDK1 and 200 folds for CDK5) [11], while the attachment of an imidazole unit to a common plant triterpene, oleanolic acid, significantly improved antiproliferative activity in solid tumour cells up to 111 folds [12] (Scheme 1).



Scheme 1. Transformation of non-alkaloids into alkaloidal compounds leads to significant increase of biological activities.

This review highlights the importance of alkaloid scaffolds in therapeutic drugs, particularly those approved in 2012, as well as the scaffolds in leads and drug candidates that are being evaluated in clinical and preclinical trials. The present review focuses on the drugs and leads for cancer and tuberculosis therapies, and for the treatment of smoking cessation. Moreover, details on the mechanism of action of an individual drug and lead are also provided.

ALKALOID SCAFFOLDS IN ANTICANCER DRUGS

In recent years, there has been increase in the number of new anticancer drugs approved by the US FDA [1], and their numbers are likely to increase in the future. In 2012, the first anticancer drug, GDC-0449 (**1**) or Vismodegib, with a novel mechanism of action of the Hedgehog signaling pathway, is approved for the treatment of metastatic or locally advanced basal cell carcinoma (Fig. (**1**)). The Hedgehog signaling pathway was first discovered in 1980 [13], however, the landmark discovery in 2002 that the steroidal alkaloid cyclopamine (**2**) (Fig. (**1**)) from the plant (*Veratrum californicum*) inhibited the Hedgehog pathway has flashed the light on cancer therapeutics [14]. Details for the mechanism of action of Hedgehog signaling pathway have been conclusively established [15-17], and thus enabling medicinal chemistry to generate several potent inhibitors as anticancer drug candidates. Apart from GDC-0449 (**1**), four small molecule inhibitors of Hedgehog signaling pathway including XL-139 (BMS-833923, structure not disclosed), PF0444913 (structure not disclosed), IPI-926 (**3**), and LDE-225 (**4**) are under clinical evaluation (Fig. (**1**)) [18-21]. Moreover, the search for new synthetic and natural inhibitors of Hedgehog signaling pathway has also been intensively studied [22-25].

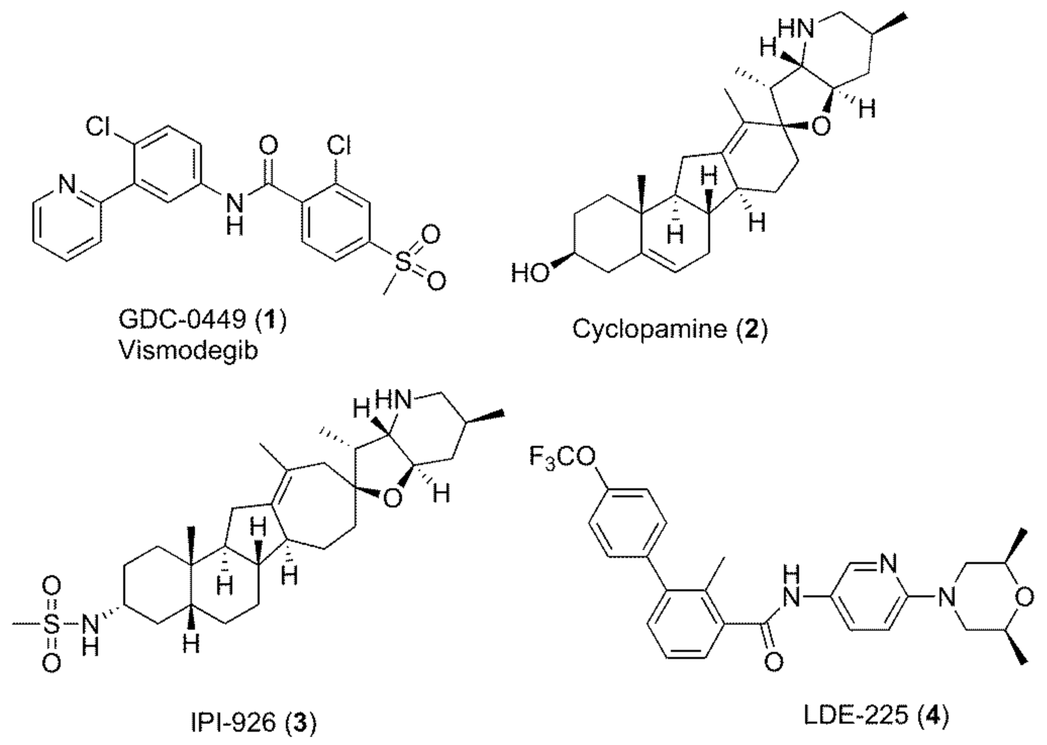


Fig. (1). Inhibitors of Hedgehog signaling pathway as anticancer drugs.

Inhibition of tyrosine kinases, the enzymes that catalyze the transfer of a phosphate group from adenosine triphosphate to target proteins, is one of the effective target therapies for cancer. There are a few anticancer drugs developed from this mechanism of action. Some tyrosine kinase inhibitors (drugs) have the alkaloid scaffolds including quinazoline for Erlotinib (**5**), CI-1033 (**6**) (Canertinib), and ZD1839 (**7**) (Gefitinib); pyridine alkaloids for BAY 43-9006 (**8**) (Sorafenib) and PTK787 (**9**) (Vatalanib); indolinone for SU5416 (**10**) (Semaxinib) and SU11248 (**11**) (Sunitinib or Sutent); and isoxazole for SU101 (**12**) (Leflunomide) (Fig. (**2**)). Normally, natural alkaloids including quinazoline [26], pyridine (e. g., nicotine derivatives) [27-29], indolinone [30-33], and isoxazole [34,35] are widely found in plant and animal kingdoms, as well as microorganisms.

As mentioned earlier that the inhibition of tyrosine kinases is one of the successful target therapies for cancer, therefore, in 2012, the US FDA approved five tyrosine kinase inhibitors for the treatment of cancers [1]. These drugs include BAY 73-4506 (**13**) (Regorafenib) for the treatment of metastatic colorectal cancer, XL184 (**14**) (Cabozantinib) for the treatment of progressive, metastatic medullary thyroid cancer, AP24534 (**15**) (Ponatinib) for chronic, accelerated or blast-phase chronic myeloid leukaemia, SKI-606 (**16**) (Bosutinib) for the treatment of chronic myelogenous leukemia, and AG013736 (**17**) (Axitinib) for advanced renal cell carcinoma (Fig. (**3**)) [1]. Again, these new anticancer drugs also posses the alkaloid scaffolds, for example, pyridine in BAY 73-4506 (**13**), quinoline in XL184 (**14**) and SKI-606 (**16**), imidazopyridazine in AP24534 (**15**), and indazole in AG013736 (**17**). While natural alkaloids including pyridine [27-29], quinoline [36-39], and imidazole [40-42] are widely found in Nature, natural indazole alkaloids are rare; so far only a few indazoles have been isolated from a plant source [43-46].

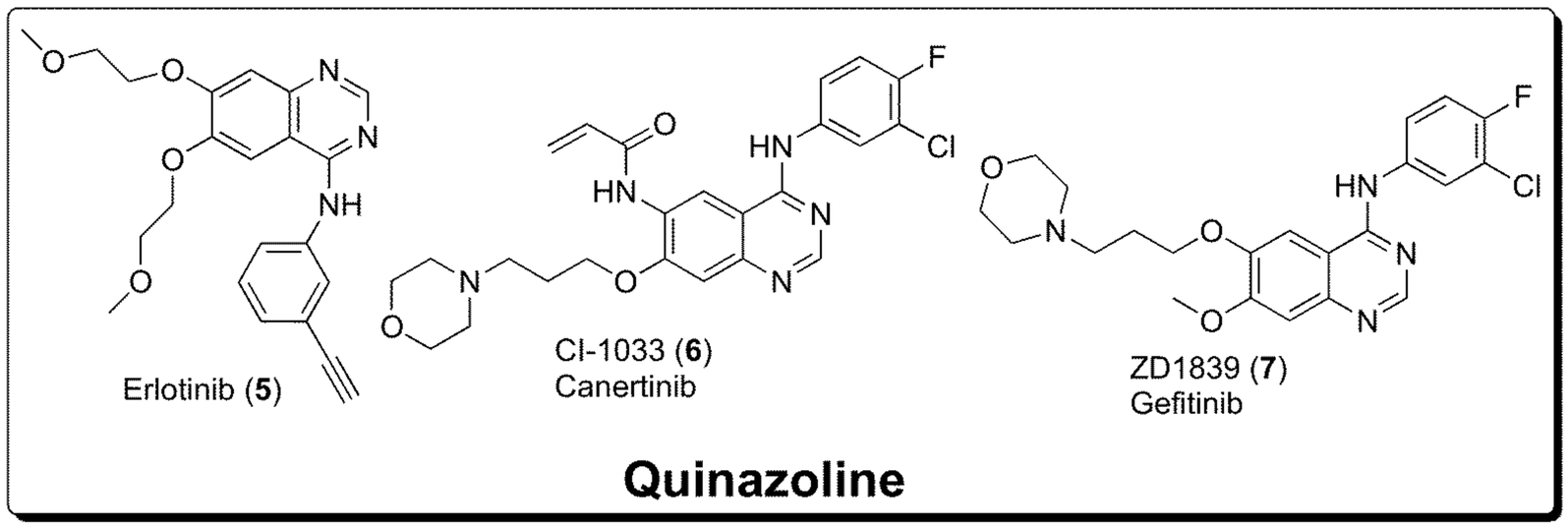


Fig. (2). Alkaloid scaffolds in tyrosine kinase inhibitors (anticancer drugs).

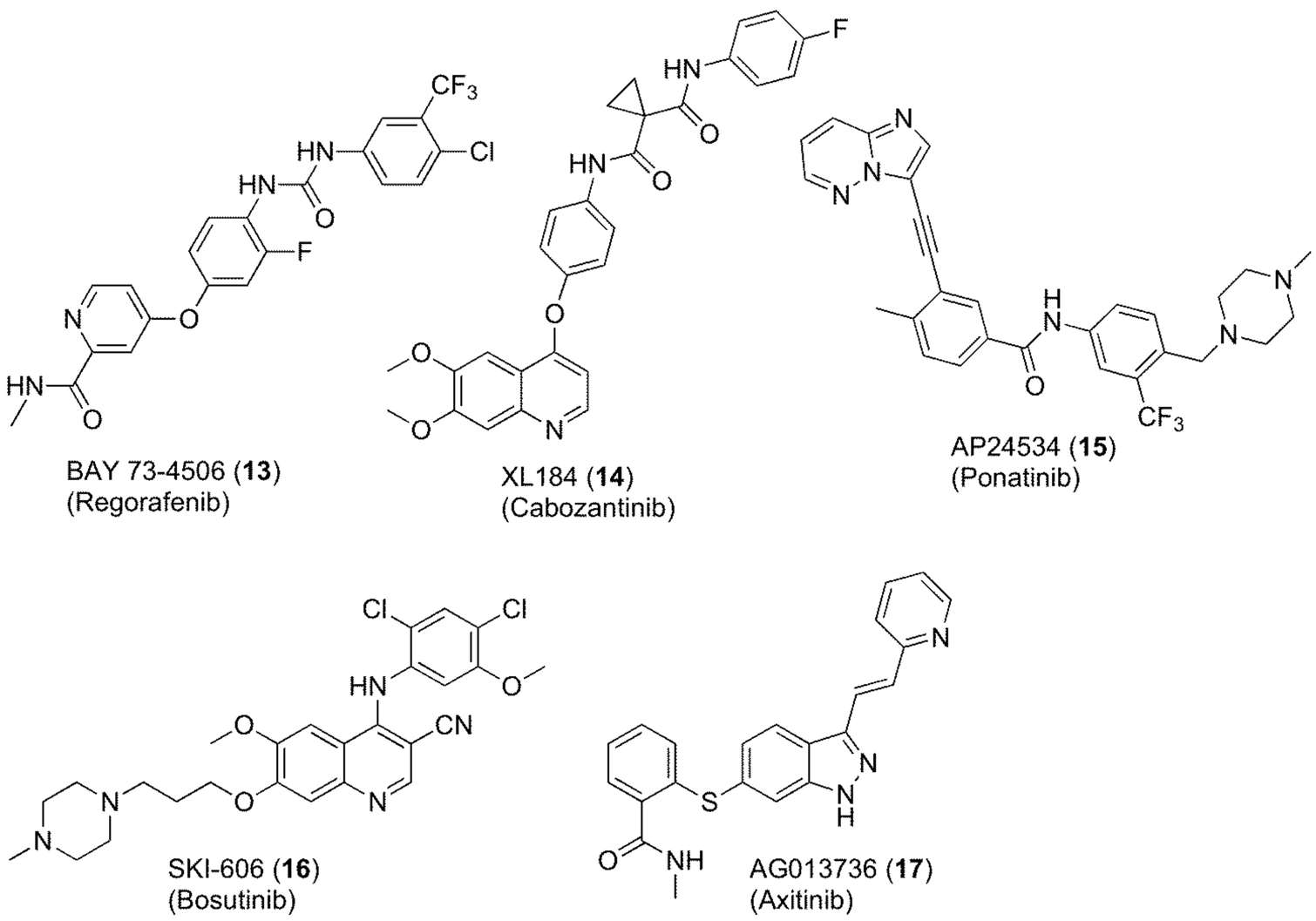
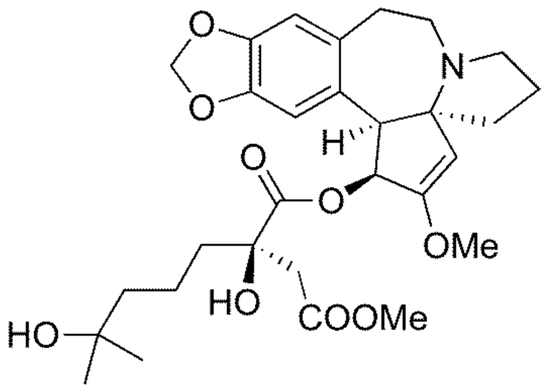


Fig. (3). Tyrosine kinase inhibitors as anticancer drugs approved in 2012.

The plant alkaloid omacetaxine mepesuccinate (**18**), or homoharringtonine, is a natural product approved as an anticancer drug in 2012 (Fig. (**4**)). Omacetaxine mepesuccinate (**18**) was first isolated in 1970 from *Cephalotaxus harringtonia*, however, at that time this class of alkaloids was collectively called as "harringtonine" [47]. This alkaloid class is also known as "cephalotaxine". The structure of omacetaxine mepesuccinate (**18**) and related alkaloids was elegantly characterized by Powell and his colleagues [48,49]. Several alkaloids from *C. harringtonia* exhibited anticancer activity against leukemia cell lines [50]. It worth noting that homoharringtonine or omacetaxine mepesuccinate (**18**) takes more than 40 years from the first isolation (and the discovery of anticancer activity) to become a clinically used drug. Omacetaxine mepesuccinate (**18**) has the mechanism of action in preventing the initial elongation step of protein synthesis, and thus inhibiting protein translation [51], and it is used to treat chronic or accelerated phase chronic myeloid leukemia with resistance and/or intolerance to two or more tyrosine kinase inhibitors.



Omacetaxine mepesuccinate (or Homoharringtonine) (**18**)

Fig. (4). The plant alkaloid, omacetaxine mepesuccinate (**18**), approved as an anticancer drug.

Thiazole alkaloids are widely found in Nature [40-42], particularly in marine invertebrates [52,53]. Epothilones are thiazole alkaloids isolated from Myxobacteria [54], and they are leads for anticancer drug. Epothilones A (**19**) and B (**20**) were first isolated in 1993 [55] and described as antifungal and cytotoxic compounds [54,55] (Fig. (**5**)). In 1995, epothilones A (**19**) and B (**20**) were found to be microtubule-stabilizing agents, both *in vitro* and in cultured cells, sharing the same mechanism of action as that of paclitaxel (taxol) [56]. The pronounced antiproliferative activity of epothilones A (**19**) and B (**20**), together with a potent ability to stabilize microtubules (also active against multiple drug-resistant cancer cells), has led to extensive research on (medicinal) chemistry and chemical biology of these natural thiazole alkaloids. Consequently, several epothilone analogs have been synthesized and tested for anticancer properties [57-59]. Among the new epothilone derivatives, BMS-247550 (**21**) (Ixabepilone), the lactam analog of epothilone B (**20**) known as azaepothilone B, was an anticancer drug approved in 2007 for the treatment of metastatic or locally advanced breast cancer in patients whose tumors are resistant to taxane and anthracycline anticancer drugs.

Another thiazole alkaloid lead is largazole (**22**), a cyclic depsipeptide isolated from a cyanobacterium of the genus *Symploca* (Fig. (**6**)) [60]. Largazole (**22**) potently inhibits class I histone deacetylases [61], and it also exhibits a broad spectrum of biological activities [62,63]. Several largazole derivatives have been prepared, and some are promising anticancer drug candidates [62].

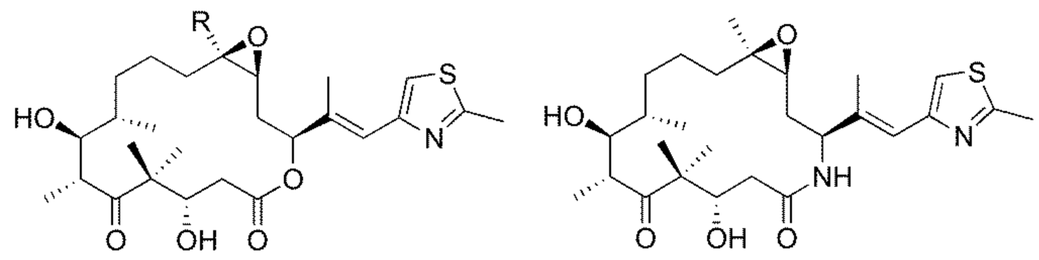


Fig. (5). Epothilones **19** and **20** isolated from Myxobacteria and an anticancer drug **21**.

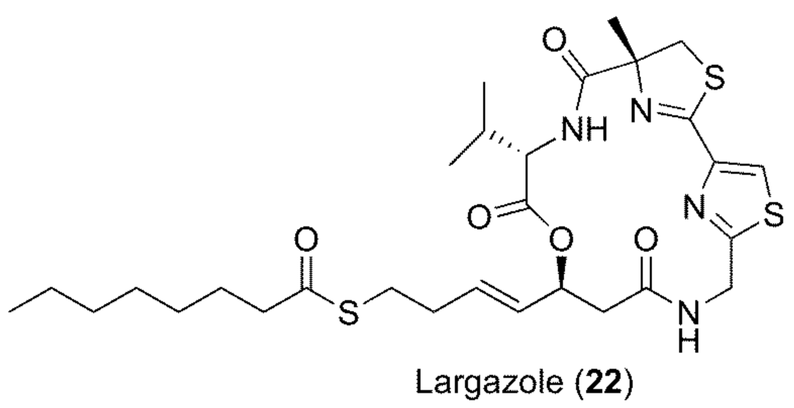


Fig. (6). Largazole (**22**) from a cyanobacterium of the genus *Symploca*

Heat shock protein 90 (Hsp90) is a chaperone protein that cancer cells use to facilitate the function of many proteins required for tumor growth. The fact that Hsp90 is essential for the tumor growth makes the Hsp90 to be one of the hot targets for cancer therapy. Undoubtedly, there are 17 Hsp90 inhibitors recently entering clinical trials [64]. Structures of several Hsp90 inhibitors are mainly inspired by two natural products, geldanamycin (**23**) and radicicol (**26**) (Fig. (**7**)). It should be noted that both geldanamycin (**23**) and radicicol (**26**) are macrolactam and macrolactone polyketides, respectively, and they do not have alkaloid scaffolds in their molecules. However, a structural transformation of the natural products **23** and **26** into alkaloid-like structures significantly improves anticancer property. As shown in Fig. (**7**), a chemical modification of the non-alkaloid geldanamycin (**23**) to the alkaloid-like structures, e. g. 17-AAG (**24**) and 17-DMAG (**25**), provided good drug properties, and the derivatives **24** and **25** are anticancer drug candidates being evaluated in clinical trials [65,66]. The resorcinol part of radicicol (**26**) is important for the inhibition of Hsp90, and the attachment of the alkaloid scaffolds to a benzene-1,3-diol derivative (a resorcinol-like unit) provides anticancer drug candidates NVP-AUY922 (**27**), CCT018159 (**28**), and AT13387 (**29**) (Fig. (**7**), which are in clinical trials [67-69]. The alkaloids scaffolds, isoxazole, pyrazole, and isoindole are attached to the derivatives **27**, **28**, and **29**, respectively. Isoxazole alkaloids [34,35] are widely present in Nature, while pyrazole [70-74] and isoindole [75-77] alkaloids are rare metabolites.

Vinca alkaloids are probably one of the most-used classes of anticancer drugs; they are dimeric indole alkaloids found in the leaves of the Madagascar periwinkle plant *Catharanthus roseus*. Vincristine (**30**) and vinblastine (**31**) were isolated from *C. roseus* (formerly known as *Vinca rosea*) in the late 1950s, and both are currently used as anticancer

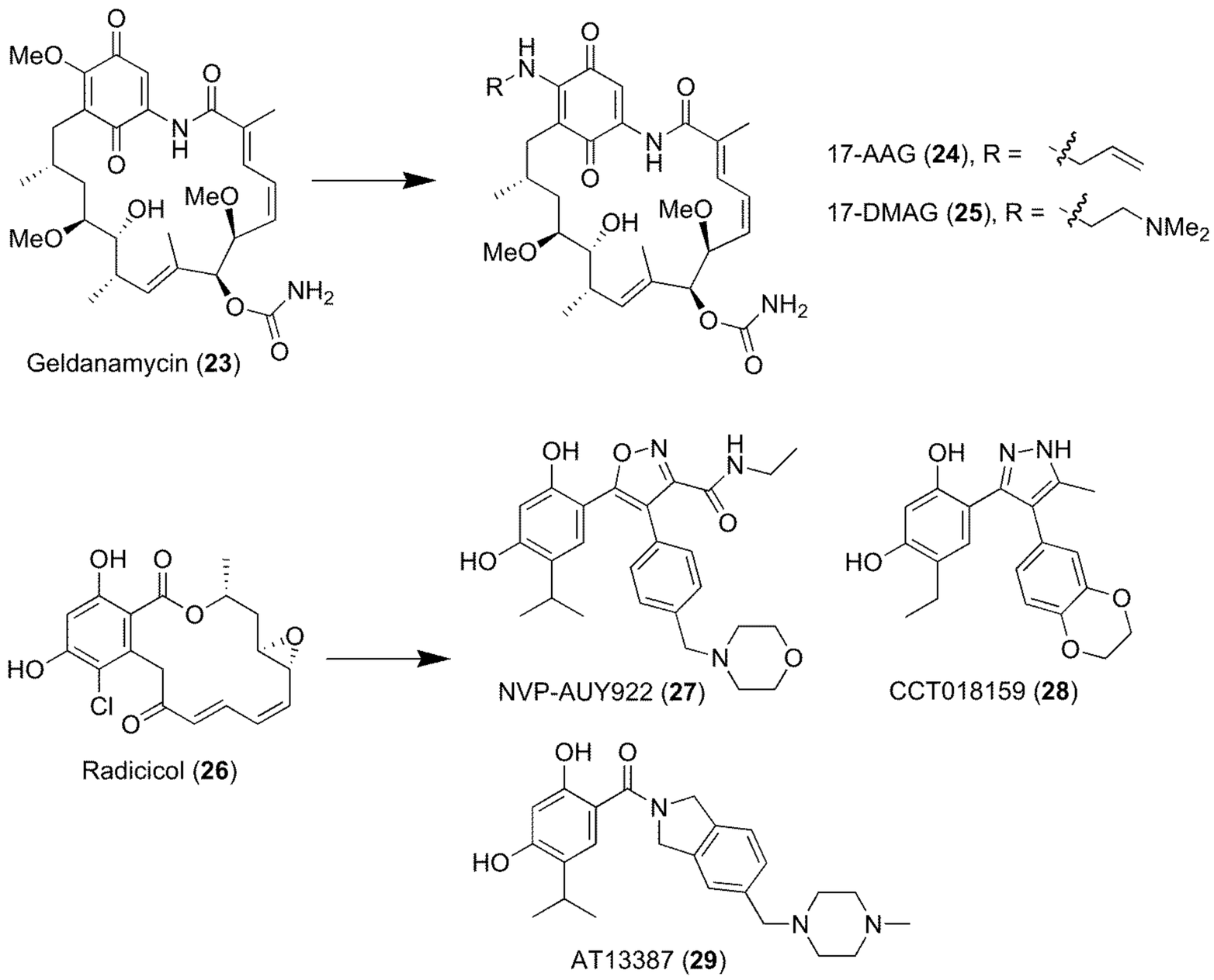


Fig. (7). Geldanamycin (**23**) and radicicol (**26**) and their derivatives decorated with alkaloid scaffolds.

drugs (Fig. (**8**)). Semi-synthetic vinca alkaloid analogs, vinorelbine and vinflunine, also play an important role in cancer chemotherapy. Vinca alkaloids exert their cytotoxicity through the inhibition of microtubule assembly by preventing tubulin polymerization. Recently, Boger and co-workers prepared a series of C20′ urea derivatives (e.g. **32**) whose potency matched or exceeded that of the parent compound, vinblastine (**31**). The findings that the hydrogen bond donor on the C20′ position is the key role for the potent vinblastine analogues open new prospects for vinblastine analogues (e.g. **32**) as anticancer leads [78]. Moreover, several potent vinca alkaloid analogs were recently prepared and extensively studied for anticancer property [79-82].

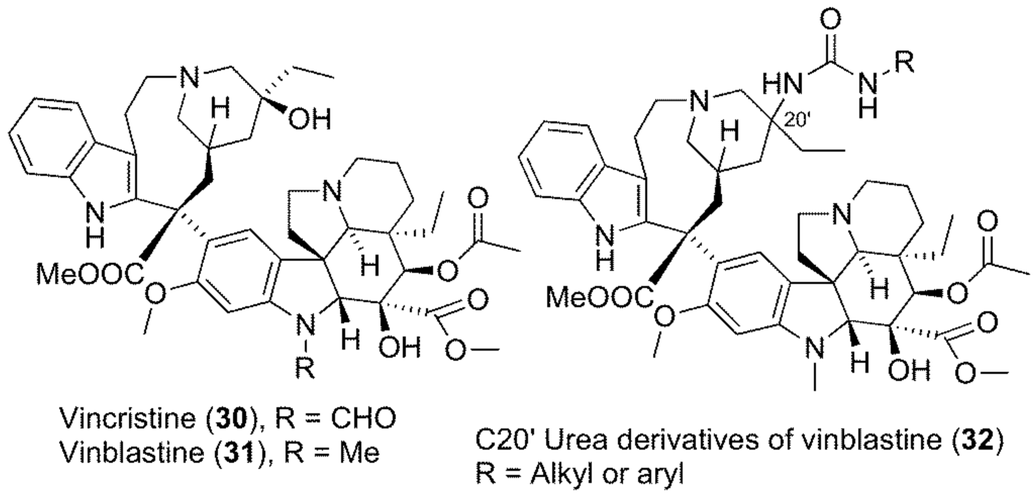


Fig. (8). Structure of vinca alkaloids (**30** and **31**) and a derivative **32**.

Ecteinascidin 743 (**33**), a tetrahydroisoquinoline alkaloid, isolated from a marine tunicate *Ecteinascidia turbinate*, was approved as an anticancer drug in 2007 (Fig. (**9**)). Ecteinascidin 743 (**33**) exhibits anticancer activity by the selective alkylation of the minor groove of DNA with preference for GC-rich triplets through covalently bonding at the N2-position of guanine [83].

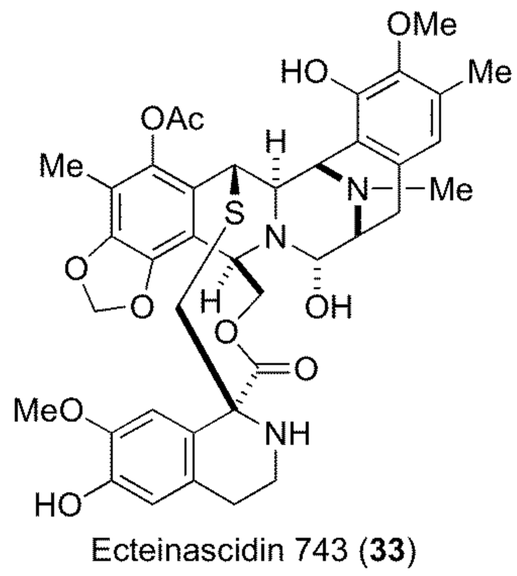


Fig. (9). Structure of ecteinascidin 743 (**33**).

Duocarmycins, i.e. duocarmycin SA (**34**), are indole alkaloids produced by the bacterium *Streptomyces* sp., and they exhibit potent cytotoxic activity by binding to the minor groove of DNA and alkylating the AT-rich adenine at the N3 position [84]. CC-1065 (**35**) and its derivatives, i.e. (+)-CBI-indole$_2$, are promising anticancer drug candidates (Fig. (**10**)) [85]. Recently, duocarmycin carbamate prodrug (**36**) was found to exhibit *in vivo* efficacy exceeded that of (+)-CBI-indole$_2$, and it also had higher therapeutic window of efficacy versus toxicity than (+)-CBI-indole$_2$ [86].

Inhibition of topoisomerases, the enzymes that control DNA supercoiling and entanglements, is an effective mechanism of action for anticancer drugs [87]. Camptothecin (**37**),

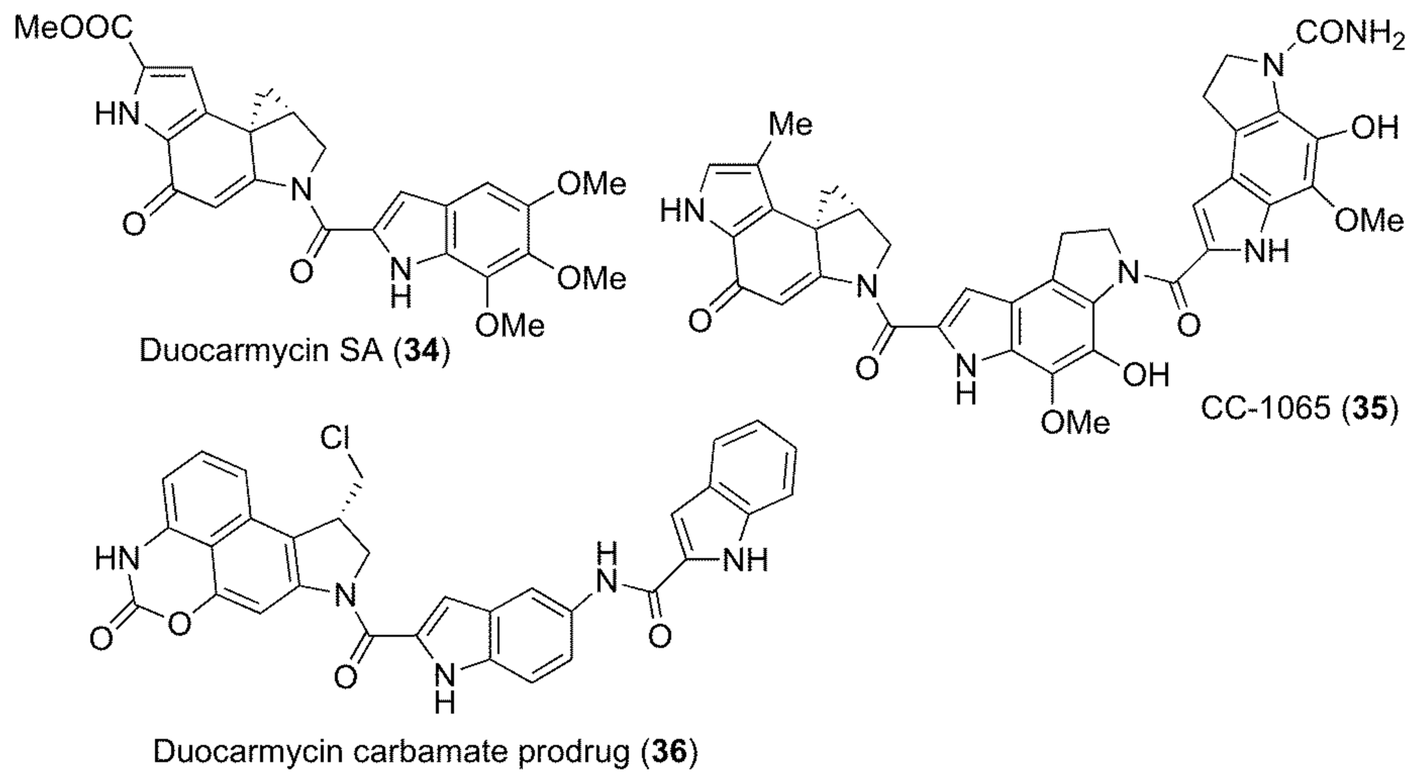


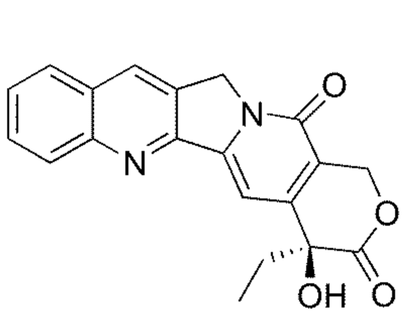
Fig. (10). Structure of duocarmycin SA (**34**) and derivatives (**35** and **36**).

a quinoline alkaloid from *Camptotheca acuminate*, displays the inhibition of topoisomerase type I (Fig. (**11**)). Camptothecin (**37**) is an anticancer lead, and its derivatives (Topotecan and Irinotecan) are approved as anticancer drugs. Several camptothecin derivatives were found to exhibit pronounced anticancer activity [88,89]. Podophyllotoxin (**38**), a lignan from many plant species of the Podophyllum family, is an anticancer lead. Two semi-synthetic podophyllotoxin derivatives, etoposide and teniposide, are currently used for the treatment of various types of cancer. It is worth mentioning that the transformation of a non-alkaloid lignan podophyllotoxin (**38**) to alkaloid-like structures, GL-331 (**39**) and F14512 (**40**), led to pronounced increase of cytotoxic activity; compounds **39** and **40** are in clinical trials for cancer treatment (Fig. (**11**)) [87,90,91]. Moreover, podophyllotoxin derivatives decorated with a pyrazole alkaloid moiety are recently found to exhibit significant antiproliferative activity [92]. Lamellarins, e.g., lamellarin D (**41**) (Fig. (**11**)), are polyaromatic pyrrole alkaloids isolated from marine tunicates and mollusks, and they have recently gained great attentions from medicinal chemists due to unique structural features and potent cytotoxicity. Total synthesis of lamellarins has been well established [93-96]; several lamellarin derivatives exhibited potent anticancer activity [97-99], and were selective inhibitors of HIV-1 integrase [99,100]. Lamellarin D (**41**) is particularly of interest, because it is an anticancer lead inhibiting topoisomerase type I [101]. Several natural topoisomerase inhibitors have been isolated from natural sources [102]; some inhibitors show potent activity and become anticancer leads, for example, taspine (**42**) from *Croton lechleri* and evodiamine (**43**) from *Evodiae fructus* (Fig. (**11**)) [103,104]. Taspine (**42**) (also known as thaspine) and its derivatives showed promising anticancer properties [105-108]. The taspine analog, HMQ1611, inhibited growth of breast cancer and non-small cell lung cancer [109,110]. The derivatives of evodiamine (**43**) showed good *in vivo* antitumor efficacy with low toxicity, and thus representing a new class of anticancer drug candidate [104].

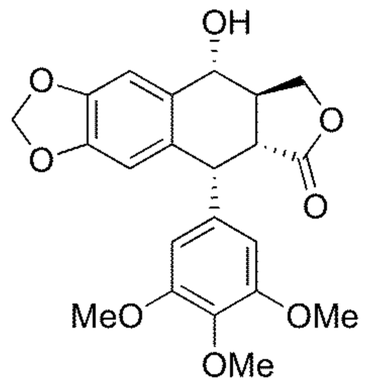
ALKALOID SCAFFOLDS IN DRUGS FOR THE TREATMENT OF TUBERCULOSIS

While a number of patients infected with tuberculosis and a number of multi- and extensively-drug resistant tuberculosis strains have gradually increased each year, only few first-line drugs including isoniazid, rifampicin, ethambutol, pyrazinamide, and streptomycin are available for the treatment of tuberculosis. In 2011, the World Health Organization (WHO) reported that 8.7 million people fell ill with tuberculosis and 1.4 million people died from tuberculosis [111]. The last drug (rifampicin) approved for the treatment of tuberculosis was in 1960s. However, due to the emergence of multi- and extensively-drug resistant tuberculosis strains and the increase number of tuberculosis infection worldwide, there is an urgent need for new anti-tuberculosis (anti-TB) drugs. Recently, there are a few anti-TB drug candidates in clinical trials, as well as in the drug pipeline. Alkaloid scaffolds play an important role in the tuberculosis drug development pipeline, as they always parts of the molecules of anti-TB agents in clinical trials. The alkaloid scaffolds in the anti-TB drug candidates are quinoline, imidazole, quinolinone, and oxazolidinone. The scaffolds of quinoline [36-39], imidazole [34,40-42], and quinolinone [112-116] are widely found in Nature, however, the oxazolidinone scaffold [117,118] is rarely seen in natural products.

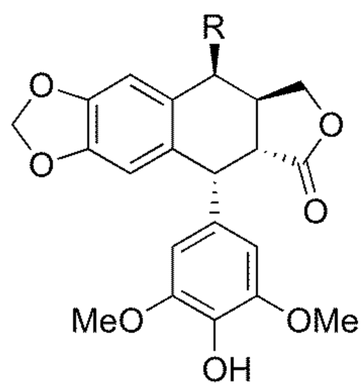
TMC207 (**44**) (also known as R207910) is a new anti-TB drug approved in 2012 by the US FDA (Fig. (**12**)), and its molecule has a quinoline alkaloid scaffold. TMC207 (**44**) is not only the first anti-TB drug in four decades, but also a new anti-TB drug with a new mechanism of action. TMC207 (**44**) targets the proton pump of adenosine triphosphate (ATP) synthase of *Mycobacterium tuberculosis*, and thus specifically inhibiting the mycobacterial ATP synthase [119]. OPC-67683 (**45**) or Delamanid is a nitroimidazole showing effectiveness in patients with multidrug-resistant pulmonary tuberculosis (Fig. (**12**)) [120], and it may be approved as an anti-TB drug in 2013 (in Europe). OPC-67683 (**45**) exerts anti-TB activity with the same mechanistic action as that of an anti-TB isoniazid drug, which inhibits mycolic acid biosynthesis that is essential process for the formation of mycobacterial cell wall [121]. The anti-TB imidazole namely PA-824 (**46**) (Fig. (**12**)), exhibiting the same mechanism of action as that of OPC-67683 (**45**), is now in Phase II clinical trials [122]. Gatifloxacin (**47**) and moxifloxacin (**48**), the fourth-generation fluoroquinolone antibiotic drugs (Fig. (**12**)), are currently in clinical trials for the treatment of

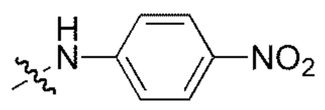


Camptothecin (**37**)

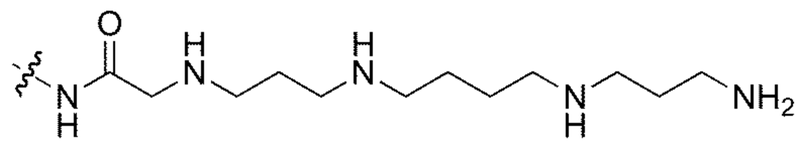


Podophyllotoxin (**38**)

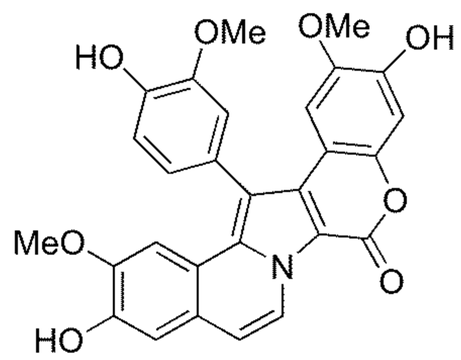




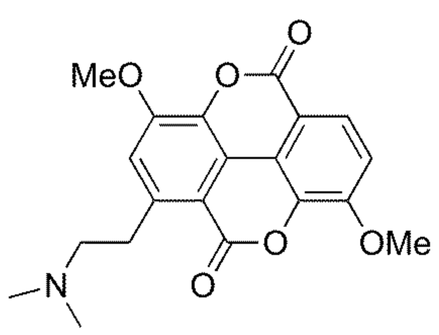
GL-331 (**39**), R =



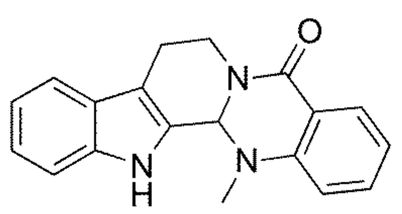
F14512 (**40**), R =



Lamellarin D (**41**)

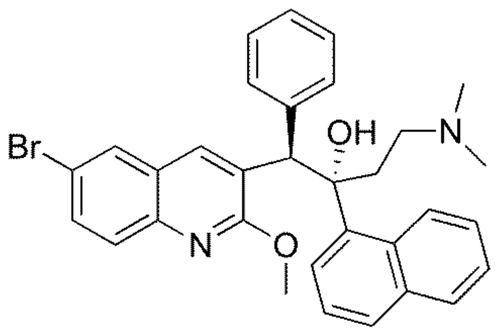


Taspine (**42**)

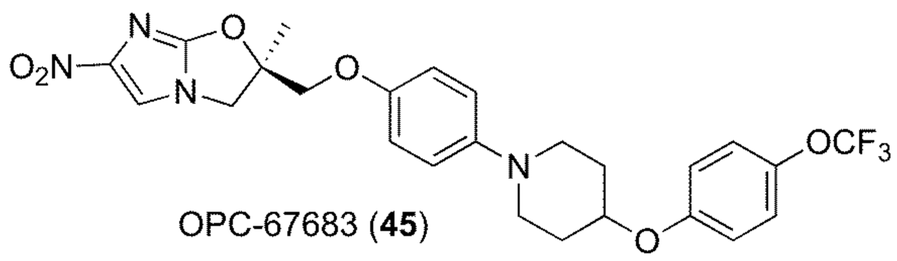


Evodiamine (**43**)

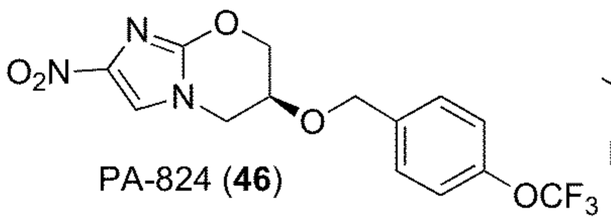
Fig. (11). Inhibitors of topoisomerases as anticancer drugs (or leads).



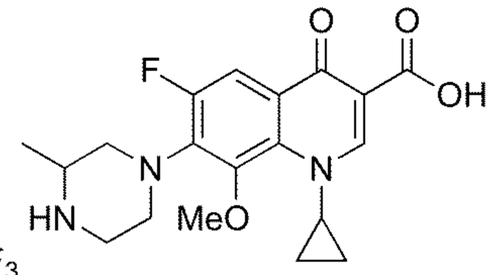
TMC207 (**44**)



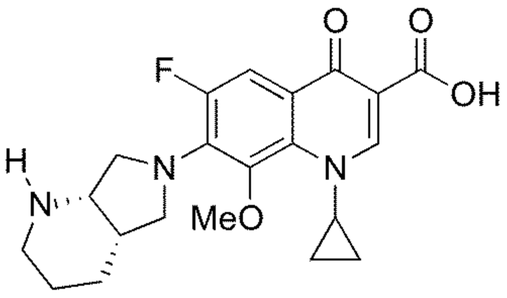
OPC-67683 (**45**)



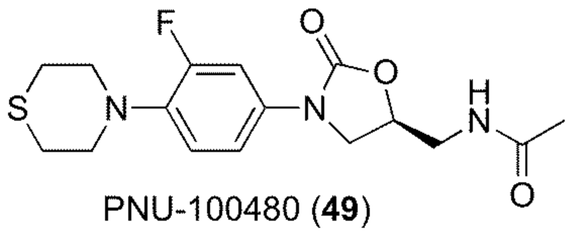
PA-824 (**46**)



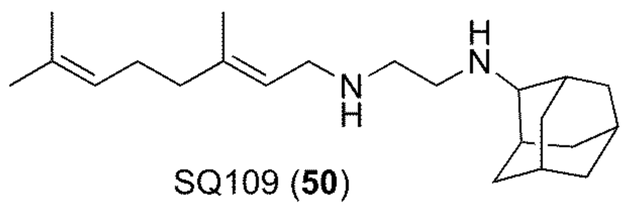
Gatifloxacin (**47**)



Moxifloxacin (**48**)



PNU-100480 (**49**)



SQ109 (**50**)

Fig. (12). Structures of a new drug TMC207 (**44**) and promising anti-TB drug candidates **45**-**50**.

tuberculosis [123,124]. The quinolones **47** and **48** inhibit *M. tuberculosis* DNA gyrase. PNU-100480 (**49**) is an oxazolidinone anti-TB agent whose mechanism of action is through the inhibition of an early step in the initiation phase of protein synthesis [125]. PNU-100480 (**49**) exhibited promising drug properties in Phase II clinical trials [126]. SQ109 (**50**) has an alkaloid-like structure with a diamine-containing geranyl moiety (Fig. (**12**)). SQ109 (**50**) affects mycobacterial cell wall synthesis, targeting at a membrane transporter of trehalose monomycolate (MmpL3) that involved in mycolic acid donation to the cell wall core of *M. tuberculosis* [127]. SQ109 (**50**) is in Phase II clinical trials [128]. The new anti-TB drug TMC207 (**44**) and the drug candidates **45**-**50** are likely to play a crucial role in future tuberculosis therapy.

There are also few potent anti-TB agents in preclinical phase. Caprazamycin and capuramycin, pyrimidine-derived antibiotics isolated from actinomycete bacteria of the genus *Streptomyces* [129,130], are anti-TB natural product leads. CPZEN-45 (**51**) is a caprazamycin analog which is in preclinical pipeline for anti-TB drug development [131], while SQ641 (**52**), a capuramycin derivative (Fig. (**13**)), exhibits significant anti-TB activity in a mouse model [132]. BDM31343 (**53**), an oxadiazole compound, is a potent inhibitor of EthR, a repressor protein of the ethionamide (a second-line anti-TB drug) resistance in mycobacteria (Fig. (**13**)) [133]. BDM31343 (**53**) is in preclinical pipeline. Alkaloids with an oxadiazole moiety are rare in Nature, only few natural oxadiazole alkaloids have been reported so far

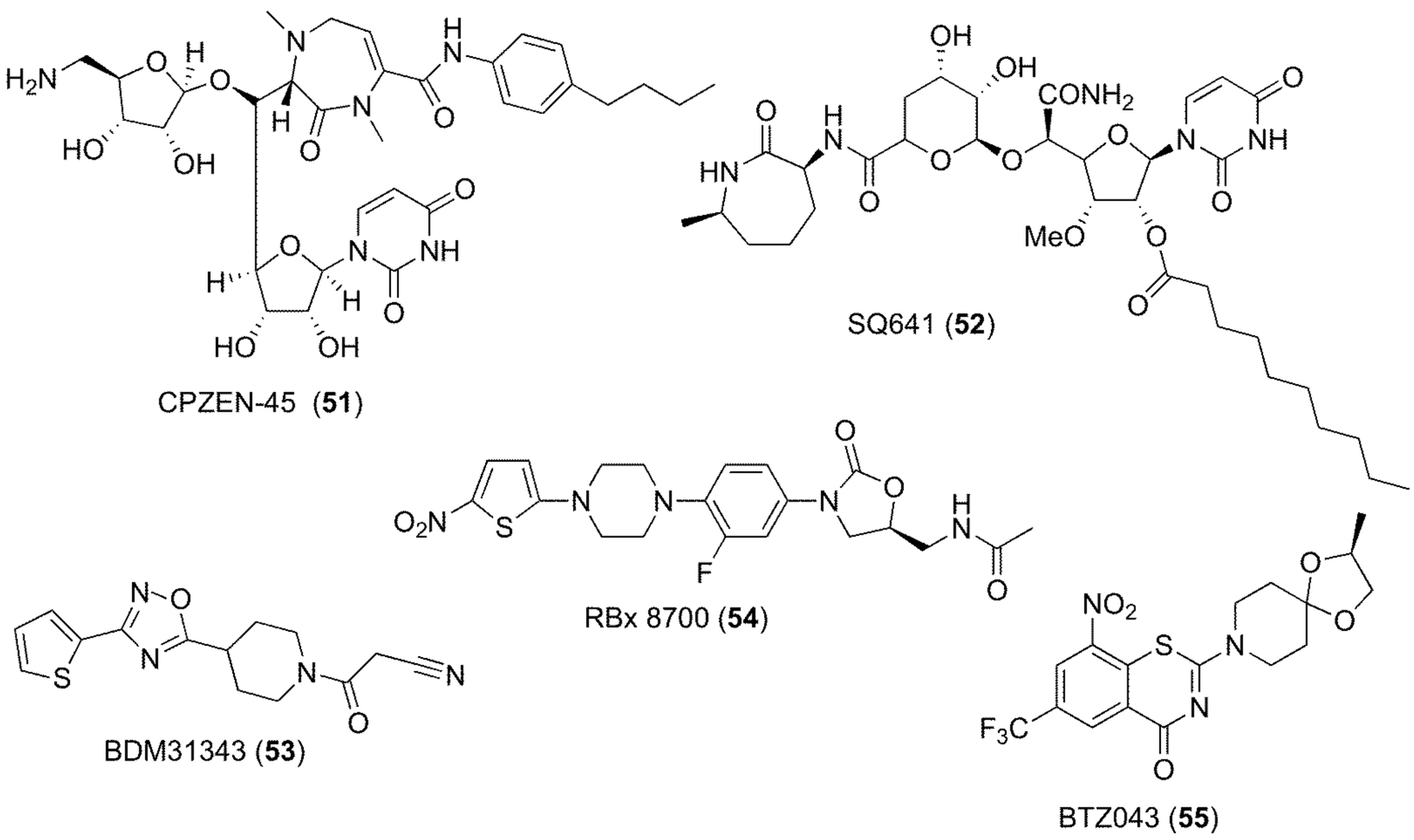


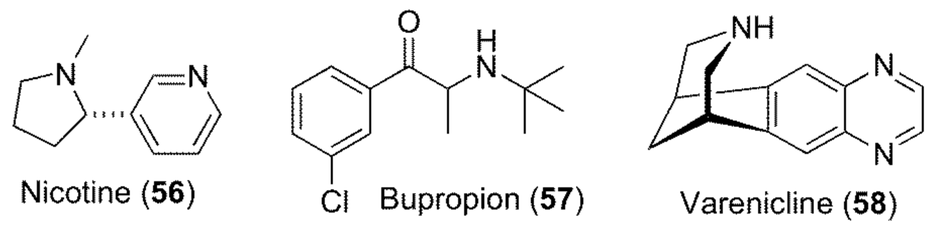
Fig. (13). Anti-TB leads (**51**-**55**) in preclinical phase.

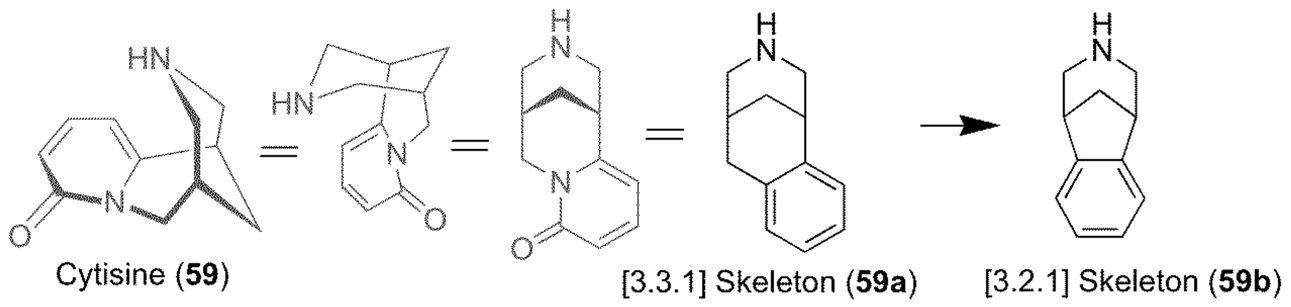
[134,135]. An oxazolidinone RBx 8700 (**54**) showed excellent antimycobacterial and antibacterial activities (Fig. (**13**)) [136,137], and thus entering a preclinical phase. Natural oxazolidinone alkaloids are rarely found in Nature [117,118]. Among anti-TB drug candidates being evaluated in preclinical phase, BTZ043 (**55**), an anti-TB lead decorated with an alkaloid-like scaffold known as benzothiazinone (Fig. (**13**)), is considered as a new class of antimycobacterial agents, because it is a prodrug that generates a nitroso intermediate *in vivo* [138]. The nitroso intermediate in turn causes a suicide inhibition of decaprenylphosphoryl-β-D-ribose 2′ oxidase, which is the enzyme responsible for cell wall arabinogalactan biosynthesis of *M. tuberculosis* [139]. Benzothiazinone is extremely rare in Nature [140].

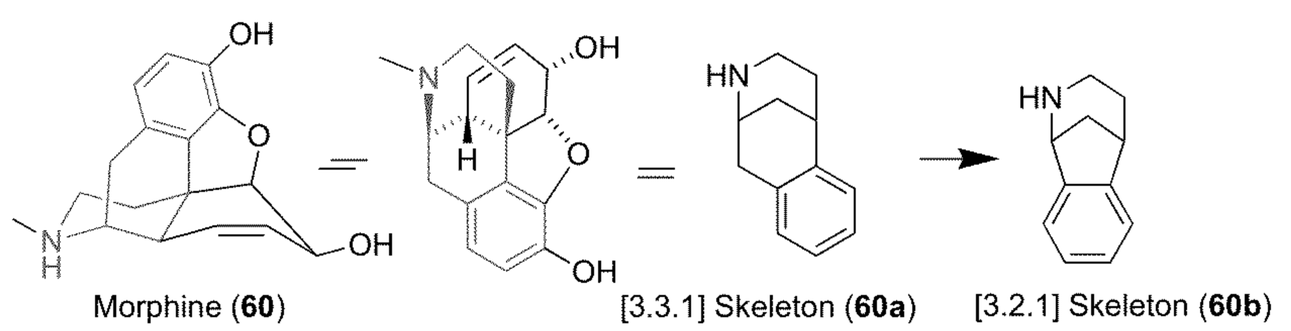
ALKALOID SCAFFOLDS IN SMOKING CESSATION DRUGS

Tobacco smoking is a serious threat to human health, and causes several health risks and particular diseases, for example, lung cancer, coronary heart disease, and chronic obstructive pulmonary disease. Nicotine (**56**), a psychoactive alkaloid in tobacco, is known to cause smoking addition (Fig. (**14**)). Actions of nicotine (**56**) are mediated by nicotinic acetylcholine receptors (nAChRs), which lead to the release of neurotransmitters such as dopamine, glutamate, and GABA (γ-aminobutyric acid) [141], and thus giving behavioral effects. The fact that the nicotine withdrawal syndrome that accompanies smoking cessation would lead to negative effects (such as anxiety, depressed mood, difficulty concentrating, disrupted cognition, and irritability) urges the need for the medication of tobacco cessation [141]. Apart from the nicotine replacement therapy (in the forms of transdermal patches, chewing gums, nasal sprays, and inhalers) that is widely employed as a substitution for tobacco smoking, non-nicotine drugs are also used for smoking cessation. The drugs for smoking cessation commonly target at nAChRs, monoamine oxidase B, dopamine D3 receptor, and cannabinoid receptor type 1.

Alkaloid scaffolds play a major role in drugs for smoking cessation therapy. Bupropion (**57**) and varenicline (**58**) are non-nicotine drugs (Fig. (**14**)) using as a first-line treatment for smoking cessation. Both bupropion (**57**) and varenicline (**58**) were initially designed as antidepressant drugs, however, they showed efficacy equal to or better than nicotine replacement therapy [142]. The mechanism of action of bupropion (**57**) is through the inhibition of dopamine and norepinephrine reuptake [143,144]. The structure of varenicline (**58**) is inspired by a plant alkaloid, cytisine (**59**) (Fig. (**14**)). Varenicline (**58**) exhibits its activity as a partial agonist of nAChRs, and thus causing the release of a constant low level of dopamine (a reward neurotransmitter after tobacco smoking) [145]. It is worth mentioning that the discovery of varenicline (**58**) skeleton was inspired by morphine (**60**) and its antinociceptive activity; it was previously found that morphine derivatives with the [3.3.1]-bicyclic skeleton (i.e. **60a**) exhibited morphine-like antinociceptive activity, as did the modified [3.2.1]-bicyclic derivative (**60b**) (Fig. (**14**)) [146]. Surprisingly, this analogy could also be applied for cytisine (**59**) and its nAChRs binding activity; the [3.2.1]-bicyclic cytisine analog (i.e. **59b**) exhibited the same activity as that of the [3.3.1]-bicyclic skeleton (**59a**) (Fig. (**14**)) [145]. Varenicline (**58**) is the [3.2.1]-bicyclic version of a natural product cytisine (**59**). A bicyclic alkaloid cytisine (**59**) is normally found in few plants including *Laburnum anagyroides*, *Sophora alopecuroides*, *Thermopsis lanceolata*, and *Caragana sinica* [147]. Although cytisine (**59**) has been widely used for smoking cessation in some countries in Eastern Europe, it has not yet been approved in U.S.A and Western Europe. Cytisine (**59**) is now in Phase III clinical trials for smoking cessation in U.S.A. [148]. Nalmefene (**61**) and naltrexone (**62**), morphine derivatives acting as opioid-system modulators (Fig. (**14**)), are in phase II clinical trials for smoking cessation [149]. Both nalmefene (**61**) and naltrexone (**62**) are originally designed for the management of alcohol dependence (alcoholism treatment).







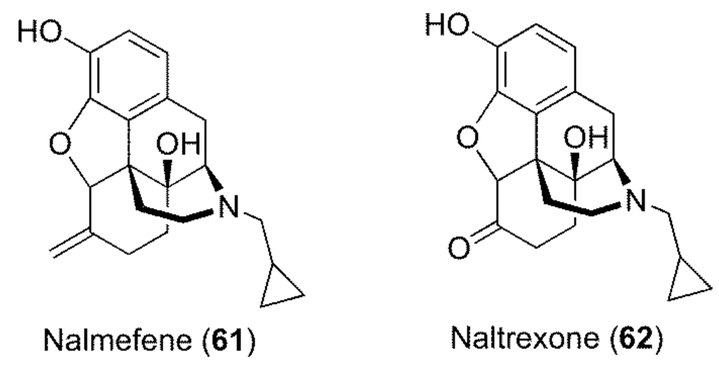
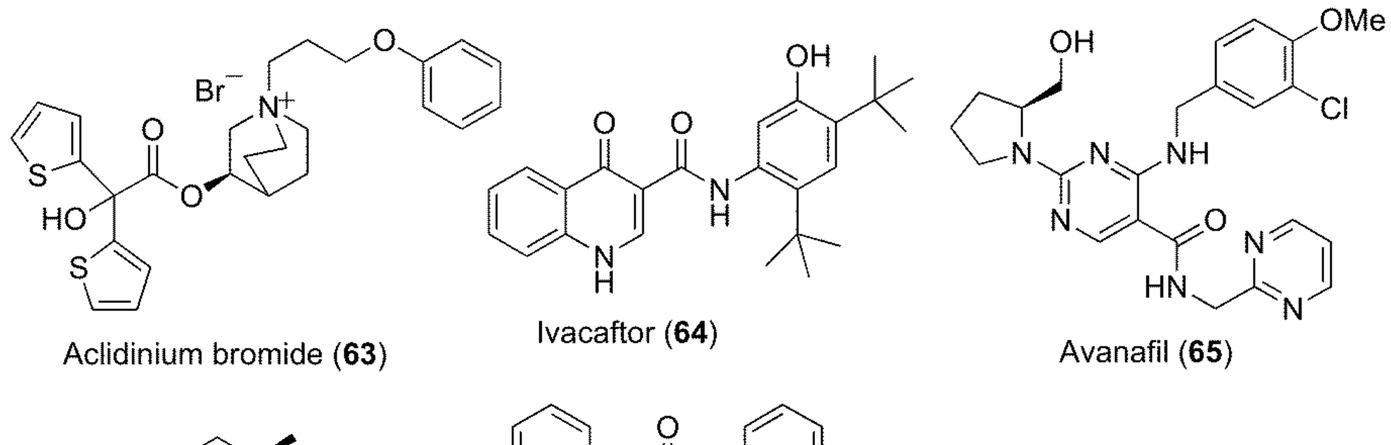
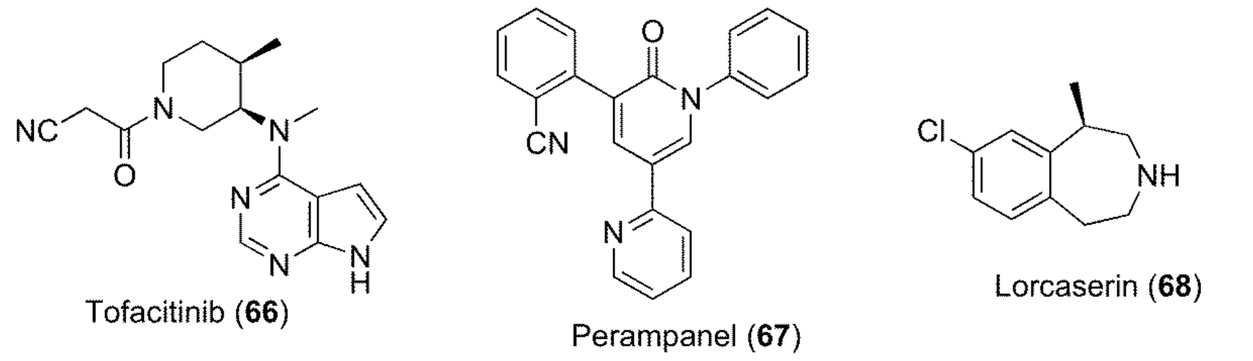


Fig. (14). Structures of nicotine (**56**), bupropion (**57**), varenicline (**58**), cytisine (**59**), and morphine (**60**); [3.3.1]- and [3.2.1]-bicyclic skeletons (**59a**, **59b**, **60a**, and **60b**); and drug candidates **61** and **62**.





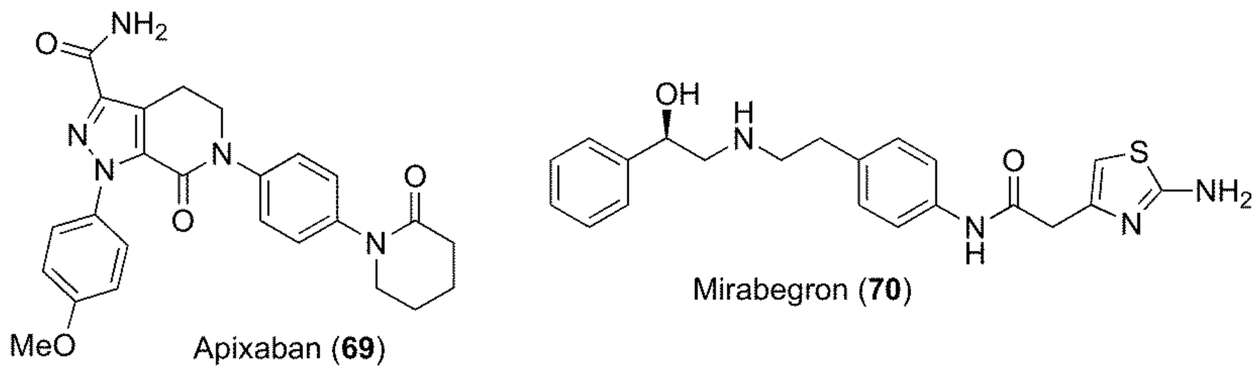


Fig. (15). Structure of aclidinium bromide (**63**), ivacaftor (**64**), avanafil (**65**), tofacitinib (**66**), perampanel (**67**), lorcaserin (**68**), apixaban (**69**), and mirabegron (**70**).

MISCELLANEOUS DRUGS (APPROVED IN 2012) WITH ALKALOID SCAFFOLDS

Aclidinium bromide (**63**) is a new drug approved in 2012 for the treatment of chronic obstructive pulmonary disease (COPD) (Fig. (**15**)). Aclidinium bromide (**63**) is a muscarinic receptor antagonist which is inspired by natural occurring atropine and scopolamine alkaloids [150]. Traditional medicine used atropine and scopolamine for centuries for the treatment of asthma [150]. Ivacaftor (**64**), a quinolin-4-one derivative, was approved for the treatment of cystic fibrosis (Fig. (**15**)). Several natural alkaloids with a quinolin-4-one scaffold are found in living organisms [36,37]. Ivacaftor (**64**), also known as Vx-770, enhances ATP-independent activity and increases the open time of wild-type cystic fibrosis transmembrane conductance regulator chloride channel in an ATP-dependent manner [151]. Avanafil (**65**), a pyrimidine derivative (Fig. (**15**)), was approved in 2012 for the treatment of erectile dysfunction; it is a potent and highly selective phosphodiesterase-5 inhibitor [152].

Tofacitinib (**66**) is an inhibitor of Janus protein tyrosine kinase family (JAK) approved in 2012 for the treatment of rheumatoid arthritis (Fig. (**15**)) [153]. The drug tofacitinib (**66**), also known as CP-690,550, is also in clinical trials for the treatment of psoriasis [154], chronic inflammatory disease (ulcerative colitis) [155], and organ transplant rejection [156]. Perampanel (**67**) was approved for the treatment of epilepsy; it is a selective α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor antagonist that modulates AMPA-mediated excitatory neurotransmission (Fig. (**15**)) [157]. Lorcaserin (**68**), a benzazepine alkaloid (Fig. (**15**)), is a selective serotonin 5-hydroxytryptamine$_{2C}$ (5-HT$_{2C}$) receptor agonist [158]. The benzazepine scaffold is found in many naturally occurring alkaloids, for example, harringtonine or cephalotaxine [48,49], isopavine [159], and lennoxamine [160]. Lorcaserin (**68**) was approved in 2012 for the treatment of obesity (weight management). Apixaban (**69**) is an anticoagulant drug for the treatment of stroke and systemic embolism in patients with non-valvular atrial fibrillation (Fig. (**15**)). Apixaban (**69**) is a potent, direct, selective, and orally active inhibitor of coagulation factor Xa [161]. Mirabegron (**70**), a thiazole derivative (Fig. (**15**)), is β_3-adrenoceptor agonist [162] approved for the treatment of overactive bladder.

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflicts of interest.

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