International Journal of Advanced Pharmaceutical Sciences and Research (IJAPSR)
ISSN: 2582-7618 (Online), Volume-4 Issue-1, December 2023

A Review Study of Proline-Derived Paclitaxel as Treatment Anti Cancers

Neamah Omar Alshhada, Haya Asmail Alhamdo, Nasser Thallaj

Abstract: ***Of the numerous helpful specialists utilized in oncology, paclitaxel (Taxol) has likely pulled in the foremost intrigued. It is utilized clinically to treat ovarian, breast and lung cancer and acts as a mitotic axle harm by advancing the get together of tubulin into microtubules and stabilizing the coming about polymer. It was initially extricated from Pacific yew (Taxus Brevifolia) and gotten by semi-synthesis of 10-deacetylbaccatin III, but is presently created by a biotechnological prepare of plant cell maturation. Paclitaxel encompasses a complex chemical structure based on a tetracyclic taxane. To recognize paclitaxel mimetics, a handle of supplanting the taxane spine with a less difficult chemical structure was carried out. The recognizable proof of a proline-derived chemical part (fragment-based medicate plan) through atomic modeling ponders driven to the advancement of a unused arrangement of paclitaxel imitates. In the interim, substitution of the taxane spine with a cyclic peptide structure utilizing proline subsidiaries was carried out. Atomic modeling considers, union and natural assessment o f paclitaxel mimetics are displayed.***

Keywords: Paclitaxel, Taxol, Tubulin, Microtubule, Cancer, Proline, Mimic, Fragment, Cyclotriproline.

I. INTRODUCTION

Medicinal chemistry is a branch of science that aims to identify, design, evaluate and develop molecules for therapeutic purposes. It uses the knowledge of chemists, biologists, pharmacokinetics and pharmacologists to discover new bioactive substances that could become the medicines of the future. As part of this "drug discovery" process, the molecules being synthesized must meet certain criteria to enter the drug candidate stage and continue the development process towards its preclinical and clinical stages. Simultaneous optimization of all these parameters is a major challenge for medicinal chemists [1,2].

Manuscript received on 18 November 2023 | Revised Manuscript received on 27 November 2023 | Manuscript Accepted on 15 December 2023 | Manuscript published on 30 December 2023.

*Correspondence Author(s)
Neamah Omar Alshhada, Student, Department of Pharmaceutical chemistry and Drug Quality Control, Faculty of Pharmacy, Al-Rachid Privet University, Damascus, Syria. E-mail: merissamccready@hotmail.com
Haya Asmail Alhamdo, Student, Department of Pharmaceutical Chemistry and Drug Quality control, Faculty of Pharmacy, Al-Rachid Privet University, Damascus, Syria. E-mail: nmasy192@gmail.com
Prof. Nasser Thallaj*, Department of Pharmaceutical Cchemistry and Drug Quality Control, Faculty of Pharmacy, Al-Rachid Privet University, Damascus, Syria. E-mail: profthallaj@gmail.com, ORCID ID: 0000-0002-6279-768X

The synthesized molecules must have biological activity and selectivity for the target, they must have good physicochemical and pharmacokinetic properties (ADME), they must not be toxic or interact with other drugs. In addition, they must have a chemically patentable structure and be industrialized for further development (Figure 1).

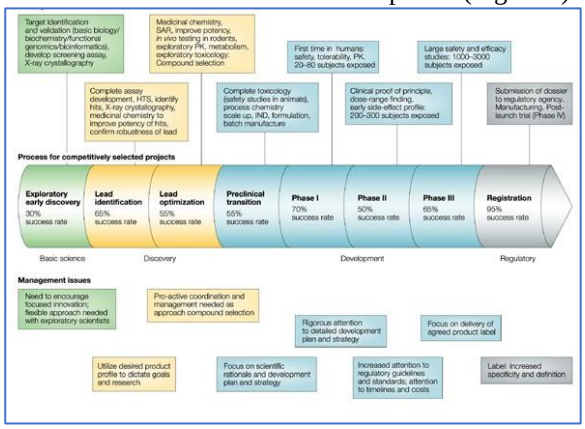

Figure 1: From Molecule to Drug Candidate: A Set of Parameters to Optimize

Thanks to the vast reserves of natural compounds, nature has provided medicinal chemists with many complex chemical compounds with many biologically active properties. These compounds are found in microorganisms, plants, and marine life and have been used to treat diseases such as cancer (Figure 2). The potential of these natural molecules for medicinal chemists is enormous, and further investigation of these compounds may reveal many new bioactive molecules [2-5].

Figure 2: Chemical Diversity Provided by Nature's Biodiversity

(a) Micro-organisms represent several million species. (b) Plants are estimated at nearly 300,000 species. (c) Marine organisms (sponges, algae, corals) are estimated at 500 000 species. The therapeutic use of paclitaxel was hindered by its low yield and reliance on non-renewable sources. Synthetic production of paclitaxel emerged as a viable alternative, allowing for large-scale manufacturing and improved availability. However, economic challenges persisted despite successful total synthesis, leading to the exploration of alternative production methods such as heme synthesis and fermentation.

To overcome the limitations of paclitaxel, researchers investigated the use of amino acids and peptides as starting points for paclitaxel mimetics. This approach relies on understanding the structure-activity relationship and spatial configuration of the natural product at the binding site. Peptides, mimicking natural non-peptide molecules, offer a promising alternative. The study aimed to determine if a peptide could effectively mimic paclitaxel, with implications similar to morphine's resemblance to peptides in structure and conformation. Morphine's binding site overlaps with endogenous peptides like enkephalin and endorphins (see Figure 3). Conversion of a complex non-peptide natural molecule into a stable peptide-like structure involves rearranging functional groups that participate in target-specific interactions **[**1-6**].**

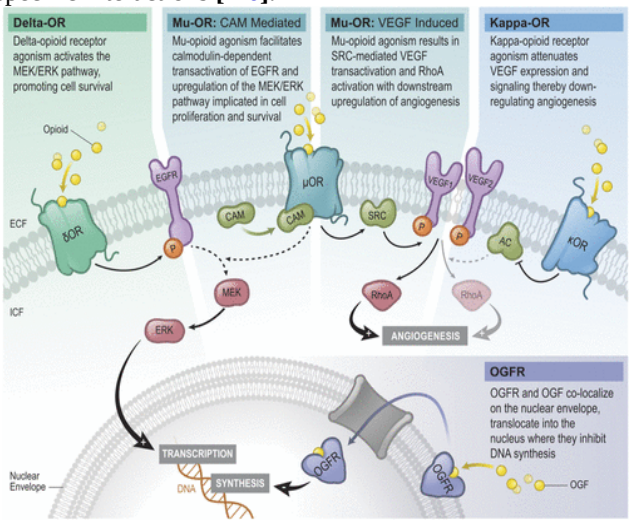

Figure 3: Common Morphine and Encephalin Interactions for the Opioid Receptor

This approach is particularly useful due to the diverse shapes and functions of amino acids, enabling the creation of different matrices. With molecular modeling techniques, a matrix can be identified to orient paclitaxel's active groups and maintain target binding, potentially improving drug efficacy.

II. CANCER AND RELATED THERAPIES

A. Cancer

a. Definition and Origins of Cancer

Cancer is a neoplastic disease characterized by uncontrolled cell growth independent of regulatory signals from neighboring cells or the organism. This abnormal cell division leads to tumor development, which can be classified as hematological malignancies affecting the blood and lymphatic system, or solid malignancies. Metastasis, the spread of cancer cells from the primary tumor to other organs, poses a significant challenge in cancer treatment. Current research aims to understand the molecular mechanisms underlying metastasis progression to develop preventive and control strategies. The incidence of cancer has risen significantly in recent centuries, but historical evidence predates this period. The term "cancer" originates from Hippocrates, who named it after the crab due to tumor shapes resembling crab claws. Galen, an ancient Greek physician, proposed a theory linking cancer to an imbalance of black bile. This theory suggested surgical interventions were ineffective for invasive tumors and viewed their appearance as a reflection of systemic dysfunction, a belief that persisted for centuries [1,2].

B. Epidemiological Data

Cancer deaths have steadily increased worldwide, reaching 12.2 million in 2023, with the highest number in France at 160,000. This trend is predicted to continue, with an estimated 14.1 million deaths in 2030. Cancer is currently the leading cause of death in our country.

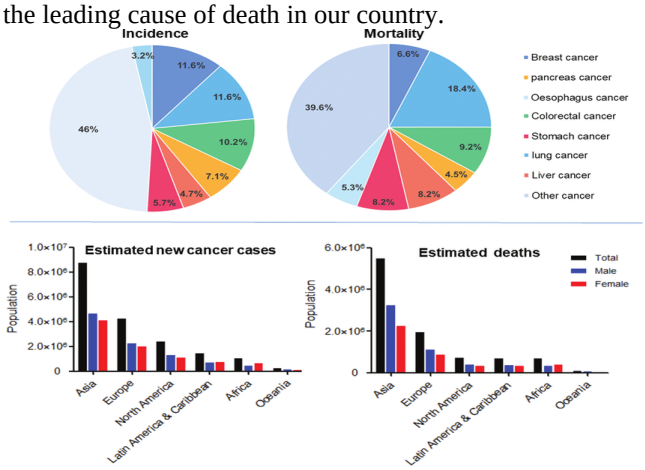

Figure 4: Mortality by Type of Cancer Worldwide in 2023

In men, lung, liver and stomach cancers cause the most deaths. In women, these are breast, lung and stomach cancers (**Figure 4**).

Experts from the International Agency for Research on Cancer (IARC) predict a significant increase in cancer cases in the coming years due to population growth and aging. Predictions concern 19.3 million cases in 2025. Social and economic changes in developing countries, transition to the lifestyle of rich countries contribute to increasing these numbers.

C. Mechanisms of Cancerisation

a. Cancer Cells

The progression of the tumor phenotype changes the properties of the cancer cells. They no longer respond to the signals that regulate their growth and spread, avoid the predetermined process of cell death (apoptosis), can multiply indefinitely, produce angiogenesis (tumor vascularization), and have invasive power into adjacent tissues. 5.6 Cancers are complex diseases with multiple causes. Genetic mutations (random or inherited) can affect the structure of a gene and prevent it from working properly. Behavioral factors (tobacco, alcohol, diet, physical activity), exposure to risk factors (UV radiation, radiation) are all factors that can eventually lead to cancer [3,4].

b. The Different Types of Cancer Genes

Three types of genes are involved in the regulation of cell growth, which play a role in the development of cancer cells. Oncogenes are genes whose expression contributes to the development of cancer.

Retrieval Number: 100.1/ijapsr.A4036124123
DOI:10.54105/ijapsr.A4036.124123
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They are caused by changes in normal genes called proto-oncogenes. Oncogenes stimulate cells to grow freely and promote the growth of cancer cells. Mutations leading to oncogenes can be inherited or caused by exposure to a carcinogen. Examples of known oncogenes are listed in Table 1.

Table 1: Examples of Known Oncogenes and Associated Cancers

Oncogenes	Role and Associated Cancers
RET	A gene that encodes a growth factor receptor, associated with breast, salivary and ovarian cancers.
HER-2	A gene that codes for a growth factor receptor, associated with breast cancer.
Ki-ras	A gene that encodes cytoplasmic relays in stimulation pathways, associated with lung, ovarian, pancreatic and colon cancers.
Bcl-2	A gene that encodes a protein that blocks cell suicide, associated with B-cell lymphomas.

Oncogenes are targeted through their signaling pathway with new therapies (monoclonal antibodies, protein kinase inhibitors) developed later. Tumor suppressor genes usually protect against cancer. They act as a brake, stopping the growth of cells and controlling their death. When tumor suppressor genes are damaged, missing, or not working properly, cell growth, division, and death are disrupted [4, 5]. Some examples of tumor suppressor genes are listed in Table 2.

Table 2: Examples of Tumour Suppressor Genes and Associated Cancers

Suppressor Genes Tumors	C Associated Cancers
Rbl	Retinoblastoma osteosarcoma
P53	Different types of Tumors
BRCAl	Breast cancer

DNA repair genes are responsible for repairing damaged genes. They correct mutations that normally occur when DNA is copied. If these genes themselves are damaged, it is possible that the mutations will not be repaired and will accumulate [6].

c. The Initiation Phase

Cancer can be caused by genetic mutations, translocation mechanisms or specific gene malfunctions. Cells can recognize these mutations and can destroy themselves (apoptosis) or repair these mutations before they are passed on to new cells. If this repair capacity is lacking and other mutations occur, the damaged cell is more likely to become cancerous. This initial change can be caused by carcinogens, but the cause is often unknown and possibly accidental [7]. At this point the cell begins to become abnormal.

d. The Promotion Phase

A cell must be repeatedly damaged before it becomes cancerous. Substances such as hormones and some drugs further damage the cell by acting as initiators. Unlike carcinogens, promoters do not cause cancer themselves, but encourage the original cell to become cancerous [8].

e. The Progression Phase

A normal cell that has undergone a change or transformation behaves, grows and functions completely differently and becomes a cancer cell. These changes encourage the cell to continue to grow and reproduce. As cancer cells grow, they can group together and form a tumor [9].

III. CANCER THERAPIES

A. The Different Types of Processing

Cancer treatment involves a combination of surgery, radiotherapy, and chemotherapy. Surgery aims to remove the tumor, lymph nodes, and metastases. It is the main treatment for solid cancers and is often used as a one-time treatment for early-stage cancers. Radiotherapy uses radiation to destroy cancer cells while preserving healthy tissue. It is used in over half of cancer patients and can be administered externally or internally. Chemotherapy uses drugs to kill cancer cells and can be given before (neoadjuvant), after (adjuvant), or as the primary treatment (palliative). It is particularly effective in hematological cancers [10].

B. Anticancer Agents

Anticancer agents encompass a variety of compounds with distinct mechanisms of action. Cytotoxic agents target components involved in cell division to induce cell death. Cancer chemotherapy aims to selectively eliminate cancer cells while minimizing harm to healthy cells, relying on drug efficacy and minimizing adverse effects. Selectivity is influenced by the similarity of healthy cell phenotypes to cancer cells. Polychemotherapy combines drugs synergistically to enhance cancer cell killing and reduce toxicity. Chemotherapy sequencing allows healthy cells to recover between cycles. Heterogeneity within the cancer cell population, arising from genetic instability and environmental factors, poses challenges. Cancer cells progress asynchronously through the cell cycle, resulting in a mix of proliferating, quiescent, and dying cells. Repeated treatment is necessary to target unaffected cells. Cancer cells can develop intrinsic or acquired resistance, leading to treatment failure and necessitating protocol switching. Targeted therapies disrupt tumor growth mechanisms with fewer side effects, often combined with chemotherapy or used as primary or secondary treatments. Immunotherapy and hormone therapy complement the treatment arsenal. Ongoing research is essential to overcome clinical and biological obstacles, emphasizing the need for personalized treatment strategies [1-8].

C. Cytotoxic Agents

a. The Cell Cycle

The cell cycle corresponds to all the steps through which a cell passes to form two daughter cells with the same genetic heritage (Figure 5).

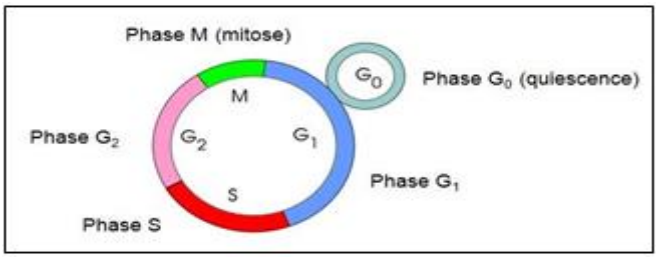

Figure 5: The Different Stages of the Cell Cycle

It is composed of two primary stages, interphase and mitosis. When the cell isn't locked in within the cell cycle, it is at that point inarestingstatecalled arrange G0. Cytotoxic specialists targetthe blend of hereditary fabric (DNA, RNA) and proteins included in mitosis. hey hence have impacts related to the stage of the cell cycle in which the cell is found.

During the interphase, there are successively:

- The G1 Phase (Gap 1) where the cell synthesizes the material necessary for its division.
- Depending on the cancer, 75 to 90% of the cells are in this phase.
- The S Phase (Synthesis) during which the cell duplicates its genetic material.
- The G2 Phase (Gap 2) during which the cell makes proteins necessary for cell division such as tubulin. During this phase, the cell synthesizes proteins and therefore needs to transcribe its DNA into mRNA.
- Mitosis or M phase which corresponds to cell division is a rapid phase.
- Prophase which corresponds to the condensation of chromosomes and then the disappearance of the nuclear membrane.
- The Metaphase where microtubules polymerize and depolymerize bydragging the equatorial location of chromosomes.
- The Anaphase during which polar migration of chromosomes takes place.
- The Telophase where cell division occurs.

Some drugs are called "cycle-dependent" since they act because it were on cells bolted in inside the cell cycle anything the organize (case of alkylating specialists). Other things are called "phase-dependent" since they are energetic because it were in the midst of a specific arrange of the cycle (e.g. mitotic hub poisonsthat are energetic in arrange M) (Figure 6).

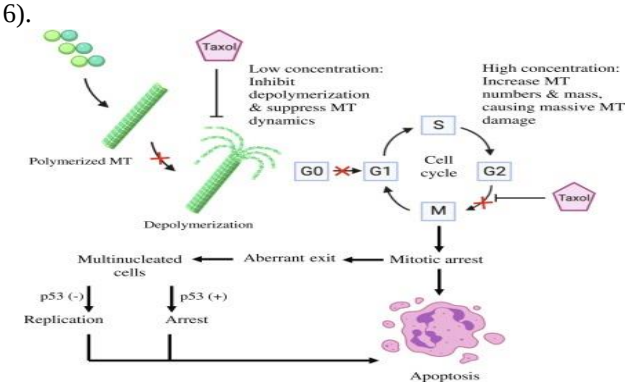

Figure 6: Site of Action of Cytotoxic Agents During the Cell Cycle

The different classes of cytotoxic agents will now be briefly presented.

b. Antimetabolites

These cytotoxic atoms, which act at the S stage of the cell cycle, have the work of restraining the blend of nucleic acids. This family of cytotoxic specialists falls into two categories: Protein inhibitors: Antifolic specialists such as methotrexate 1-1 (Figure 7) which is able to substitute for folic corrosive when it plays the part of coenzyme in DNA blend.

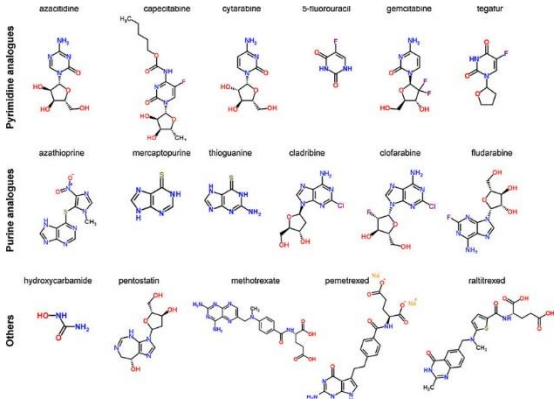

Figure 7: Antimetabolite Agents

Imitation compounds, such as 6-mercaptopurine 1-2 or 5-fluorouracil 1-3 (Figure 7), which have a structure comparable to that of nitrogenous bases (purine or pyrimidic) and are joined into the structure of nucleic acids which leads to the cessation of their amalgamation [2-9].

c. Alkylating Agents

Alkylating operators formcovalent bonds with the DNA contained in cells. Amid cell division, the duplication of the two strands of DNA gets to be troublesome and translation is ceased at the level of the alkylating specialist causing the cell cycle to halt. A qualification is made between mono-functional alkylating operators, which have as it were one chemical interface with DNA, and bifunctional specialists, such as cis-platinum 1-6, which make genuine bridges between diverse segments of DNA Figure 8.

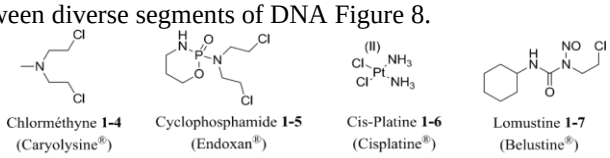

Figure 8: Alkylating Agents

d. Intercalating Agents

The intercalating specialists are put within the grooves of the DNA and shape a trimeric complex with DNA and topoisomerase sort II. This preparing comes about within the blocking of translation. An tricyclene's are antimicrobials extricated from actinobacteria of the sort Streptomyces (doxorubicin 1-8, daunorubicin 1-9) that are intercalated between the two strands of DNA which pieces the activity of topoisomerase II Figure 9.

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DOI:10.54105/ijapsr.A4036.124123
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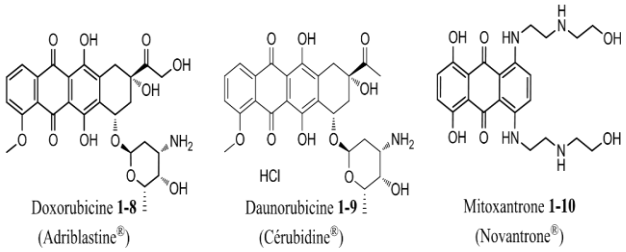


Figure 9: Intercalating Agents

e. Topoisomerase Inhibitors

Topoisomerases are chemicals competent of incidentally cutting DNA in arrange to control its topology. These cuts make it conceivable to loosen the weaving of the DNA (expansion or cancellation of superturns) by dodging the marvels of overtensecaused by its replication and translation. Topoisomerases I and II cause, separately, single-stranded and double-stranded breaks Figure 10.

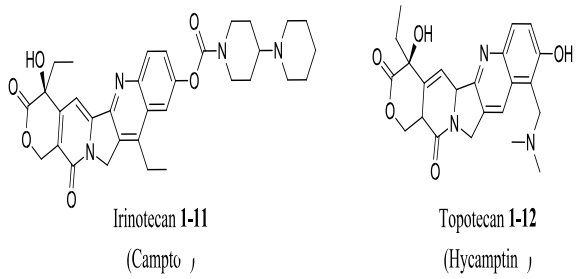


Figure 10: Topoisomerase I Inhibitors

Inhibitors of these enzymes act as stabilizers of the topoisomerase DNA complex. They thus prevent DNA replication and transcription, and lead to cell death Figure 11. [8-11].

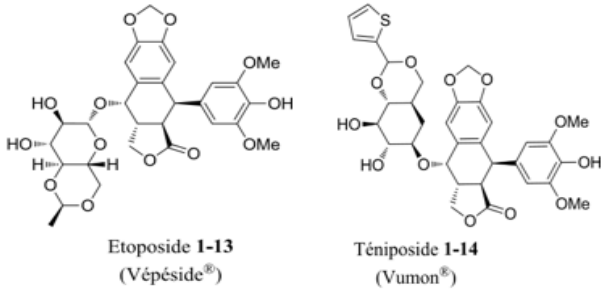


Figure 11: Topoisomerase II Inhibitors

f. Mitotic Spindle Poisons

Mitotic spindle poisons act during mitosis (phase M) on microtubules.

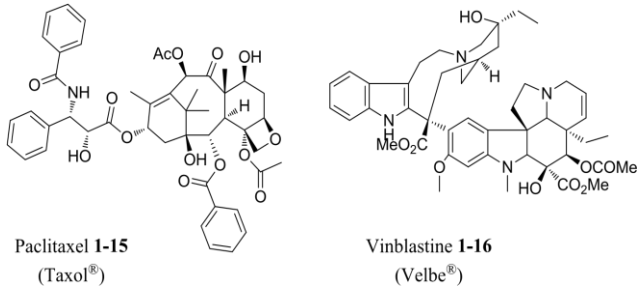


Figure 12: Mitotic Spindle Poisons

Two families of products of natural origin must be distinguished (Figure 12):

- Vinca alkaloids that inhibit the polymerization of tubulin into microtubules.
- Paclitaxel 1-15 and its derivatives that stabilize the polymerized form.

In both cases, cell division is prevented.

g. New Cancer Therapies

These new classes of cancer treatments include monoclonal antibodies and protein kinase inhibitors.

h. Monoclonal Antibodies

Over the past fifteen years, the use of monoclonal antibodies has become a crucial approach in combating tumors and hematological diseases. The concept of using antibodies to treat cancer can be traced back to the 1960s when antigens expressed on tumor cell surfaces were identified through serological methods. Specific therapeutic targets, which are overexpressed, mutated, or selectively expressed in comparison to normal cells, have been identified. Various approaches have been employed for utilizing monoclonal antibodies. Currently, twelve monoclonal antibodies have been approved by the FDA for treating solid tumors and hematological malignancies. Examples include trastuzumab (Herceptin), which targets ErbB2 and is used for breast cancer and gastroesophageal carcinoma treatment, and bevacizumab (Avastin), which inhibits angiogenesis by targeting VEGF and is used in combination with 5-fluorouracil for colon cancer treatment.

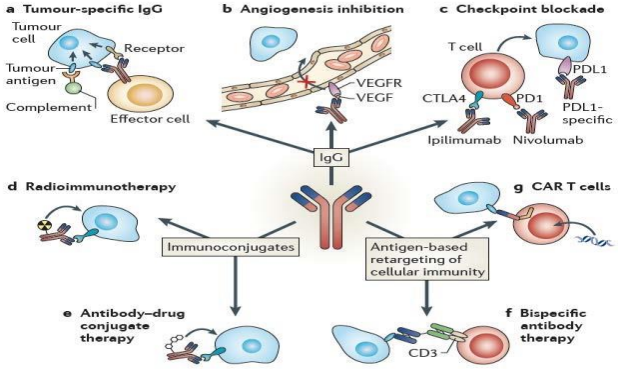


Figure 13: Cancer Strategy based on the Use of Monoclonal Antibodies

(a)The immunoglobulin G (IgG) molecule binds directly to the tumor cell. (b) The monoclonal antibody can target a growth factor (VEGF) involved in angiogenesis. (c) target receptors by direct or indirect action on tumor cells. The antibody can also be conjugated and deliver a radioisotope (d) or molecule (e) directly to the tumor cell. The conjugated antibody can also approach tumor cell partners using a bispecific approach(f) and (g). Blintumomab (Blincyto), utilized for the treatment of intense lymphoblastic leukemia, is the primary bispecific monoclonal counter acting agent to get FDA promoting authorization in December 2014.

This compound, co-marketed by Amgen, has an yearly fetched of $178,000, making it the foremost costly cancer treatment to date. 3 within the treatment of colon cancer [10-13].

i. Protein Kinase Inhibitors

Protein kinases are phosphorylation proteins. The disclosure of the administrative part of these proteins within the 1950s by Edwin G. Krebs and Edmond H. Fischer was granted the Nobel Prize in Medication in 1992 [6-12]. They permit the exchange of a phosphate gather of ATP to a hydroxyl work of a serine, threonine or tyrosine buildup display in a target protein. Protein kinases are frequently oncogenes that alter the movement of the target protein and along these lines induce an actuation cascade. Within the case of cancer, this will lead to the preventionor survival of tumor cells. For this reason, protein kinases speak to helpful targets of choice for the treatment of cancers. It ought to be famous that a few monoclonal antibodies target proteins with tyrosine kinase movement (case of EGF receptors) Figure 14.

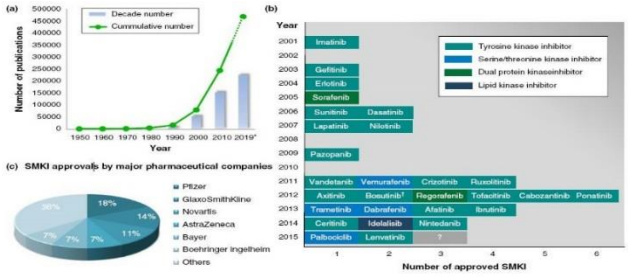


Figure 14: Development of Kinase Inhibitors in Cancer Treatment 13

(a) Cumulative (green) and decade of kinase inhibitor publications since 1950*. Projected number. (b) FDA-approved kinase inhibitors between 2001 and 2015. (c) Pharmaceutical players in the kinase inhibitors for cancer treatment market. Imatinib 1-17 was the primary little particle endorsed by the FDA in 2001 for the treatment of patients with incessant myeloid leukemia. The advancement of newkinase inhibitors at that point proceeded to increment. Over the period 2003-2009, 8 unused kinase inhibitors were endorsed. Over the period 2011-2015, 19 extra compounds were included to the restorative arms stockpile. This family of compounds isnow the one that gives the foremost unused compounds for cancer treatments Figure 15.

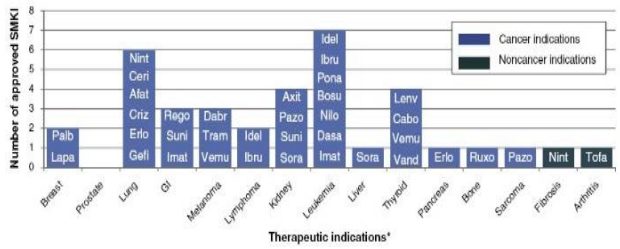


Figure 15: Therapeutic Indications for FDA-Approved Kinase Inhibitors [13].

The panel of small molecule protein kinase inhibitors now covers a wide range of therapeutic indications in oncology.

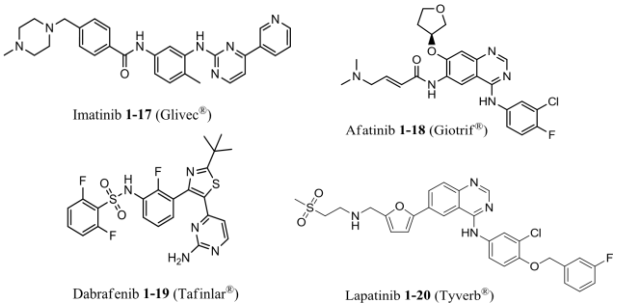


Figure 16: Exemple of FDA-Approved Kinase Inhibitors

There are four sorts of kinase inhibitors. Sort 1 and 2 inhibitors, which act on the dynamic and dormant adaptation of protein kinase, separately, target the ATP authoritative location. Allosteric inhibitors that act exterior the ATP official location Figure 16. Covalent inhibitors shape a steady bond inside the dynamic location o f the protein kinase (most frequently with a cysteine buildup) as within the case of afatinib [1-18].

j. Immunotherapy

In any case of the utilize of monoclonal antibodies, dynamic immunotherapy could be a treatment that points to invigorate the body's safe resistances against cancer cells.
The utilize ofcytokines invigorates the multiplication of resi stant cells. 14 To date, interleukin 2 (IL-2) has been endorsed by the FDA for the treatment of metastatic melanoma and interferonα (IFN-α) is utilized as adjuvant treatment within the treatment ofstage III melance. Investigate into helpful immunizations for the treatment of cancer is right now in full advancement
Figure 17. The FDA's endorsement in 2010 of a helpful immunization (sipuleucel-T Provenge) for the treatment of a metastatic frame of prostate cancer(mCRPC) was a to begin with victory. Numerous antibodies are as of now in stage III clinical improvement for the treatment of prostate, breast, lung, pancreatic, colorectal and melanoma cancers [15].

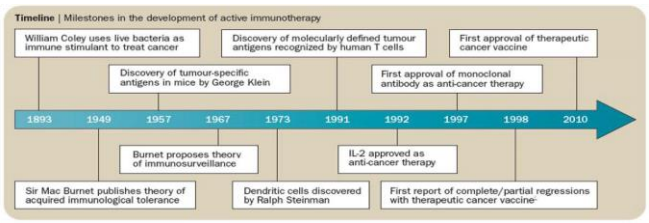


Figure 17: Development of Cancer Immunotherapy Treatments

k. Hormone therapy

Hormone treatment is aimed at depriving cancer cells of the hormones they rely on for growth, either by blocking hormone activity or production. This creates an unfavorable environment that leads to the long-term demise of tumor cells.

Certain cancer cells thrive when hormones bind to receptors on their surface, triggering pathways that accelerate cell division.
• Prostate Cancer: Testosterone fuels prostate cancer growth. Hormone therapy seeks to suppress testosterone production through surgical means (testicle removal) or medication (LHRH analogs or anti-androgens).
• Breast Cancer: Estrogen and progesterone can promote the growth of specific breast tumors. Hormone therapy can counteract their stimulating effects through surgical interventions (ovary removal), radiation therapy, or medication (anti-estrogens like Tamoxifen).
The array of treatment options empowers oncologists to customize treatment plans for individual patients. While this overview focuses on approved drugs, numerous new compounds are being developed to expand the therapeutic landscape. These include protein kinase inhibitors, monoclonal antibodies, and protein-protein interaction inhibitors. The subsequent discussion will delve deeper into the tubulin-microtubule system, a crucial target for anti-cancer therapies.

D. The Tubulin-Microtubule System

a. From Tubulin to Microtubules

Microtubules are polymers that are among the building pieces of the cytoskeleton of a eukaryotic cell. They play distinctive parts inside this cell. They take part within the upkeep of cellular structure, advance intracellular transport (of proteins, organelles, vesicles or signaling particles) and organize themselves in mitotic fuse to permit the division of chromosomes amid mitosis. [16]
Microtubules comprise of an gathering of tubulin. This protein could be a heterodimer comprising of two subunits α and β (55 kDa for each subunit). These heterodimers tie "head to tail" to create thirteen protofilaments that relate along the side and parallel t, driving to a empty barrel 24 nm in distance across (Figure 18) [17].

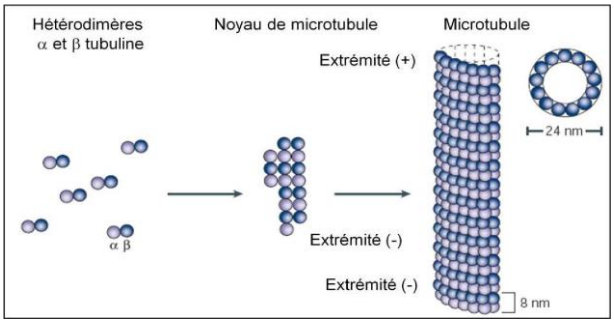


Figure 18: Polymerization of Microtubules

Microtubules exhibit dynamic instability, constantly transitioning between growth, shrinkage, and periods of inactivity. These cycles of growth and shrinkage are crucial for the various functions of microtubules in the cell. Microtubules have polarity, with one end labeled as (+) and the other as (-). The association and dissociation occur more rapidly at the (+) end, which is free in the cytoplasm, while the (-) ends are often embedded in the centrosome. The assembly of microtubules from tubulin occurs in two stages: nucleation, where tubulin heterodimers reversibly and non-covalently associate to form a small core, and elongation, where the association of tubulin heterodimers is faster than the depolymerization of microtubules. At a steady state, microtubule growth is balanced by shrinkage caused by the disassembly of tubulin heterodimers. Both α and β tubulin subunits have a GTP binding site, with GTP in the α subunit located at a non-hydrolyzable or exchangeable site (N site). GTP in the tubulin subunit can be hydrolyzed to GDP (see Figure 19) [19].

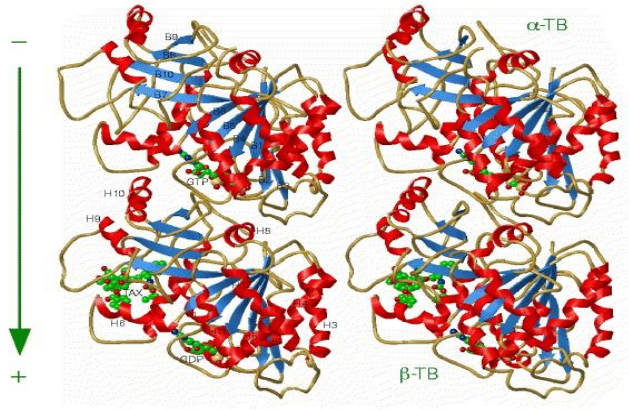


Figure 19: GTP Official Location in Tubulin Monomers α and β [20]

In arrange for a tubulin heterodimer to tie to a developing microtubule, the subunit β on the (+) conclusion of the microtubule must be bound to a GTP particle at its Replaceable location (E). Taking after the affiliation, GTP will be hydrolyzed to GDP which can stay bound to tubulin in this frame Figure 20 [21,22].

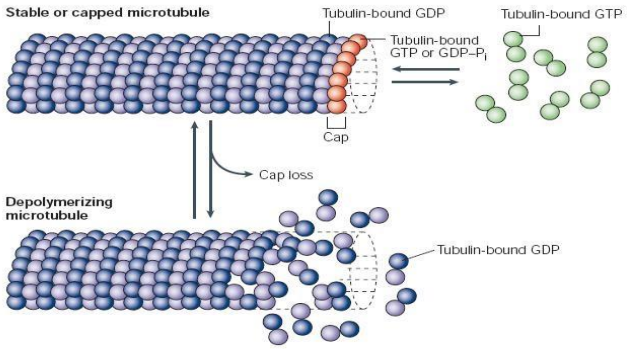
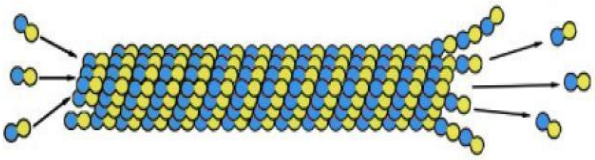


Figure 20: Polymerization Dynamics and GTP Cap

Tubulin-bound GTP is hydrolyzed to GDP and inorganic phosphate (Pi) as tubulin includes to the tip of the microtubule. A microtubule bound to GTP or GDP-Pi shapes a GTP cap. The misfortune of the cap at GTP destabilizes themid-crotubule which leads to a sudden separation (catastrophe) and shortening of the microtubule. Amid a development stage, on the off chance that the expansion of a modern tubulin heterodimer happens more quickly than the hydrolysis of GTP from the past heterodimer, at that point there's amassing of subunits β containing GTP and arrangement, on the side of the conclusion (+), of a "GTP cap" which stabilizes the microtubule and advances its prolongation.

This moreover makes a difference keep up the round and hollow shape and inflexibility of the microtubule. [19-23] may bea moment marvel characteristic of the energetic insecurity of icrotubules. There's expansion of a tubulin heterodimer on the conclusion (+) and dismantling on the conclusion (-). This marvel subsequently does not influence the in general length of the polymer whereas there's a consistent stream of tubulin on both closes. This wonder happens primarily amid metaphase and anaphase (Figure 21).



Addition of Heterodimers Assembly at the end (+) at the end (-)

Figure 21: Treadmilling of the Microtubule

Microtubule-associated proteins (MAPs) incredibly. Microtubule-associated proteins (MAPs) significantly reduce the risk of abrupt disassembly (referred to as "catastrophe") and can also promote growth and decrease the rate of microtubule shortening. The binding sites for these proteins are located on the outer surface of the microtubules. Among these proteins, MAP4 (the most abundant) and the tau protein stabilize the microtubules against depolymerization. The +TIPs protein specifically binds to the growing (+) end and influences microtubule dynamics. The study of proteins associated with microtubules is currently a thriving field, providing valuable insights into their roles and functions.

E. The Role of Microtubules During Mitosis

Figure 22: The Different Stages of Mitosis

Microtubules play a significant role in various stages of mitosis. During prophase, chromosomes condense into chromatids, and the centrosome organizes microtubule attachment. In metaphase, the nuclear envelope disappears, and chromosomes align with the cell's equatorial plane after binding to microtubules through kinetochores. In anaphase, chromatids separate and move to opposite poles of the cell using shrinking kinetochore microtubules and elongating polar microtubules, resulting in cell elongation. In telophase, kinetochore microtubules disappear, nuclear envelopes form around daughter chromosomes, and other microtubules extend until two daughter cells are formed. Microtubules are essential for cell division, and their disruption during metaphase leads to cell apoptosis by blocking cell division [23].

IV. ANTIMICROBIAL TUBULES

A variety of compounds, including natural products and synthetic derivatives, have the ability to bind to microtubules and influence their dynamic equilibrium. These compounds can be classified into two main groups based on their mechanism of action. Microtubule destabilizing agents (MDAs) inhibit tubulin polymerization at high concentrations. This group includes Vinca alkaloids (vinblastine, vincristine, vinorelbine), colchicine, and combretastatin. On the other hand, microtubule stabilizing agents (MSAs) promote microtubule polymerization and stabilize the formed polymer. This group includes paclitaxel and its derivatives, epothilones, discodermolide, laulimalide, and pelorusiside A. Compounds that affect microtubule structure have traditionally been classified as either stabilizing or destabilizing based on their effects on microtubule mass at high concentrations. However, all compounds that bind to microtubules can influence microtubule dynamics at lower concentrations. Currently, compounds targeting microtubules are categorized based on their binding site on tubulin. Compounds that bind to the vinblastine or colchicine binding site exhibit microtubule polymerization inhibition, while compounds that bind to the paclitaxel or laulimalide binding site can promote microtubule polymerization and stabilize the polymer [22-26].

A. Compounds Binding to the Vinca Domain

The vinblastine authoritative location is at the interface between the β subunit of one heterodimer and the α subunit of the another heterodamer, in a locale near to the GTP/GDP trade location. Figure 23.

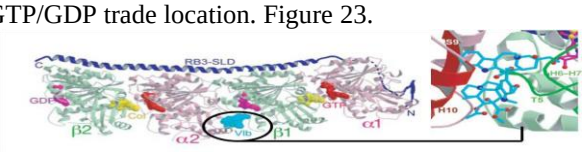


Figure 23: Structure of the Tubulin-RB3-SLD-Vinblastine Complex

Vinblastine 1-16 (cyan, Vlb) is found at the interface between two tubulin heterodimers (α1-β1 and α2-β2), each monomer complexing a nucleotide (a GTP on the α subunits and a GDP on the β subunits). Vinblastine authoritative comes about in a alter in compliance between tubulin heterodimers. Protofilaments receive a bended compliance that avoids mic rotubule gathering Figure 24 [20-24].

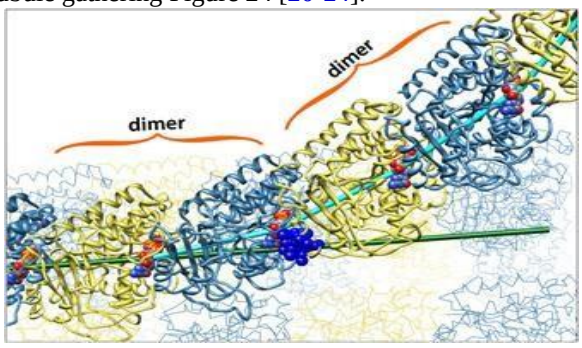
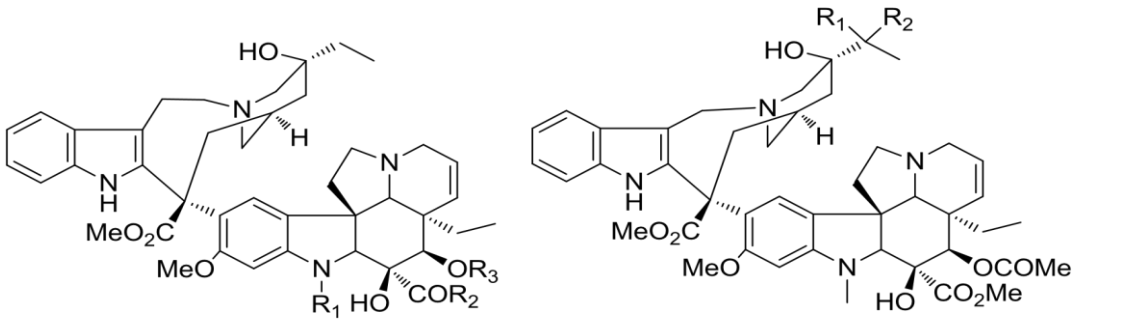


Figure 24: Protofilament Conformation after Binding with Vinblastine

Vinblastine 1-16 (blue) ties to the interface of two tubulin heterodimers αβ . The alteration of the protofilament adaptation (sky blue hub vs. green hub) disfavors the polymerization of microtubules. Vinblastine 1-16 [25]. and vincristine 2-1 [26]. are two alkaloids inferred from the Madagascar periwinkle Catharanthus roseus. These compounds have been utilized clinically for over fifty a long time. Engineered analogs, such as vindesine 2-2, [27] [60]. vinorelbine 2-3 [28]. and vinflunine 2-4 [29]. with an progressed pharmacological profile, were in this way created. Vinorelbine [23] is nowadays the foremost broadly utilized compound in this family of compounds for the treatment of breast and lung cancer Figure 25.



	R_1	R_2	R_3		R_1	R_2
Vincristine **2-1** (Velbe)	CHO	Ome	Come	Vinorelbine **2-3** (Navelbine)	H	H
Vinblastine **1-6** (Onconvin)	CH_3	Ome	Come	Vinflunine **2-4** (Javlor)	F	F
Vindesine **2-2** (Eldisine)	CH_3	NH_2	H			

Figure 25: Vinca Alkaloids Used Clinically

B. Colchicine-Binding Compounds

The colchicine official location is found at the interface of the two subunits α and β of tubulin, near to the GTP official location within the α subunit Figure 26.

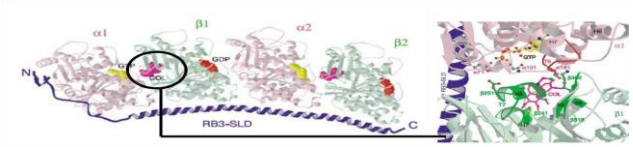


Figure 26: Structure of the Tubulin-RB3-SLD-Colchicine Complex

The complex comprises two tubulin αβ heterodimers with colchicine 2-5 bound to the subunit β at the interface of the subunit α. The authoritative of colchicine 2-5 at its official location leads to a alter within the adaptation of the heterodimer (ebb and flow) in this way avoiding polymerization Figure 27.

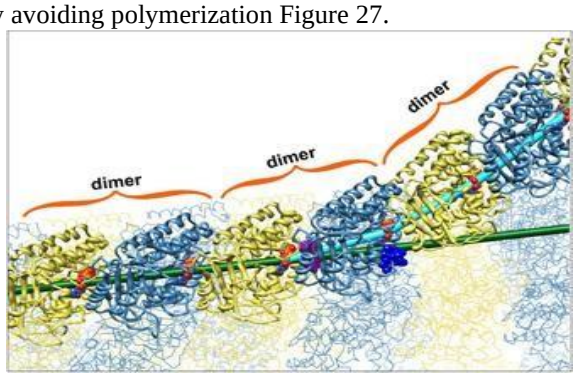
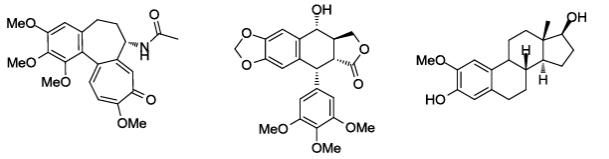


Figure 27: Modification of Microtubule Vectorization After Binding to the Colchicine 2-5

Colchicine 2-5 (fuchsia) ties to the interface of two tubulin heterodimers αβ . The alteration of the protofilament adaptation (sky blue hub vs. green hub) disfavors the polymerization of microtubules Figure 28. Numerous compoundscan involve the authoritative locat ion of colchicine in tubulin 31.



Colchicine **2-5** Podophyllotoxine **2-6** 2-Methoxyestradiol **2-7**

Figure 28: Main Compounds Binding to the Colchicine Domain

Colchicine (2-5) is isolated from Colchicum autumnale. Due to its high toxicity, it is not clinically used for cancer treatment but rather for gout and certain rare diseases (intermittent illness, Behçet's disease). Unlike some similar analogs, podophyllotoxin (2-6) cannot be clinically utilized due to its toxicity. These compounds do not function as antimitotic agents but as inhibitors of topoisomerase II (Etoposide, Teniposide). 2-Methoxyestradiol (2-7), known as Panzem, exhibits antiangiogenic and apoptotic properties and is currently undergoing clinical development for breast cancer. Combretastatin A4 (2-9) is a natural molecule derived from the Combretum caffrum tree. Fosbretabulin (2-8), also known as combretastatin A4 phosphate (CA4P) or Zybrestat, is a water-soluble prodrug of combretastatin A4 (2-9). It undergoes conversion to combretastatin A4 (2-9) by non-specific endogenous phosphatases present in plasma and endothelial cells.

In addition to its antimitotic activity, this compound targets the endothelial cells of tumor blood vessels. It is currently being studied in numerous clinical trials, either alone or in combination with other anticancer agents (see Figure 29).

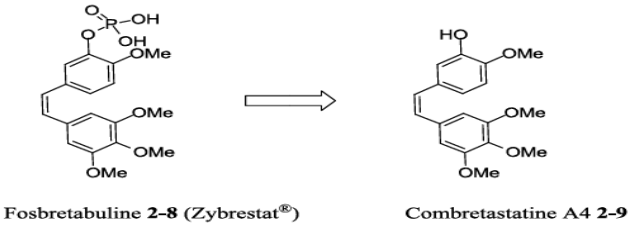


Figure 29: Combretastatin A4 2-9 and Its Prodrug

C. Taxane-Binding Compounds

Taxanes are compounds that particularly target a authoritative location within the lumen of microtubules. They tie to a GTP-bound subunit β of tubulin and stabilize this structure by altering its adaptation. [29-32][59]. The structure in this way stabilizede adjusts impeccably with the development vector of the microtubules. This has the impact of advancing the polymerization of microtubules Figure 30.

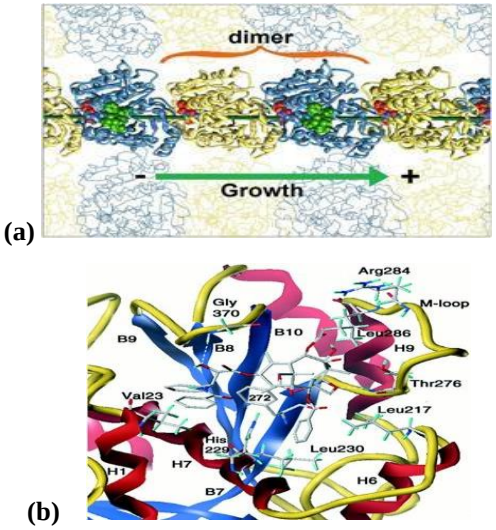


Figure 30: Stabilization of Microtubules with Paclitaxel 1-15 and Obsession with Tubulin β. 19.37

(a) See of paclitaxel 1-15 (green) bound to a subunit β of tubulin within the lumen of microtubules. The heterodimeric development vector is adjusted with the microtubule development hub. (b) Mode of official of paclitaxel 1-15 in tubulin. Among the compounds that tie to this official location are paclitaxel 1-15 [33-38]. and its subordinates Figure 31.

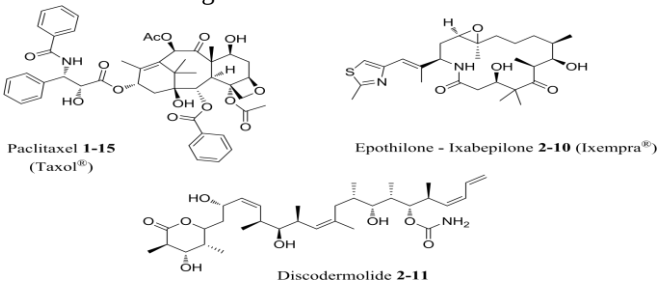


Figure 31: Major Binding Agents in the Taxane Binding Domain

Épothilones are macrolides derived from the myxobacterium Sorangium cellulosum. Among the six types of epothilones discovered so far, epothilones A and B stabilize microtubule formation and competitively inhibit paclitaxel at its binding site. These compounds exhibit a similar affinity to paclitaxel but, unlike paclitaxel, they are not substrates of P-glycoprotein, making them potentially valuable for paclitaxel-resistant tumors. Ixabepilone (Ixempra), a derivative of epothilone B, was FDA-approved in 2008 for the treatment of metastatic breast cancer. Other analogs, such as patupilone or sagopilone, are currently in clinical development. Discodermolide, isolated from the marine sponge Discodermia dissoluta, was identified in 1990 and binds to the taxane binding site similarly to epothilones. Like epothilones, it does not interact with P-glycoprotein. However, Novartis had to halt the clinical development of discodermolide during Phase I due to pulmonary toxicity. Other compounds, such as dictyostatin or zampanolide, are also capable of binding to the taxane binding site [34-39].

D. Compounds Binding to the Laulimalide Domain

Laulimalide 2-12 and peloruside A 2-13 are two compounds that interact with the monomer β of tubulin in a distinct manner compared to compounds targeting the taxane site [40-44]. These macrocyclic structures stabilize the M-loop of tubulin and associate with a neighboring tubulin dimer along the protofilament. Laulimalide 2-12, also known as fijianolide B, is a macrolide isolated from the marine sponge Cascopongia mycofijiensis in 1988. It binds to tubulin β near the intradimeric interface, close to the GTP hydrolysis site, which is exposed on the inner surface of mid-crotubules (Figure 32) [45-49]. The binding of laulimalide 2-12 to its designated site is sensitive to the presence of GTP at position E. When bound to tubulin β, the heterodimer undergoes a conformational change that promotes polymerization.

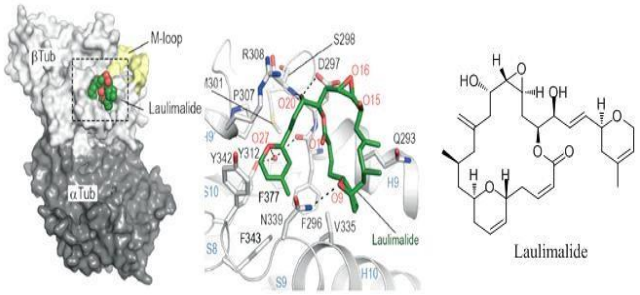


Figure 32: Binding site of Laulimalide 2-12 in Tubulin

Peloruside A **2-13** is also a macrolide that was isolated from a *Mycale hentscheli* marine sponge [50-52]. This compound binds to tubulin at the same binding site. These compounds have shown interesting results, particularly on taxa-resistant lines. However, they are not clinically developed at this time Figure 33.

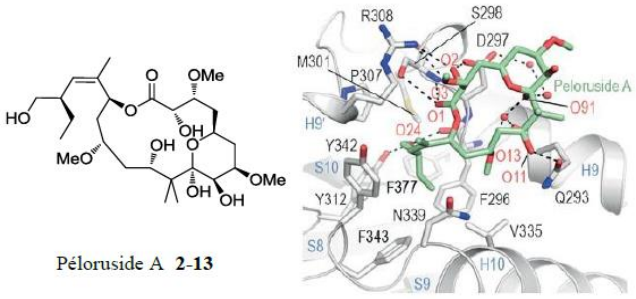


Figure 33: Peloruside A 2-13 and its Binding Mode in Tubulin

Many compounds are able to bind to microtubules and act on their dynamic balance by destabilizing or stabilizing the polymer formed. Of these, paclitaxel 1-15 is the anticancer agent that has attracted the most interest. The singular history of this molecule and its derivatives will now be developed [52-54].

V. PACLITAXEL

A. History of Paclitaxel

In the early 1960s, the National Cancer Institute (NCI) initiated a major research program aimed at discovering new anti-cancer compounds of plant origin. The realization of this mission was entrusted to the US Department of Agriculture (USDA). In 1962, Arthur S. Barclay, a botanist working for the USDA, collected 650 plant samples on the west coast of the United States (California, Oregon and Washington), including bark, leaves and strands from the Pacific yew (*Taxus brevifolia*) [55].

Figure 34: Pacific Yew (Taxus Brevifolia)

The Pacific yew, a slow-growing conifer predominantly found on the northwest coasts of the United States, exhibits a maximum height of 15 m with a trunk diameter rarely exceeding 50 cm. Its dark green leaves are approximately 3 cm long and 2 to 3 mm wide [6-12]. The tree produces red-colored fleshy envelopes called arils (refer to Figure 34). In 1964, the cytotoxic potential of Taxus brevifolia extracts was evaluated on KB cells (human oral epidermoid cells), yielding positive results. Dr. Wall and Dr. Wani from the Research Triangle Institute (RTI) subsequently isolated the compound responsible for this cytotoxic activity in 1967, naming it taxol. Bristol-Myers Squibb adopted this name as a trade name for the market, while the international nonproprietary name (INN) for the compound became paclitaxel 1-15. Determining the structure of paclitaxel 1-15 proved challenging. Initial mass spectrometry and elemental analysis studies revealed its crude formula as C47:51NO. [14]. The limited availability of paclitaxel 1-15 hindered the preparation of derivatives for X-ray diffraction analysis. However, a combination of X-ray diffraction studies on degradation products and NMR analyses on the initial compound led to the elucidation of its structure in 1971 (see Figure 35). This polyoxygenated diterpene molecule possesses a tetracyclic structure with 11 stereogenic centers and a double bond [29-33].

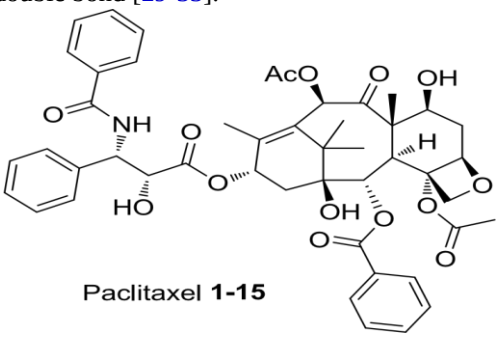


Figure 35: Elucidation of the Structure of Paclitaxel 1-15 in 1971

In the early 1970s, initial enthusiasm for paclitaxel waned due to disappointing cell tests, low water solubility, and low extraction yield from Pacific yew. The molecule's structural complexity posed challenges for total synthesis. However, in 1979, Susan Horwitz discovered the novel mechanism of action of paclitaxel, which promoted the assembly of αβ tubulin into microtubules. Her findings sparked interest among biologists studying cellular processes. Preclinical evaluations continued based on Horwitz's results, and paclitaxel was selected as a drug candidate. Phase I clinical trials began in 1983. To address its low solubility, paclitaxel was formulated in an ethanol/Cremophor EL mixture and administered via infusion to mitigate allergic reactions. Modified administration methods yielded positive results in advanced clinical phases for ovarian and breast cancer treatment. Supply became a concern due to low extraction yield and non-renewable sources. The discovery of 10-deacetyl-baccatin III (10-DAB III) in European yew needles provided a renewable precursor for paclitaxel synthesis [55].

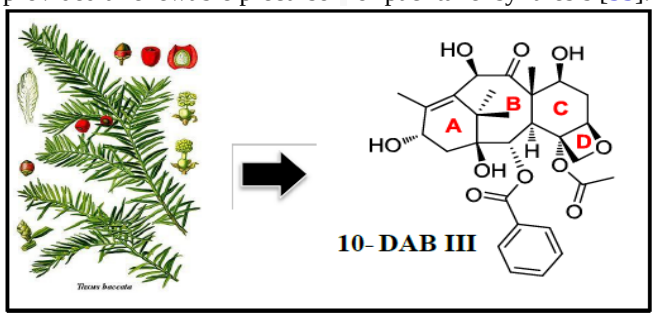


Figure 36: Discovery of 10-Deacetylbaccatin III in Taxus Baccata Needles

In 1988, the first hemi synthesis of paclitaxel 1-15 using 10-DAB III was performed by Greene and Potier (Figure 37). However, the high temperature and the long reaction time during the esterification step result in epimerization on the $C_{2'}$ carbon of the side chain.

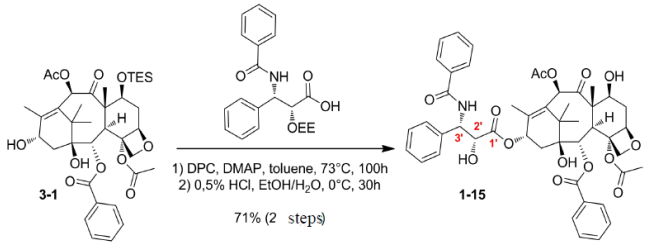


Figure 37: Hemi synthesis of Paclitaxel 1-15 by Greene and Potier

Holton's team concurrently developed a hemisynthetic process using a protected analogue of Baccatin III and a β-lactam intermediate (refer to Figure 3-5). This method employs DMAP as a catalyst and necessitates the use of 5 β-lactam equivalents with a relatively extended reaction time. Subsequently, Ojima made improvements to this process [52, 53]. The optically pure β-lactam, specifically (3R,4S)-4-phenylazetidin-2-one, was coupled with the NaHMDS-deprotonated derivative of 7-TES baccatin III. The reaction occurred at low temperature and completed within 30 minutes using a slight excess of β-lactam (1.2 equivalents to baccatin). The adoption of this process under license allowed Bristol-Myers Squibb to advance the clinical development of the molecule. Paclitaxel 1-15 received FDA approval in 1992 for ovarian cancer treatment, followed by approvals for breast cancer in 1994 and non-small cell lung cancer in 1999 (see Figure 38) [54].

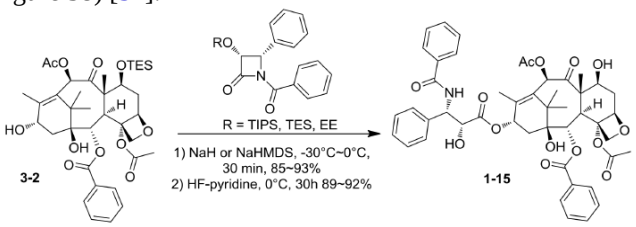


Figure 38: Hemisynthesis of Paclitaxel 1-15 using Ojima - Lactam

In 2005, nab-paclitaxel (nanoparticle albumin-bound), marketed as Abraxane, was approved for the treatment of breast, lung and pancreatic cancers. This novel technological process was developed by Abraxis Bioscience (now Celgene). Albumin plays a central role in the delivery of hydrophobic molecules to target tissues. Paclitaxel 1-15 reversibly binds to albumin with high affinity and can thus be transported. Evidence suggests that this binding to a plasma protein promotes passage through the cell membrane. The results of clinical studies of nab-paclitaxel demonstrated an increase in the therapeutic index compared to paclitaxel 1-15.

B. Paclitaxel Derivatives Used Clinically

Figure 39 displays synthetic derivatives of paclitaxel. One such derivative is docetaxel 3-3, also known as Taxotere. This compound was developed through modifications of the side chain of paclitaxel 1-15 in Pierre Potier's laboratory, involving acylation of 10-DAB III. Docetaxel, a product of CNRS and Rhône-Poulenc Rorer (now Sanofi), features a C 3'-N-tert-butoxycarbonyl motif on the side chain and a free hydroxyl group on carbon C10. While sharing the same mechanism of action as paclitaxel 1-15, docetaxel exhibited improved cytotoxic activity. The FDA approved docetaxel for the treatment of non-small cell lung cancer in 1999, and breast and prostate cancer in 2004. Furthermore, in 2010, cabazitaxel 3-4 (Jevtana), an analogue of docetaxel 3-3 with two methoxy moieties on carbon atoms C7 and C10, received FDA approval for the treatment of prostate cancer refractory to hormone therapy [33-39].

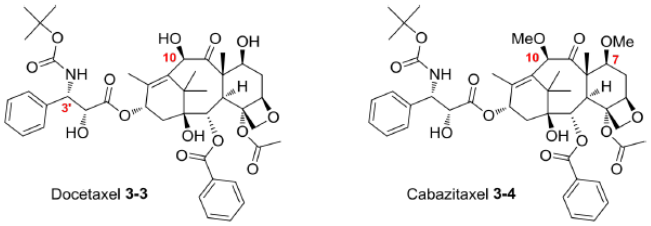


Figure 39: Docetaxel 3-3 (Taxotere) and Cabazitaxel 3-4

C. Paclitaxel Derivatives in Clinical Development

Many paclitaxel 1-15 analogues are still in clinical development. Paclitaxel derivatives must be distinguished from newer taxane analogues. Paclitaxel poliglumex 3-5 (Opaxio), [56,57]. developed by Cell Therapeutics, entered Phase III clinical development in 2014 (Figure 40). This compound is used in combination with capecitabine (Xeloda) for the treatment of metastatic breast cancer. [49] Compound 3-5 corresponds to paclitaxel 1-15 bonded to a polymeric chain of L-glutamic acid. This combination seeks to increase the therapeutic index by improving the pharmacokinetic profile (water-soluble formulation).

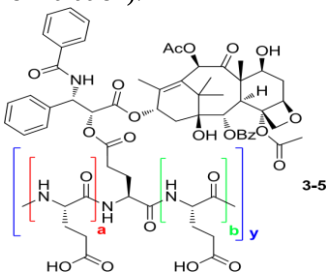


Figure 40: Structure of Paclitaxel Poliglumex 3-5 (Opaxio)

Endotag-1, developed by Medigene AG, is a lipid formulation that encapsulates paclitaxel 1-15. This formulation selectively targets endothelial tumor cells and demonstrated promising results in phase II studies conducted in 2013. Genexol-PM (Cynviloq), developed by Sorrento Therapeutics Inc., is a micellar polymeric formulation consisting of paclitaxel 1-15 and a low molecular weight amphiphilic copolymer (mPEG-PDLLA). It is currently undergoing phase III evaluation for the treatment of metastatic breast cancer. DHA-paclitaxel (Taxoprexin), developed by Protarga Inc., binds paclitaxel 1-15 to docosahexaenoic acid (DHA), which is readily absorbed by tumor cells. The bond between paclitaxel and DHA is cleaved inside the cell, leading to increased concentrations of the cytotoxic agent within the cell. Phase II studies of this compound were published in 2009. Tesetaxel 3-6, developed by Genta, is an orally administered derivative of paclitaxel 1-15, currently in phase II clinical development. Genta recently announced an exclusive development agreement with Daiichi Sankyo for this molecule. Ortataxel 3-7, developed by Spectrum Pharmaceuticals, is a next-generation taxane derived from 14β-hydroxybaccatin III, undergoing evaluation in a phase II clinical study.

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DOI:10.54105/ijapsr.A4036.124123
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TPI-287, developed by Archer Biosciences, is a taxane capable of crossing the blood-brain barrier and has shown effectiveness in preclinical studies for reducing brain metastases in breast cancer. Larotaxel 3-9, developed by Sanofi, is a hemisynthetic derivative obtained from 10-deacetylbaccatin III. It exhibits low affinity for glycoprotein P (Pgp), enabling it to penetrate the blood-brain barrier. Sanofi decided to discontinue the development of this compound after phase III studies (see Figure 41) [40-44].

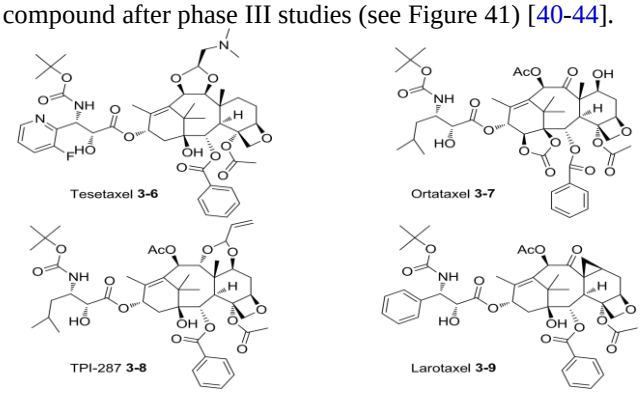

Figure 41: Novel Taxane Derivatives in Clinical Development

D. Total Synthesis of Paclitaxel

The total synthesis of paclitaxel, with its complex structure and multiple stereogenic centers, posed a significant challenge in medicinal chemistry. The Holton and Nicolaou groups independently published the first two total syntheses in 1994. Subsequently, several other groups, including Danishefsky, Wender, Mukaiyama, Kuwajima, and Takahashi, successfully completed the total synthesis. While these syntheses are not suitable for large-scale industrial production of paclitaxel, they have paved the way for the development of new methodologies and strategies in organic synthesis. As a result, taxane skeletal analogues, such as Tesetaxel, Ortataxel, TPI-287, and larotaxel, have been synthesized and are currently undergoing clinical studies. These compounds offer potential advancements in cancer treatment, including oral administration, blood-brain barrier penetration, and reduced brain metastases. However, Sanofi halted the development of larotaxel after phase III studies. Figure 42.

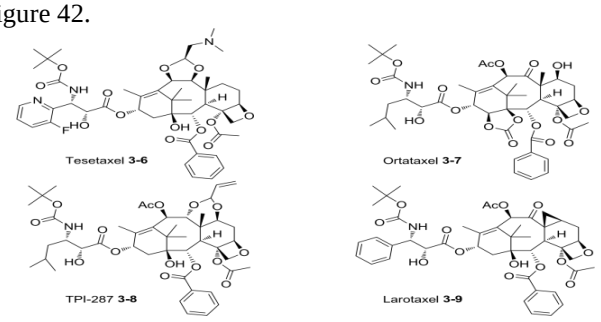

Figure 42: Novel Taxane Derivatives in Clinical Development

E. Total Synthesis of Paclitaxel

The total synthesis of paclitaxel 1-15 posed significant challenges in medicinal chemistry due to its complex structure and numerous stereogenic centers. The Holton and Nicolaou groups published the first two total syntheses almost simultaneously in 1994. Subsequently, the Danishefsky's groups, Wender (shortest total synthesis in 37 steps), Mukaiyama's, and Takahashi's groups successfully accomplished the task. However, these total syntheses are not suitable for large-scale industrial production of paclitaxel 1-15. Nevertheless, they have facilitated the development of new methodologies and strategies applicable to organic synthesis. This work has also enabled the design and synthesis of taxane skeletal analogues [33-38].

F. Structure and Activity Relationship of Paclitaxel

Work on paclitaxel 1-15 and its derivatives has led to the synthesis of a very large amount of analogues (Figure 43). The biological evaluation of these compounds on many tumor lines has made it possible to obtain a precise idea of the structure-activity relationship of this molecule [56-58].

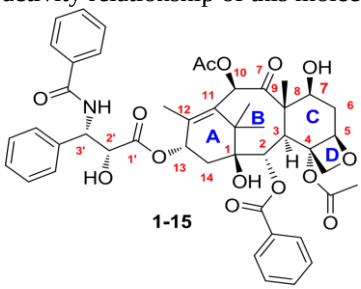

Figure 43: Paclitaxel Numbering 1-15

The (2'R,3'S)-N-benzoyl-3'-phenylisoserine side chain carried by carbon C-13 is crucial for the activity of paclitaxel 1-15. This chain has received significant attention due to its importance and the subsequent synthetic developments after the discovery of 10-DAB III. The chain must possess a free hydroxyl group on carbon C2' or a hydrolyzable ester bond, as seen in DHA-paclitaxel. Various prodrugs of paclitaxel 1-15 have been synthesized based on this position. Introducing a methoxy group or replacing the hydroxyl group with a fluorine atom significantly reduces its activity. Numerous modifications have been accepted on the carbon atom C3' and nitrogen atom N3' of the side chain, with docetaxel 3-3 being a notable example. The side chain is connected to the taxane ring via an ester bond. The southern part of paclitaxel 1-15 carries a hydroxyl group on carbon C1, a benzoate group on carbon C2, and an acetate group on carbon C4. The hydroxyl group on carbon C1 is relatively unimportant for the compound's activity, while the absence of the acyl group on carbon C2 or a reversed stereogenic center configuration leads to a significant decrease in activity. Substituting the phenyl core of the benzoate group at different positions does not result in a significant loss of activity. The absence of the acetate group on carbon C4 negatively affects cytotoxic activity and microtubule assembly. Similarly, 4-deacetoxypaclitaxel is significantly less active than paclitaxel 1-15. The structure-activity relationship around the oxetane cycle has been extensively discussed, with the presence of the oxygen molecule being necessary for desirable activity. Substituting oxygen with sulfur or nitrogen leads to less active or inert compounds. Replacing the oxygen molecule with a carbon molecule results in a compound capable of microtubule polymerization activation but with a decrease in cytotoxic activity.

Substituting oxetane with cyclopropane or simple D-seco compounds has yielded compounds that can activate microtubule polymerization similar to paclitaxel 1-15.

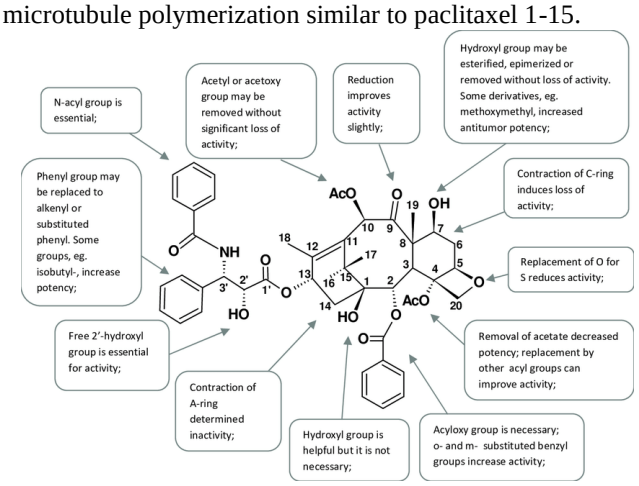

Figure 44: Structure Activity Relationship of Paclitaxel 1-15

There are moderately few illustrations of changes to headingC6. As it were the presentation of hydroxyl, azidos or amino bunches has been detailed. On a few tumor lines, the compound bearing the azido bunch incorporates a cytotoxic movement prevalent to that of paclitaxel 1-15 [53-58].

The hydroxyl bunches carried by the Carbones C 7 and C 10 as well as the carbonyl bunch carried by the carbon C9 don't appear basic to the action of paclitaxel 1-15. It is possible
to alter these distinctive bunches without misfortune of activity as can be seen within the case of docétaxel 3-3 and cabazitaxel 3-4 to require as it were the compounds right now utilized within the clinic.

G. Mimes Derived from GTP

Howarth et al. proposed that paclitaxel 1-15 functions as a mimic of GTP. The taxane skeleton corresponds to the guanosine portion of GTP, while the side chain carried by the C13 carbon of paclitaxel corresponds to the triphosphate group of GTP. Based on this hypothesis, the researchers synthesized hybrid compounds where the triphosphate motif was replaced by the side chain of paclitaxel 1-15 (Figure 45). However, the authors did not complete their approach as they did not synthesize the deprotected compounds. The protected compound 3-16 exhibited a cytotoxic activity of approximately 20 µM against SW480 cells, derived from colorectal adenocarcinoma, without any reported tubulin polymerization/depolymerization tests.

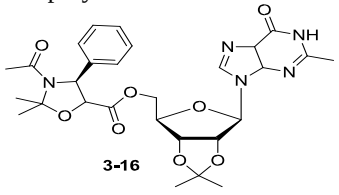

Figure 45: Examples of Mime Synthesized [58]

H. Paclitaxel Macrocyclic Mimes

Gentile *et al.* synthesized more water-soluble mimes than paclitaxel 1-15. The superposition of a macrolactam dimeric motif with paclitaxel appeared satisfactory. Both the naked cyclic dime and the paclitaxel side chain were synthesized and evaluated on a rodent melanoma line B16-F10 (Figure 46). Compounds 3-17 and 3-18 showed similar cytotoxicity of the order of 45-M without Present activity on a tubulin polymerization test [44-47].

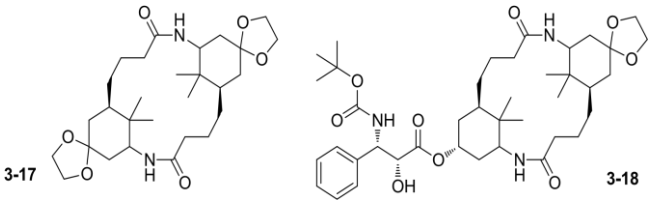

Figure 46: Example of Mimes Synthesized [58]

I. Steroid Skeleton Mimes

Roussi *et al.* described the replacement of the taxane skeleton with a steroid motif. The authors sought to identify a simple and rigid pattern with two oxygen atoms 4 Å apart in order to vectorize the side chain carried by carbon C 13 as well as the benzoate carried by carbon C_2 of paclitaxel **1-15**. This research guided by a superposition work with the T-docetaxel conformation led to the identification of derivatives of cholic acid 3-19, 3-20, 3-21 and 4-androsten-3,17-dione 3-22 (Figure 47).

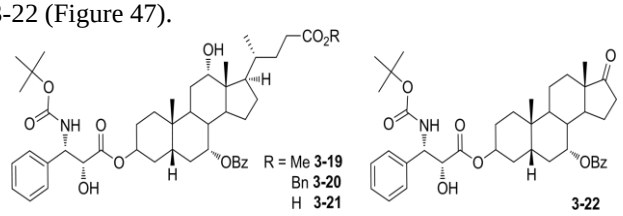

Figure 47: Mimes Described [57]

These compounds did not exhibit inhibition of microtubule disassembly in an in vitro tubulin depolymerization assay. Surprisingly, compound 3-20 demonstrated unexpected inhibitory activity on microtubule polymerization with an IC50 value of 3.8 µM (while vinblastine 1-16 inhibits 50% polymerization at a concentration of 2 µM under the same conditions). These compounds displayed cytotoxic activity against KB cells (IC50 ranging between 2 and 8 µM). Therefore, the cytotoxic activity of these compounds is not attributed to the same mechanism of action as paclitaxel 1-15.

VI. FRAGMENTED APPROACH

A. Proline as a Starting Fragment

There are 22 proteinogenic amino acids that are incorporated into proteins during ribosomal mRNA translation. Among them, it is necessary to distinguish the 20 standard amino acids encoded by the nuclear DNA codon from the two amino acids encoded by the stop codon (selenocysteine and pyrrolysine). The human body is able to synthesize 12 protein-forming amino acids, the rest of which must be obtained from food.

Proline is an amino acid that plays an important structural role due to its cyclic nature, causing conformational stress and the presence of a secondary amine that prevents hydrogen bonding when the nitrogen atom is attached to the apeptide sequence.

As a result, proline is mostly involved in loops, turns and polyproline helices (PPII) structures Figure 48.

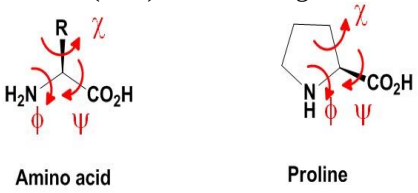

Figure 48: Amino Acid Torsion Angles

The cyclic nature of the amino acid proline imposes a restriction on the torsion angle φ, which is fixed around -60°. Therefore, the conformational space available to L-proline depends on rotations around the torsion angle ψ, which has two constrained values around -30° and +120°, corresponding to the helical and extended regions of the Ramachandran plot (see Figure 49). Proline exhibits two significant conformational equilibria. Cis/trans isomerism is observed at the amide bond. Within proteins, the amide bond predominantly adopts a trans conformation in 95% of cases (see Figure 49a). The pyrrolidine ring of proline assumes an envelope-like conformation. The two harmonious forms are defined by the values of the torsion angle χ (N-Cα-Cβ-Cγ) of the side chain: -30° corresponds to the Cγ-endo/Cβ-endo conformation, and +30° corresponds to the Cγ-endo/Cβ-exo conformation (see Figure 49b).

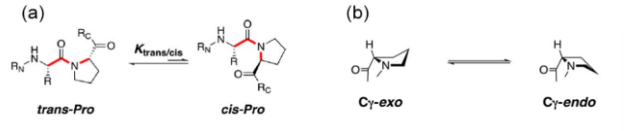

Figure 49: (a) Cis/trans Isomerism at the Amide Bond (b) Pyrrolidine Ring Conformations

The use of substituted prolines, otherwise known as chimeric prolines, makes it possible to maintain the conformational stress of proline and to integrate pharmacomodulation (by introducing a new stereogen centre on the pyrrolidine ring). Different classes of substituted prolines have been developed according to the position of substitution on the pyrrolidine ring (Figure 50).

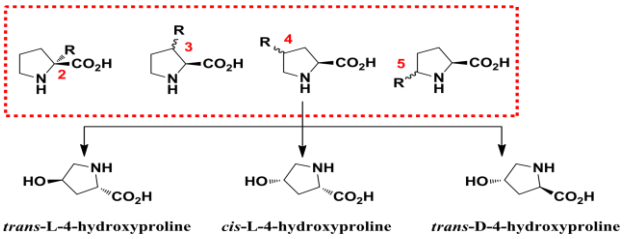

Figure 50: Chimeric Prolines and Selected Fragments

The proline derivatives substituted at position 4 (trans-L-4-hydroxyproline, cis-L-4hydroxyproline and trans-D-4-hydroxyproline), which have the prerequisites defined above, have been selectedto serve as starting material for the synthesis of the first generation of paclitaxel mimes (Figure 50).

B. Mimics of First-Generation Paclitaxel

a. Molecular Modelling

The design of paclitaxel mimics was conducted through molecular modeling. The selected structures were subjected to a search for lower energy conformers using the AMBER 12 force field. The resulting minimized structures were then superimposed onto the 1JFF-Taxol structure. This initial series of paclitaxel mimics demonstrated satisfactory alignment at the phenylisoserine side chain and the paclitaxel benzoate motif. By utilizing three different stereoisomers of 4-hydroxyproline, nine first-generation paclitaxel mimics were designed (see Figure 51). These compounds vary in stereochemistry at the pyrrolidine ring and also include functional modifications on carbon atom C2 (derived from proline and subsequent introduction of the benzoate motif) as well as on the nitrogen atom of the pyrrolidine cylidine [58].

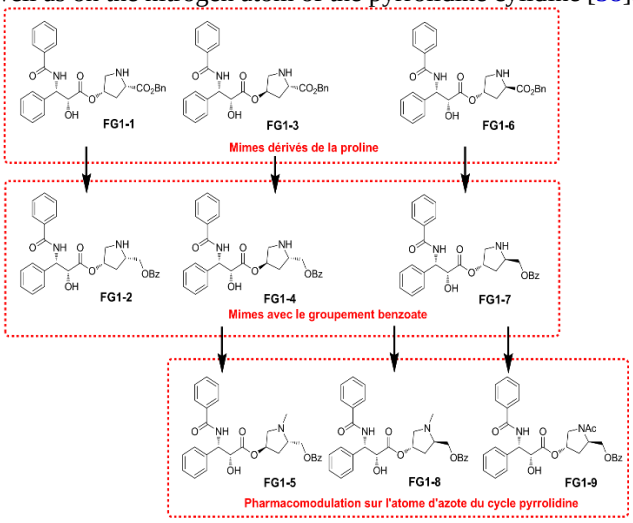

Figure 51: First-Generation Mimes of Paclitaxel

b. Outcomes and Discussions

The retrosynthetic analysis of the different first generation mimes is identical depending on whether trans-L, cis-L- or trans-D-4-hydroxyproline stereoisomers are considered as starting material (Figure 52).

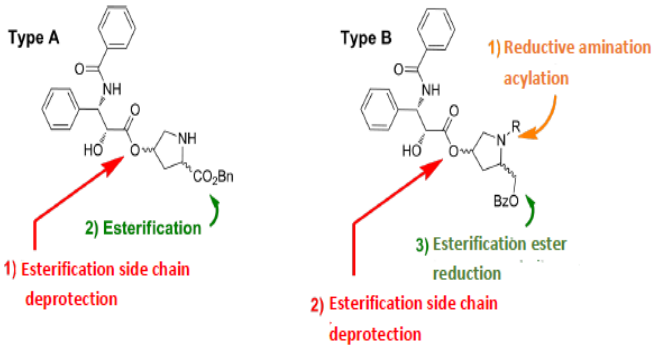

Figure 52: Retrosynthetic Analysis of First-Generation Paclitaxel Mimes

For type **A** compounds, the paclitaxel side chain is introduced by an esterification reaction according to Steglich conditions as well as by an esterification reaction on a protected derivative of 4-hydroxyproline. For type B compounds, an acylation or reducing amination reaction makes it possible to substitute the nitrogen atom of the pyrrolidine ring. In the same way, an esterification reaction according to Steglich conditions makes it possible to introduce the side chain of paclitaxel.

Finally, two successive steps of reduction and esterification allow to introduce the benzoate unit on a derivative orthogonally protected 4-hydroxyproline (Figure 52).

The synthesis diagram of the compounds FG1-3, FG1-4 and FG1-5 is shown in Figure 53. The compound trans-L-4-hydroxyproline enantiomerically pure 4-1 is successively protected orthogonally in the form of methyl ester by action of thionyl chloride in the presence of methanol quantitatively then in the form of tert-butyl carbamate by treatment with di-tert-butyl dicarbonate and finally in the form of a silylated ether with TIPSCl in the presence of imidazole to lead to Compound 4-2 with an overall return of 57% on the 3 stages of synthesis.

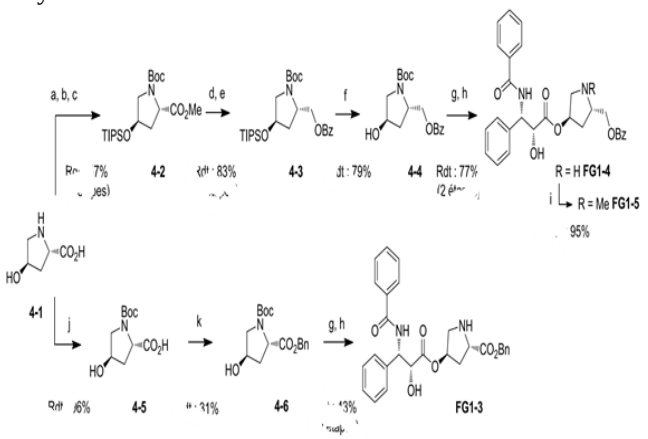

Figure 53: Synthesis of Compounds FG1-3, FG1-4 and FG1-5

The ester reduction of a derivative of 4-hydroxyproline is commonly performed using lithium borohydride, DIBAL-H, or systems involving sodium borohydride alone or in combination. In the case of compound 4-2, a NaBH4-CaCl2 system in an ethanol/THF mixture was employed to reduce its methyl ester. The resulting hydroxyl group can be esterified using conventional Mitsunobu conditions or Steglich conditions. For compound 4-3, the latter conditions were utilized with benzoic acid, EDC, and DMAP in dichloromethane to yield the desired product. The alcohol function of compound 4-3, initially protected as a silylated ether, was deprotected with TBAF, resulting in a 79% yield. The precursor of the paclitaxel side chain, protected as an oxazolidine, was introduced through an esterification reaction under Steglich conditions on compound 4-4. Deprotection in an acidic medium allowed for both the opening of the oxazolidine ring and the deprotection of the amine, leading to the formation of compound FG1-4 with a 77% overall yield. A reductive amination reaction using formaldehyde, acetic acid, and sodium triacetoxyborohydride in dichloromethane was employed on compound FG1-4 to functionalize the nitrogen atom and generate the N-methylated derivative FG1-5. Finally, compound 4-6, protected as a tert-butyl carbamate and a benzyl ester, was obtained in two steps from trans-L-4-hydroxyproline 4-1 with a 29% yield (see Figure 54).

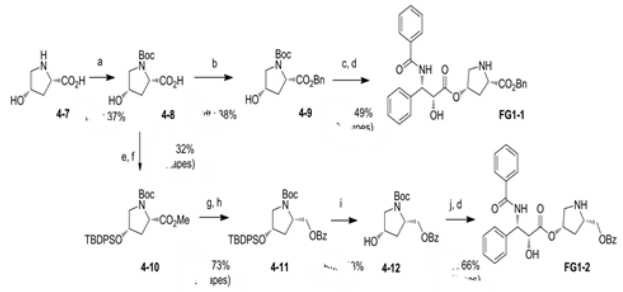

Figure 54: Synthesis of FG1-1 and FG1-2 Compounds

Theco-off with the paclitaxel side chain under Steglich conditions followed by deprotection in an acid medium led to the obtaining of the compound FG1-3. The compounds FG1-1 and FG1-2 (Figure 54) were synthesized under conditions analogousto those described above from cis-L-4-hydroxyproline 4-7. An identical synthetic approach was also used from the compound trans-Dhydroxyproline 4-13 (Figure 55). The compound FG1-9 was thus synthesized under the same conditions as those described for the synthesis of compounds FG1-1 and FG1-3. The FG1-6 compound is obtained similarly to the FG1-2 and FG1-4 compounds. The FG1-8 compound is obtained in one step by a reductive amination reaction from the FG1-6 compound. The nitrogen atom of intermediate 4-16 is deprotected in an acidic medium and then acetylated with acetic anhydride to provide compound 4-18 precursor of compound FG1-7.

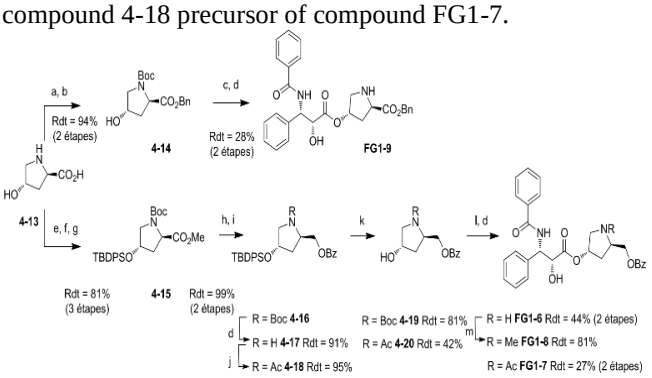

Figure 55: Synthesis of Compounds FG1-6, FG1-7, FG1-8 and FG1-9

The search for the first generation of paclitaxel mimes focused on compounds with a pyrrolidine skeleton and a central skeleton. The synthesis of more elaborate bicyclic central skeletons should allow a greater overlap with the central taxane skeleton of paclitaxel [55-58].

VII. SECOND-GENERATION PACLITAXEL MIMES

A. Molecular Modelling

This novel generation of bicyclic compounds incorporates indolizidin one units (FG2-1, FG2-2, FG2-3), pyrroloazepin ones (FG2-4, FG2-5), and pyrroloazocin ones (FG2-6), which maintain the expected interatomic distance between oxygen atoms (Figure 56). The approach relies exclusively on trans-D-4-hydroxyproline as the starting point. Prior to compound synthesis, a molecular modeling study, similar to the first-generation mimics, was conducted.

Retrieval Number: 100.1/ijapsr.A4036124123
DOI:10.54105/ijapsr.A4036.124123
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The conformational energy of the new paclitaxel mimics was minimized using the AMBER 12 force field, and their structures were superimposed onto the 1JFF-Taxol structure. The second-generation paclitaxel mimics exhibited satisfactory superposition, with a notable alignment of the phenylisoserine side chain attached to carbon atom C13 and the benzoate group attached to carbon atom C2 of paclitaxel. Additionally, these mimics displayed a better restoration of the taxane ring compared to the first-generation mimics.

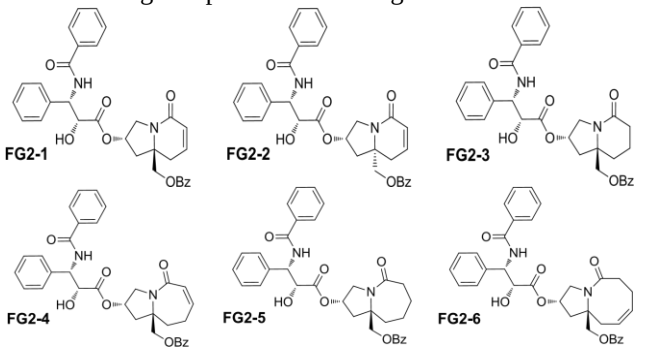

Figure 56: Second-Generation Mimes of Paclitaxel

The synthesized compounds differ from previously described paclitaxel mimics by the attachment of the benzoate motif to the central skeleton through the carbon atom at the ring junction. To achieve optimal overlap, the stereogenic center carrying the benzoate must have an absolute configuration of R (FG2-1), as evidenced by the interatomic distance between the two oxygen atoms (O2-O8) measuring 4.72 Å. While it is possible to superimpose the phenylisoserine side chain and benzoate with a stereogenic center of absolute configuration S (FG2-2), it does not allow for optimal superimposition of the central skeleton with respect to the taxane backbone, and the interatomic distance between the two oxygen atoms (O2-O8 = 3.88 Å) is unsatisfactory. Additionally, enlarging the bicyclic motif to construct the pyrroloazepinones (FG2-4 and derivatives FG2-5) and the pyrroloazocinone derivative (FG2-6) enables effective superimposition of the taxane motif. This enlargement brings the carbon skeleton closer to the M-loop region in the tubulin binding site, which is crucial for the mechanism of action of microtubule stabilizing agents. Similarly, the interatomic distances (O2-O9 = 4.84 Å for FG2-4 and O2-O10 = 4.71 Å for FG2-6) align with that measured for paclitaxel (4.9 Å). The retrosynthetic analysis of second-generation mimics is depicted in Figure 89, with the methodology remaining the same for the synthesis of indolizidinone (FG2-1, FG2-2, and FG2-3), pyrroloazepinone (FG2-4, FG2-5), and pyrroloazocinone (FG2-6) units. The introduction of the paclitaxel side chain, protected as an oxazolidine, was achieved through a Steglich esterification reaction under similar conditions as used for first-generation mimics Figure 57. Bicyclic intermediates can be obtained through cyclizing metathesis reactions, with precursors obtained from the acylation of the nitrogen atom of pyrrolidine and alkylation reaction of proline at position 2. Orthogonal protection of the compound 4-hydroxyproline can be achieved in three synthesis steps from trans-D-4-hydroxyproline.

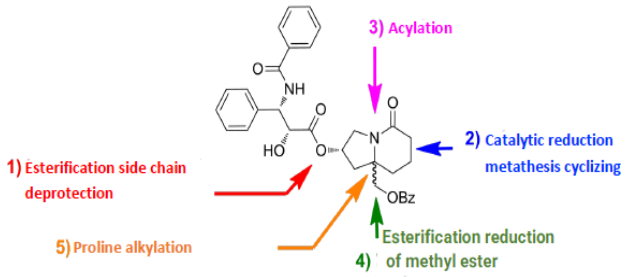

Figure 57: Retrosynthetic Analysis of Second-Generation Paclitaxel Mimes

B. Cyclotriproline

a. IIX-I. Identification of the Peptide Matrix

Proline was used as a chemical fragment in the previous to synthesize a new series of paclitaxel mimes. The objective of this second part is to identify and synthesize a peptide matrix capable of covering the polycyclic taxane structure and of correctly orienting the side chain carried by the carbon atom C_{13} and the benzoate group carried by the carbon atom C_2 of paclitaxel.

b. Identification of the Peptide Matrix by Molecular Modelling

The utilization of a flexible linear peptide matrix to imitate the taxane's polycyclic structure has been disregarded. Research efforts have focused on identifying a cyclic peptide structure instead. The inherent conformational strain induced by cyclic proline enables the construction of small cyclic peptide motifs that are unattainable with non-cyclic amino acids. By incorporating substituted prolines at different positions of the pyrrolidine ring, subsequent pharmacomodulation becomes a possibility. In this study, the decision was made to employ the 4-hydroxyproline monomer to introduce the lateral chain and benzoate group found in paclitaxel [42,55,57].

c. Size of the Peptide Matrix

A molecular modeling study was conducted to determine the optimal peptide matrix size for mimicking the polycyclic taxane skeleton. The study considered cyclodipeptide, cyclotripeptide, and cyclotetrapeptide matrices. Various cyclodiproline structures (proline-proline 2,5-diketopiperazines) were energy-minimized using the AMBER 12 force field and aligned with the 1JFF-Taxol structure. Superimposing these units did not reveal a suitable coverage for effective vectorization of the side chain attached to carbon atom C13 and the benzoate group attached to carbon atom C2 of paclitaxel from the pyrrolidine rings. On the other hand, the cyclotetraproline matrix was found to be excessively large compared to the size of the polycyclic taxane motif to be mimicked.

d. Cyclotriproline as a Peptide Skeleton

Molecular modeling identified cyclotriproline as the optimal framework for mimicking the polycyclic taxane structure (Figure 58).

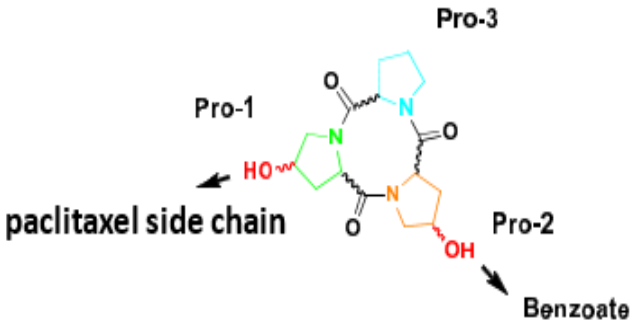

Figure 58: Generic Matrix Selected after Molecular Modelling Study

Determining the absolute configurations of the three prolines was essential for orienting paclitaxel's substituents in the desired directions. Modeling involved matrices with two 4-hydroxyproline monomers for substituent binding and one proline monomer.

Eight compounds, representing all possible absolute configurations of the three amino acids, were energy-minimized using the AMBER 12 force field and aligned with the paclitaxel structure (1JFF-Taxol). Analysis focused on the vectorization of the side chain and benzoate motifs through the two oxygen atoms. The distance between these oxygen atoms was measured and compared to that of paclitaxel (O2-O13). Results indicated that only the structure composed of trans-L-4-hydroxyproline, trans-D-4-hydroxyproline, and D-proline monomers was suitable for constructing a cyclic peptide mimic of paclitaxel. Importantly, this model exhibited the shortest distance between the two oxygen atoms designated for paclitaxel substituents [52].

e. Cyclic Peptides

Peptides have garnered attention as potential therapeutics due to their selectivity, efficacy, and low toxicity. However, their limited oral bioavailability and short half-life pose challenges for clinical use. Fortunately, chemical and structural modifications offer strategies to enhance peptide stability. Techniques such as C/N-terminal capping, incorporation of D-amino acids, N-methylation, and non-natural amino acids (β-amino acids, peptoids) can significantly improve peptide stability. Cyclization serves as an alternative method to protect against proteolytic degradation. Cyclic peptides like gramicidin S, discovered during World War II, have paved the way for cyclic peptide therapeutics. Currently, several cyclic peptides, including octreotide (Sandostatin), cyclosporine A (Sandimmun), and colistin (Colimycin), are clinically utilized. The cyclization strategies employed depend on the peptide sequence, utilizing N-C terminal cyclization, side chain-N/C-terminal cyclization, or side chain-side chain cyclization. Lactamization, lactonization, and disulfide bridge formation are common reactions for achieving cyclization. Dilute reaction solutions are crucial to minimize undesired polymer formation resulting from intermolecular side reactions. Successful N-C terminal macrolactamization heavily relies on the desired ring size, and synthesizing small cyclic peptides, such as cyclotetrapeptides or cyclopentapeptides, can be challenging or even infeasible. Meticulous selection of C- and N-terminal residues in the linear sequence is pivotal for the successful cyclization of small cyclic peptides. Figure 59 provides an example where only the specific linear chain H-Phe-Leu-Pro-Ala-Ala-OH, activated as a pentafluorophenyl ester (Pfp), yielded the desired cyclic peptide, while other linear sequences resulted in cyclodimers, cyclotrimers, or failed to cyclize altogether [53].

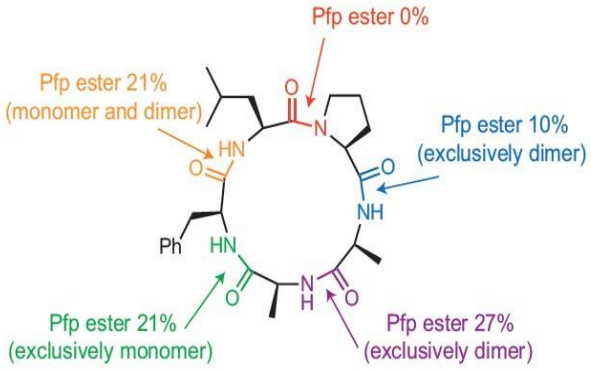

Figure 59: Influence of the Linear Sequence in Cyclization Success

The success of a macrolactamization reaction depends on the spatial proximity of the reactive ends in the linear precursor. Introducing a cis amide bond in the middle of the linear sequence, resembling an elbow β pattern, can bring the partners closer for the reaction. Proline, known for its propensity to form cis amide bonds, allows the synthesis of cyclo(L-Pro-L-Pro-L-Pro). Incorporating a heterochiral D-Pro-L-Pro sequence initiates β-hairpin structuring, making it favorable for macrolactamization. Introducing a D-amino acid into an L-amino acid sequence induces an elbow in the linear sequence. Similarly, N-methylated amino acids can form cis amide bonds and induce β-type elbows. Alternatively, pseudo-prolines (heterocyclic amino acids derived from serine, threonine, or cysteine) can be used. This approach enabled the synthesis of a cyclo[Pro-Thr(ψMe,MePro)-Pro] matrix. Pseudo-proline structures offer the advantage of potentially restoring the serine, threonine, or cysteine residue in a subsequent step **Figure 60**

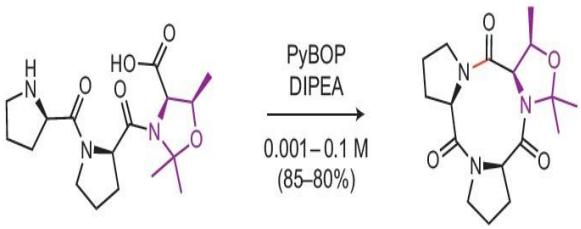

Figure 60: Use of Pseudo-Prolines in Cyclotripeptide Synthesis

The use of non-covalent auxiliaries (metal ions) to facilitate the macrocyclization reaction utilizes the fact that many cyclic peptides are potent ionophores and have the ability to formstable complexes with metal ions. The complexes thus formed make it possible to bring the reactive ends closer together in order to promote the cyclization reaction (**Figure 61**).

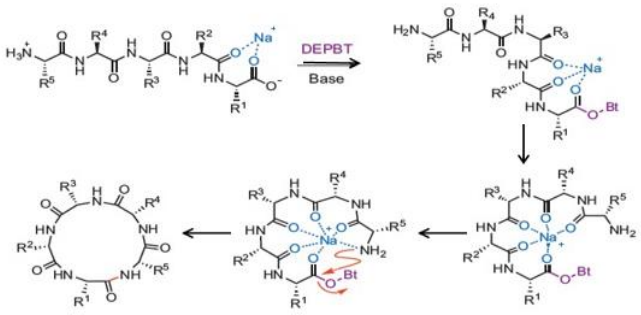

Figure 61: Use of a Metal Auxiliary to Promotethe Cyclization Reaction

Other possibilities leading to macrolactamization exist such as the use of auxiliaries containing sulfur or by ring contraction following the intermediate formation of a lactone. The use of the cyclizing metathesis reaction (RC M) can also bring together the reactive ends then promoting the macrolactamization reaction (Figure 62).

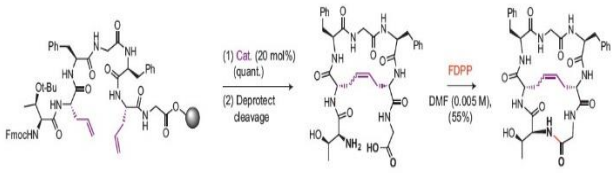

Figure 62: Use of the Cyclizing Metathesis Reaction to Promote the Macrolactamization Reaction

C. The Cyclotriproline Matrix

a. Molecular Modelling of the Cyclotriproline Matrix as a Mime of Paclitaxel

Molecular modeling of the different cyclotriproline matrices (Figure 5-3) showed that the cyclo[L-Pro-D-Pro-D-Pro] **CTP-1** combination had the best profile for the synthesis of CTP-2 and CTP-3 mimes (Figure 63). Prior to the synthesis of CTP-2 and CTP-3 mimes, the development of operating conditions for synthesizing the CT P-1 peptide matrix was carried out.

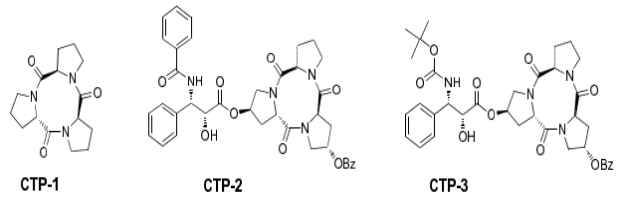

Figure 63: Structure of CTP-1, CTP-2 and CTP-3 Compounds

The structures of the CTP-2 and CTP-3 compounds, bearing the side chain of paclitaxel and docetaxel as well as the benzoate motif, were minimized with the AMBER 12 force field and superimposed on the 1JFF-Taxol structure confirming the good vectorization observed previously [57].

VIII. CONCLUSION

Proline-derived Paclitaxel, a novel anti-cancer compound, offers promising potential in combating various cancers. Structural modifications address the limitations of conventional Paclitaxel, enhancing solubility, anti-cancer activity, and reducing toxicity. This promising compound warrants further exploration and development to significantly impact cancer treatment and improve patient outcomes.

DECLARATION STATEMENT

Funding	No, I did not receive.
Conflicts of Interest	No conflicts of interest to the best of our knowledge.
Ethical Approval and Consent to Participate	No, the article does not require ethical approval and consent to participate with evidence.
Availability of Data and Material/ Data Access Statement	Not relevant.
Authors Contributions	All authors have equal participation in this article.

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AUTHOR'S PROFILE

Dr. Nasser Thallaj, PhD in Chemical Sciences
Professor Member of American Chemical Society (ACS)
2020- presente time: professor in the biomedical Science program.
2020- Present time: *Assistant professor* position. Faculty of pharma *alrashed university*, Damascus , syria
From 15 june 2019 – 31 July 2020: President Of *AlJazeera University*, Damascus, Syria.
From Abril 1st 2019 – 15jun: vice president for scientific affairs and Dean of Faculty of pharmacy AlJazeera University, Damascus, Syria.
From October 1st 2018-15 march 2020: Dean of Faculty of pharmacy *AlJazeera University*, Damascus, Syria.
2017-31 July2020: *Assistant professor* position. Faculty of pharmacy, *AlJazeera University*, Damascus, Syria
- 2015-2017: *Assistant professor* position. Faculty of pharmacy, *Syrian Private University*, Damascus, Syria
- 2015- 2016: Consultant in Ugarit Education Group: foundation of *AlManara University*.
- 2014-2015: vice president for scientific affairs (in charge), *University of Kalamoon*, Dier Attieh, Syria.
- 2014-2015: In charge of higher education affairs, *University of Kalamoon*, Dier Attieh, Syria.
- 2012-2014: Dean of Faculty of applied Sciences, *University of Kalamoon*. Dier Attieh, Syria.
- 2010-2013: Head of Department of Chemistry. Faculty of applied Sciences, *University of Kalamoon*. Dier Attieh, Syria
-2008: *Assistant professor* position. Faculty of applied Sciences, *University of Kalamoon*. Dier Attieh, Syria
2007-2008 : Post-Doctoral position. *Laboratory of NanoOrganic Chemistry, and Supramolecular Materials*, thesis title : *drug delivery system Department* of Chemistry. *University Notre Dame de la Paix*. Namur, Belgium.

Neamah Omar Alshhada Undergraduate student. Pharmaceutical chemistry and drug quality control Department, Faculty of Pharmacy, Al-Rachid Privet University, Damascus, Syria. pharmacy student at Rasheed Ru University and registration date at the university 2017 - 2018 First aid certificate ICDL Certification Fourth level in English from LTC.

HIGHLIGHTS:
A broad-based experience in synthesis and characterization of organic and organo-metallic compounds. Multiple-step organic and organometallic synthesis. Carbohydrate Chemistry, Microwave synthesis, Solid phase synthesis, Enantioselective synthesis, Homogenous catalysis, Synthetic techniques including working on a Schlenck line, through a glovebox and in a clean rooms.

Crystallogenesis experience especially in growing single crystals under inert conditions. Characterization of organic products and organometallic complexes by a variety of NMR techniques (1H, 13C, 31P, 15N, 19F) 1D and 2D, 1HNMR, FT-IR spectroscopy, UV-Visible-NIR spectroscopy, variable temperatures, Mass spectrometry, electrochemistry (conductimetry, cyclic voltammetry), chromatography techniques, including column, TLC preparative, GC, GC mass and HPLC chromatography.

Haya Asmail Alhamdo, Undergraduate student. Pharmaceutical chemistry and drug quality control Department, Faculty of Pharmacy, Al-Rachid Privet University, Damascus, Syria. pharmacy student at Rasheed Ru University and registration date at the university 2017 - 2018 First aid certificate. ICDL Certification. Fifth level in English from LTC.
HIGHLIGHTS:
A broad-based experience in synthesis and characterization of organic and organo-metallic compounds. Multiple-step organic and organometallic synthesis. Carbohydrate Chemistry, Microwave synthesis, Solid phase synthesis, Enantioselective synthesis, Homogenous catalysis, Synthetic techniques including working on a Schlenck line, through a glovebox and in a clean rooms Crystallogenesis experience especially in growing single crystals under inert conditions.
Characterization of organic products and organometallic complexes by a variety of NMR techniques (1H, 13C, 31P, 15N, 19F) 1D and 2D, 1HNMR, FT-IR spectroscopy, UV-Visible-NIR spectroscopy, variable temperatures, Mass spectrometry, electrochemistry (conductimetry, cyclic voltammetry), chromatography techniques, including column, TLC preparative, GC, GC mass and HPLC chromatography.