A Review on Synthesis and SARs of Select Natural Alkaloids as Anticancer Agents

By

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A thesis submitted to the school of pharmacy in partial fulfillment of the requirements for the degree of Bachelor of Pharmacy

School of Pharmacy
Brac University
October, 2024

Declaration

It is hereby declared that

1. The thesis submitted is my/our own original work while completing degree at Brac University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
4. I/We have acknowledged all main sources of help.

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Approval

The thesis titled "A Review on Synthesis and SARs of Select Natural Alkaloids as Anticancer Agents" submitted by Md. Saif Hossain Siam (Student ID: 20146065), of Spring, 2020 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy (B. Pharm.)

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Ethics Statement

This study does not involve any kind of animal or human trial.

Abstract

Cancer is the leading cause of death worldwide. It is defined as the uncontrolled growth of abnormal cells in the body that affects healthy cells, have deleterious effects on vital organ functions and eventually death. New and potent anticancer medications are urgently required. There are many different sources of alkaloids that may have anticancer properties. Several of them have the potential to be local anesthetics but their application is primarily restricted to clinical uses based on the patients need. Ongoing efforts by scientists persist in the development of more complex semisynthetic and synthetic alkaloids obtained from natural alkaloids. These alkaloids may exhibit intriguing activity for medicinal, pharmacological and many other beneficial qualities. Consequently, the present review article outlines the modes of action of naturally occurring alkaloids that may have anticancer properties, select synthetic methods and SARs of these privileged motifs. Current knowledge in this sector is expected to be beneficial for scientists and students alike.

Keywords: Natural Alkaloid, Anticancer, Pharmacology, Mode of Action, Synthesis, SARs.

Dedication

Dedicated to my Parents.

Acknowledgement

Firstly, I would like to convey my appreciation to Allah (SWT) As the Supreme Being for His boundless gifts, benevolence, and empathy. He deserves all praise for bestowing upon me tremendous patience, fortitude, bravery, erudition, and sagacity.

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List of Acronyms

BBR	Berberine
MDR	Multi drug resistance
DNA	Deoxyribonucleic Acid
SAR	Structure activity relationship
MOA	Mechanism of action
BBB	Blood brain barrier
TSG	Tumor suppressor gene
NPs	Nano-particles
NK	Natural killer

Chapter 1: Introduction

1.1 Introduction to cancer and it's prevalence

Cancer is regarded as the uncontrolled growth of abnormal cell or tissues in the body. During the developing stage of cancer instead of dying, old cells grow rapidly and form new abnormal cells continuously which is uncontrollable. These uncontrolled abnormal cells cause severe problems in DNA replication and it prevents the protein secretion of normal cells in our body. It is a lethal disease which is responsible for the deaths of millions of people around the whole world. It is one of the major human diseases with highest death rates. The most recent International Agency for Research on Cancer (IARC) data state that there were about 1 crore cancer-related deaths and 1.93 crore patients having cancer related cases worldwide in 2020. If we examine the WHO's main sheet, cancer claimed around 9.6 million lives worldwide in 2018 and was a factor in one out of every six deaths. From a recently published survey it is proved that lung and breast cancer are the most injurious which accounts for about 2.4 million deaths combinedly (Rawat & Vijaya Bhaskar Reddy, 2022).

Along with the traditional therapies there are some conventional therapies available for cancer treatment such as chemotherapy, radiotherapy, surgery and so on. The negative part of all this treatment is it causes damage to the normal cells in our body. All of these treatment carries side effects which accompanied with a number of adverse consequences, including medication resistance, recurrence, metastatic development, partial tumor excision, and persistent pain. Despite of considering all the genetic risks, epidemiological research revealed a link between a high cancer risk and certain lifestyle factors, such as smoking, binge drinking, eating poorly, and not exercising (Sun et al., 2024a)

Considering the fact that the majority of cancers have unclear causes but it is also clear that there are a number of identified risk factors, many of which include certain factors like tobacco

use and excess body weight which are possibly controllable. On the other hand, others like inherited genetic abnormalities are not controllable. These risk factors have the potential to start and/or encourage the growth of cancer concurrently or sequentially. It is possible to avoid a significant percentage of cancers, including all cancers brought on by tobacco smoking and other harmful habits. Moreover, screening can lower the death rate for identifying cancer at early stage, when treatment is comparatively less sensitive and more visible, these malignancies as well as cancers of the breast, lung and prostate. In contrast, the chance of getting cancer in women's risen gradually during the previous ten years. If we lead a healthy lifestyle and proper exercise may ensure our health safety and prevent the formation of various disease include the injurious cancer (Lu et al., 2012)

This methodology indicates that the stage is in situ if the cancer is contained to the layer of cells where it first started to develop and has not transmitted. Once cancer cells have broken through the first tissue layer then the disease is considered invasive and is classified as local, regional, or distant depending on how far the cancer has spread. This technique is not able to stage some cancers (such as brain tumors and leukemia), hence the stage distribution for all cancers combined is not available. TNM is another staging approach that is more often applied by professionals. It stands for tumor size, nodes involvement, and metastatic presence. In a similar manner, TNM evaluates the growth and spread of cancer and designates a stage, ranging from 0 (in situ) for the most advanced illness to I, II, III, or IV for less advanced stages. Additional tumor-specific characteristics have been added to the staging process for multiple cancers as our understanding of the biology of cancer improves. Several studies have shown that well-funded and complete tobacco control programs and evidence-based policies such as higher taxes, laws that are completely smoke-free, coverage for barrier-free tobacco cessation treatment, graphic warnings on cigarette packaging, and restrictions on the sale of menthol and aroma, can all improve health and save lives(Lu et al., 2012)

1.2 **Overview of Alkaloids as anticancer agents**

Alkaloids are a broad class of chemical compounds that exist naturally and have one or more nitrogen atoms which might differ with amido or amino in their structures. These compounds' alkalinity is a result of these nitrogen atoms and these atoms of nitrogen are often arranged in a ring-based manner. Making more understandable with example like compounds with a nitrogen atom in the indole ring system are known as indole alkaloids and this can be differed with other alkaloids based on their structure which contains ring system. Furthermore, based on structural similarities, alkaloids are often divided into groups such steroids, pyrrolidines, pyrrolizidines, indoles, quinolines, and isoquinolines, as well as tropanes. Alkaloids can form salts by reacting with acids just like inorganic alkalis. In the acid -base reaction nitrogen atom act like a base. Pure alkaloids are typically odorless, colorless crystalline solids; however, they can occasionally be liquids with a yellow tint and they are frequently taste bitter or harsh. Currently, around 3000 alkaloids from over 4000 plant species are known to exist (Kurek & Kurek, 2019).

At first, there are many different sources of alkaloids that may have anticancer properties. The majority of the alkaloids belong to distinct families, and their production shows variability as well. For instance, evodiamine is obtained from the roots in tryptophan, whereas berberine is isolated from the roots in phenylalanine and tyrosine. Secondly, these alkaloids exhibit a range of pharmacological actions. As an example, berberine and piperine are used to treat diarrhea and epilepsy respectively but both of these substances have pharmacological effects that include anticancer properties. Thirdly, these anticancer alkaloids have different study focuses. Research on most other alkaloids is mostly focused on cancer treatment but particularly on the assessment of antiproliferative efficacy, while research on piperine is often focused on cancer prevention(Lu et al., 2012)

In addition to sharing the same generic term - alkaloids, they differ greatly in their chemical composition. Because of the vast spectrum of effects these chemicals have affecting both human and animal species and some of them appear to have been known to humans for many years. Alkaloids have been used in plant extracts for thousands of years as medications but these extracts' potent effects are a result of the alkaloids' presence. In present days, organic chemists, biologists, biochemists, pharmacologists and chemists continue to be very interested in alkaloids which are often found in plants rather than animals. Morphine, strychnine, quinine, atropine, caffeine, ephedrine, and nicotine are examples of well-known alkaloids (Kurek & Kurek, 2019)

The importance of the mechanism by which natural alkaloids act as anticancer agents is diverse:

1. **Personalized Medicine**

- An understanding of the mechanism by which alkaloids exert their anticancer effects is crucial for the development of adapted therapeutics. These substances often exhibit interactions with certain cellular constituents, such as DNA, enzymes, or receptors, therefore impeding the proliferation of cancer cells or triggering apoptosis (programmed cell death).

2. **Pharmaceutical Development**

- Alkaloids include a substantial reservoir of innovative pharmaceutical prospects. The understanding of their processes enables scientists to alter these molecules in order to improve their effectiveness, decrease their harmful effects, and overcome the resistance to drugs in the treatment of cancer.

3. **Managing and conquering drug resistance**

- A significant number of malignancies acquire resistance to traditional treatments. Alkaloids of natural origin frequently possess distinct modes of action that may

circumvent or surmount these resistance mechanisms, therefore offering alternate or supplementary therapies.

4. **Beneficial properties**

- Certain alkaloids may be used with other medications to improve the overall therapeutic efficacy. Gaining insight into their mechanism facilitates the development of combination medicines that can work together to enhance the efficacy of cancer cell death.

5. **Mitigating adverse reaction**

- Conventional chemotherapy is often linked to significant adverse effects because of its non-selective impact on both malignant and healthy cells. Alkaloids, via their unique processes, may provide more precise targeting, hence possibly minimizing adverse effects and enhancing the quality of life for patients.

6. **Directing clinical implementation**

- An understanding of the processes enables the prediction of the specific forms of cancer that a certain alkaloid may be efficacious against. The provided information is of utmost importance in directing clinical trials and customized medicine strategies, therefore guaranteeing that patients get the suitable medication.

7. **Facilitating scientific research on natural products**

- Gaining insight into the mechanisms of action fosters the wider sector of natural product research, therefore promoting the investigation of additional natural substances as prospective anticancer medicines.

Understanding the mechanism of natural alkaloids in cancer therapy is crucial because it has the potential to enable the development of more efficient, specific, and safer medicines(Shaik et al., 2022)

1.3 **Pharmaceutical and medical use of alkaloids**

Alkaloids shown a wide range of therapeutic effects. Although several of them have the potential to be local anesthetics but their application is primarily restricted to clinical uses based on the patients need. Morphine is a widely recognized alkaloid that has been and is now used for biological therapeutic applications. However, the effectiveness of this alkaloid as a narcotic for pain relief is limited by its addictive properties. Codeine which is a methyl ether derivative of morphine that is found naturally in opium poppies close to morphine and it has been demonstrated to have good analgesic properties that to be mostly nonaddictive. These alkaloids stimulate the heart or breathing systems. After that comes atropine which is an alkaloid that finds widespread usage in medical applications as medication. As an example, bradycardia at low heart rate is treated with an injection of atropine(Kurek & Kurek, 2019)

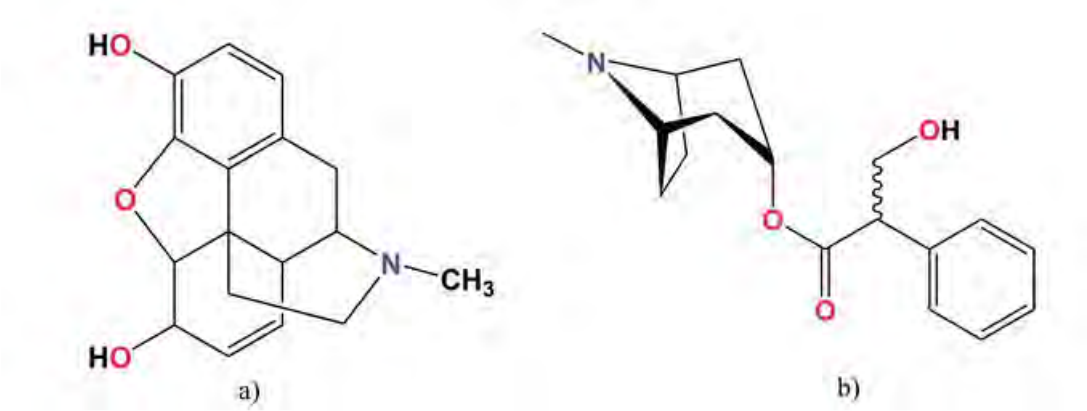

Figure 1: Structure of alkaloids (a) morphine (b) atropine (Kurek & Kurek, 2019)

The alkaloid tubocurarine is used as a muscle relaxant in surgical procedures and is also a significant constituent of poison curare. Vinblastine and vincristine, alkaloids, are used as chemotherapeutic medicines to treat certain types of cancer. One of the powerful local anesthetics found in Erythroxylum coca is cocaine which is an alkaloid. Alkaloids that act as blood vessel constrictors include ephedrine which is extracted from Ephedra species and ergovine. Ephedrine is also used to treat bronchial asthma and to alleviate the symptoms of common colds, sinusitis, and hay fever (Kurek & Kurek, 2019)

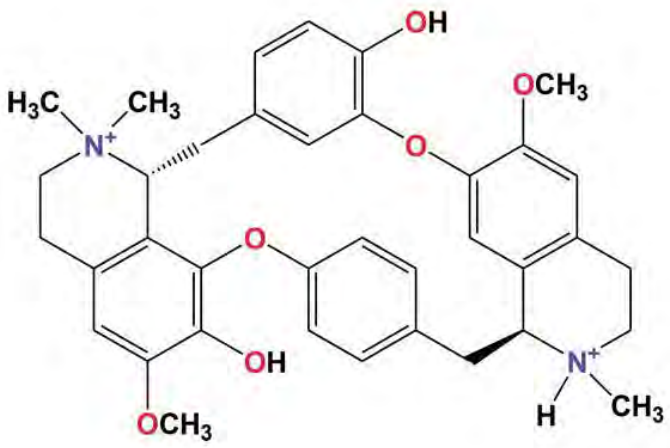

Figure 2: Structure of tubocurarine(Kurek & Kurek, 2019)

Strong antimalarial quinine is often replaced by synthetic medications since they are less harmful and more effective. Quinidine is another alkaloid from the Cinchona species that is used in medicine to treat arrhythmias or abnormal heartbeats.

On the other hand, alkaloid found from colchicine which has been utilized for years to treat acute gout seizures. Lobeline is derived from Lobelia inflata that has several different modes of action which is another alkaloid that is commonly used in medical applications.

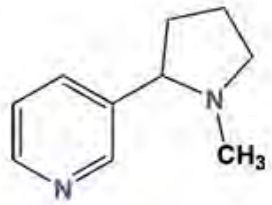

Figure 3: Structure of nicotine(Kurek & Kurek, 2019)

Alkaloids exert stimulatory effects on human organisms, such as the central nervous system, or directly interact with the human brain. Nicotine, an alkaloid derived from the tobacco plant Nicotiana tabacum, is a powerful stimulant and the primary component found in tobacco used for smoking in pipes, cigars, and cigarettes. This alkaloid has a considerable addictive nature.(Kurek & Kurek, 2019)

Figure 4: plant source of caffeine and its structure and powdered caffeine(Kurek & Kurek, 2019)

Numerous alkaloids are constituents of the human diet, found in both food and beverages. Alkaloids found in the human diet include not only coffee seeds (caffeine), cacao seeds (theobromine and caffeine), and tea leaves (theophylline, caffeine), but also tomatoes (tomatine) and potatoes (solanitin). The predominant alkaloid is caffeine, which finds use as a component in carbonated beverages such as Coca-Cola to enhance their flavor and in beverages designed for physically active individuals engaged in sports. Quinine, an exogenous alkaloid with a bitter taste, is extracted from Cinchona species and utilized as a component in tonics.

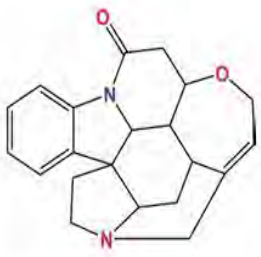

Figure 5: Strychnine (Kurek & Kurek, 2019)

Certain alkaloids are considered illegal substances and toxic agents. Poisonous properties of some alkaloids have been recognized for centuries. Among these compounds is strychnine, derived from Strychnos species. One particularly renowned poison, curare, derived from

Chondrodendron tomentosum and employed in South Africa as a narrow poison, includes the alkaloid tubocurarine.

The synthesis of natural alkaloids by plants is a fundamental aspect of their defensive systems against herbivores and pathogens. Throughout the years, it has been shown that these chemicals exhibit strong biological activity, including powerful anticancer characteristics. The benefit of alkaloids is that they may selectively target cancer cells while, in most situations, causing little damage to healthy cells. Multiple methods are used by these agents, including disruption of cellular division, impairment of the cell's genetic material (DNA), or enhancement of the body's immune response to identify and eliminate cancer cells. Alkaloids may effectively combat cancer by stimulating many pathways, making them particularly useful against malignancies that may exhibit resistance to other therapeutic regimens. The following are several primary mechanisms by which these natural chemicals function as anticancer agents.

1. **Inhibition of DNA repair enzymes**

- The compound camptothecin is derived from the Chinese tree Camptotheca acuminata. It inhibits the activity of topoisomerase I, an enzyme involved in DNA fixation during cell division.
- Etoposide and Teniposide are pharmaceuticals that induce the death of cancer cells by inhibiting the activity of another enzyme, topoisomerase II, which is derived from a plant toxin known as podophyllotoxin. This results in DNA fractures.

2. **Interfering with cellular division**

- The compounds vincristine and vinblastine are derived from the Madagascar periwinkle plant. Their attachment is to cellular structures known as microtubules, which function as pathways facilitating cell division. Obstructing these pathways prevents the cells from undergoing normal division and ultimately leads to their demise.

- Paclitaxel: This medicine, which originates from the Pacific yew tree, likewise causes cell death by making the microtubules overly stable, preventing them from undergoing the necessary shape changes during cell division.

3. Suppressing the activity of DNA & RNA manufacturing

- Berberine, present in plants such as Berberis, intersperses itself between the DNA strands, therefore interfering with the DNA replication and RNA synthesis activities crucial for cellular proliferation and division. Consequently, this interference results in the demise of cancer cells
- Quinine and quinidine derivatives have the ability to integrate into DNA, therefore disrupting its regular processes and impeding the proliferation of cancer cells.

4. Inducing tumor cell death

- Sanguinarine is derived from the bloodroot plant and induces cell death by generating detrimental compounds known as reactive oxygen species (ROS). These chemicals adversely affect the vital components of the cell, resulting in its demise.
- Evodiamine is a compound that is extracted from the Evodia rutaecarpa plant. It activates proteins that regulate cell death, thereby eliciting the demise of cancer cells.

5. Modifying cellular signaling

- Harmine is a compound present in the plant Peganum harmala that inhibits the transmission of signals directing cell growth and division. By doing this, it serves to inhibit the proliferation of cancer cells.

- Matrine: A plant extract from Sophora flavescens, matrine inhibits the growth and dissemination of cancer cells by disrupting specific pathways that are typically overactive in cancer.

6. Inhibiting the formation of new blood vessels

- Vinpocetine, derived from the alkaloid vincamine, selectively inhibits the proliferation of new blood vessels necessary for tumor development. In the absence of a blood supply, tumors are unable to get the necessary nutrients.
- Tetrandrine, derived from the plant Stephania tetrandra, selectively inhibits signals that promote the development of new blood vessels, therefore depriving the tumor of essential nutrients.

7. Enhanced immune system activity

- Gelsemine is a chemical in the fungus Gelsemium elegans that has the ability to increase the efficiency with which the immune system attacks cancer cells.
- Black pepper contains the chemical piperine, which has the ability to increase the body's immunological response and hence aid in the destruction of cancer cells.

To sum up, natural alkaloids are rich in potential as a source for potential anticancer medications due to their multi-pronged assault on cancer cells. These chemicals could prevent tumor development and kill cancer cells by interfering with their DNA repair, cell division, and signaling mechanisms. There is promising research on the use of natural alkaloids as a cancer treatment. They provide a wide range of cancer treatments that are both effective and safe, which is great news. Better therapies, better results, and a higher quality of life for cancer patients might result from ongoing research in this field(Dhyani et al., 2022)

1.4 Objective of the review article

Cancer exists as a predominant cause of mortality globally, and the need for innovative anticancer drugs remains an urgent priority in medicinal chemistry. Natural products, especially alkaloids, have significant promise as anticancer drugs owing to their varied chemical structures and extensive biological activity. This review seeks to provide a thorough examination of the synthesis methodologies and structure-activity relationship investigations of alkaloids with established anticancer properties, providing insights into their prospective advancement as chemotherapeutic drugs. In order to demonstrate the promise of natural alkaloids as primary compounds for anticancer drug development, this review article aims to give a thorough analysis of the synthesis, structural changes, and structure-activity correlations (SARs) of naturally alkaloids with therapeutic properties. The objectives of this article given below:

1. To provide a summary of the several natural alkaloids exhibiting anticancer properties, emphasizing their origins and structural variety.
2. To examine the synthesis techniques used for acquiring these alkaloids, encompassing both conventional extraction procedures and contemporary synthetic strategies that improve their accessibility.
3. To examine the structure-activity associations (SARs) of these alkaloids, highlighting the impact of certain structural characteristics on their anticancer efficacy.
4. To examine the methods by which these alkaloids have anticancer effects, including specific molecules and pathways implicated in the suppression of cancer cells.
5. To ascertain obstacles in the formulation of alkaloid-derived anticancer pharmaceuticals, including toxicity, drug susceptibility, and accessibility, and provide potential remedies.

6. To suggest future research possibilities in the synthesis, alterations, and biological assessment of organic alkaloids that might improve their medicinal efficacy.

1.5 Methodology

The material was sourced from scholarly papers, research, and publications archived in different digital libraries. Several well-known pharmaceutical databases, including PubMed, Frontiers, MDPI, Research Gate, ScienceDirect, and Google Scholar, are examples of such resources. The search for relevant papers included the use of keywords such as "anti-cancer medication," "mechanism of action," "synthesis of natural alkaloids," "different classes of natural alkaloids," and "SAR" among others. Relevant articles were gathered, and further context was examined. The formulation of a comprehensive literature search strategy has facilitated the review of all requisite publications. Only articles from respectable journals published within a certain time frame were included, whereas publications in languages other than English were eliminated. The research examined the SAR, synthesis methods, and modes of action of natural alkaloids as anticancer agents. Upon selecting a subject, an outline was constructed, with all necessary headers and subheadings.

Chapter02

2.1 Anticancer mechanisms of Berberine (BBR)

In this chapter we will review the mechanism of actions of select natural alkaloids as anticancer agents. The treatment of bacterial diarrhea usually involves the use of berberine (BBR), a small molecule isoquinoline alkaloid obtained from the rhizomes of coptis chinensis and hydrastis canadensis plants. According to the recent research it is proved that BBR has been shown to have anti-tumor properties and to lower glycemic index and cholesterol. Extensive research on the mechanisms behind BBR's hypoglycemic effects has shown that it exerts its effects via inhibiting mitochondria and activating AMPK., BBR can enhanced insulin activity. Changes in the cell cycle facilitate the growth of cancer. Consequently, the creation of compounds that enhance the intestinal absorption of BBR may hold significant promise for cancer therapy. (Wang et al., 2020)

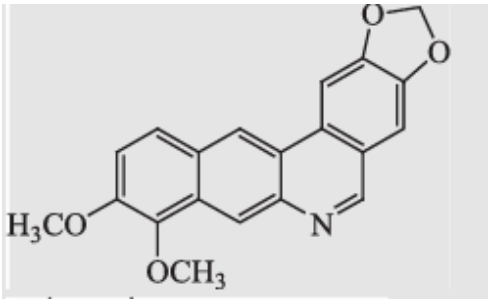

Figure 6: Berberine Structure(Jain et al., 2019)

In order to change the surrounding tumor microenvironment and encourage tumor cell growth and spread, it is necessary for tumor cells to produce cytokines. BBR caused cell death in osteosarcoma by Reducing the activity of the caspase-1/IL-1β messenger pathway that eventually changed the inflammatory microenvironment. In order to more precisely regulate the tumor microenvironment (TME), Berberine (BBR) reduces inflammation, inhibits

angiogenesis (blood vessel formation), and modulates immune responses to promote anti-tumor activity (Wang et al., 2020)

Cell autophagy regulation mechanism by berberine -

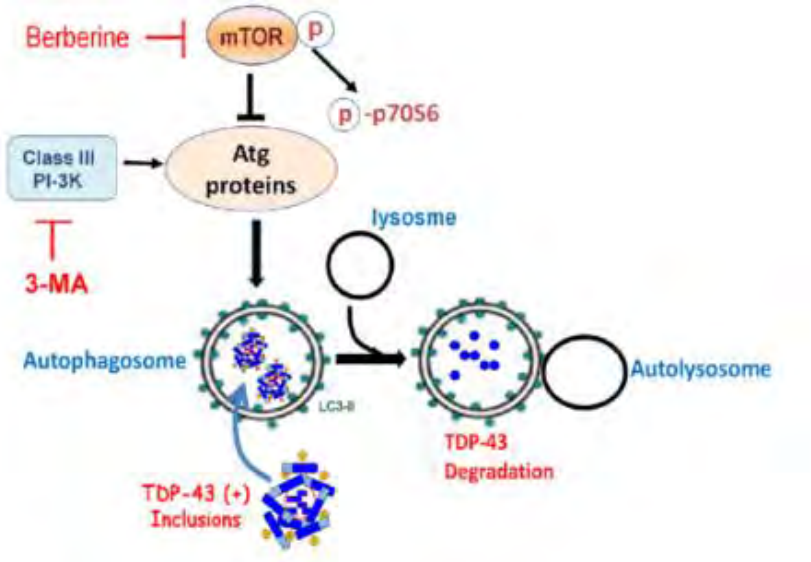

Figure 7: Schematic diagram of the mechanism of berberine(Wang et al., 2020)

The figure demonstrates how Berberine facilitates the elimination of deleterious TDP-43 protein inclusions by enhancing autophagy, the cellular mechanism for degrading and recycling impaired constituents. Berberine specifically inhibits the mTOR pathway, a crucial regulator that typically reduces autophagy. By inhibiting mTOR, Berberine enhances the production of autophagosomes, which are structures that sequester and isolate detrimental protein aggregates. Here, 3-MA (3-Methyladenine) functions as an autophagy inhibitor. It inhibits Class III PI-3K, a protein essential for the early phases of autophagosome development. This inhibition obstructs the initiation of autophagy, resulting in the buildup of TDP-43 protein inclusions. Consequently, Berberine promotes cellular autophagy, but 3-MA inhibits this activity (Wang et al., 2020)

2.2 Anticancer Mechanisms of Indole

Natural compounds such alkaloids and hormones from plants, animals, and microorganisms contain indole that is a bicyclic heterocycle. Compounds containing indole indicate a wide range of pharmacological properties including as antifungal, antibacterial, and anticancer effects. Vincristine and vinblastine, two antimitotic indoles isolated from Catharanthus roseus, have found widespread use in the war against cancer, sarcomas of the bone and soft tissue (Dadashpour & Emami, 2018b)

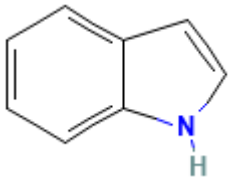

Figure 8: Indole Structure(Jain et al., 2019)

The potential of indole and its derivatives to target several pathways involved in cancer formation and progression makes them viable anticancer medications. Naturally occurring indoles, such as Indole-3-carbinol (I3C) and its metabolite DIM (3,3'-Diindolylmethane), are useful in treating hormone-sensitive malignancies, such as breast and prostate cancer (Sun et al., 2024b)

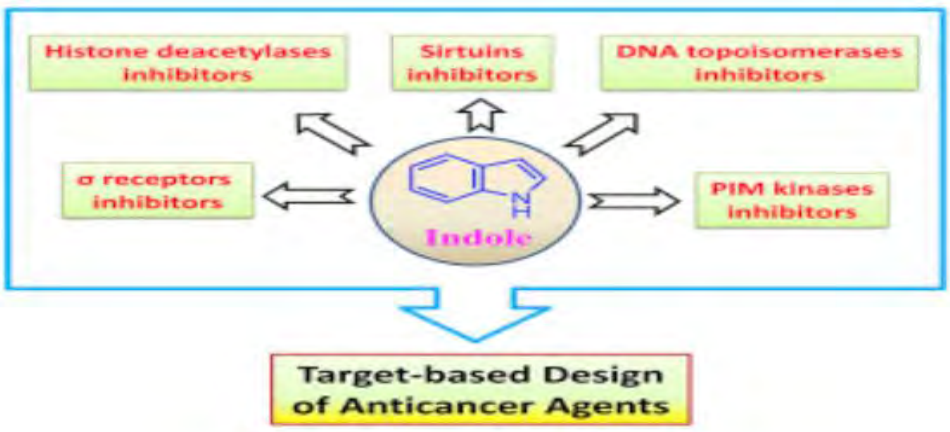

Figure 9: Indole mechanism as anticancer agent(Dadashpour & Emami, 2018b)

This schematic describes the process of designing cancer medications that target many critical processes inside cancer cells using indole as a particular chemical structure. Indole-based chemicals have the potential to hinder the cancer cells' capacity for self-repair by inhibiting proteins such as histone deacetylases and sirtuins. Additionally, these chemicals inhibit cancer cell division by blocking DNA topoisomerases, which are enzymes essential for DNA replication. Aside from that, indole-based medicines block sigma receptors—proteins involved in cell communication and stress response—and PIM kinases—which aid cancer cell survival. Indole chemicals retard cancer cell development and increase therapy sensitivity by focusing on these pathways(Dadashpour & Emami, 2018a)

2.3 Anticancer mechanism of Vinblastine and Vincristine

Among the Vinca alkaloid family the vinblastine has been researched most extensively. In order to address Hodgkin's lymphoma, non-small cell lung cancer, brain cancer, melanoma, and testicular cancer are the medical concerns. Vinblastine and Vincristine are two significant chemo medicines that are part of the Vinca alkaloid class. By preventing cells from dividing (mitosis), these medications are mostly used to treat cancer.

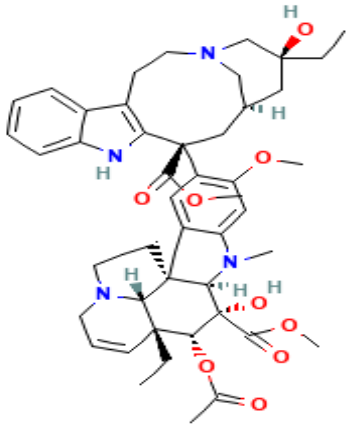

Figure 10: Vinblastine Structure(Jain et al., 2019)

Many different types of cancer, including breast, testicular, non-Hodgkin's, and Hodgkin's lymphomas, are treated with vinblastine. It accomplishes its function by interfering with the process of mitotic spindle development, an essential cellular component for chromosomal separation. Cancer cells are unable to divide and ultimately die if their spindle is not functioning properly.

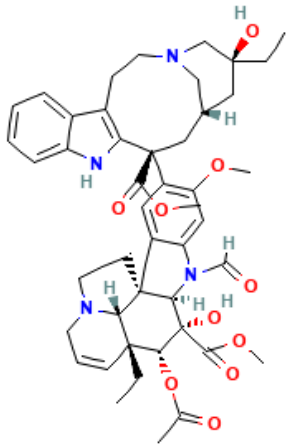

Figure 11: Vincristine structure(Jain et al., 2019)

Vincristine therapeutic use in cancer - Acute lymphoblastic leukemia with no Philadelphia chromosome, B-cell lymphoma, metastatic melanoma, and estrogen-receptor negative Glioma, colorectal cancer, breast cancer, Rhabdomyosarcoma, Neuroblastoma and Hodgkin's lymphoma.

Vinblastine therapeutic use in cancer- Leukemia, Ewing's sarcoma, nephroblastoma, non-Hodgkin's and Hodgkin's lymphomas, Malignancies affecting the testes, germ cell tumors, and small-cell lung cancer (Patel et al., 2022)

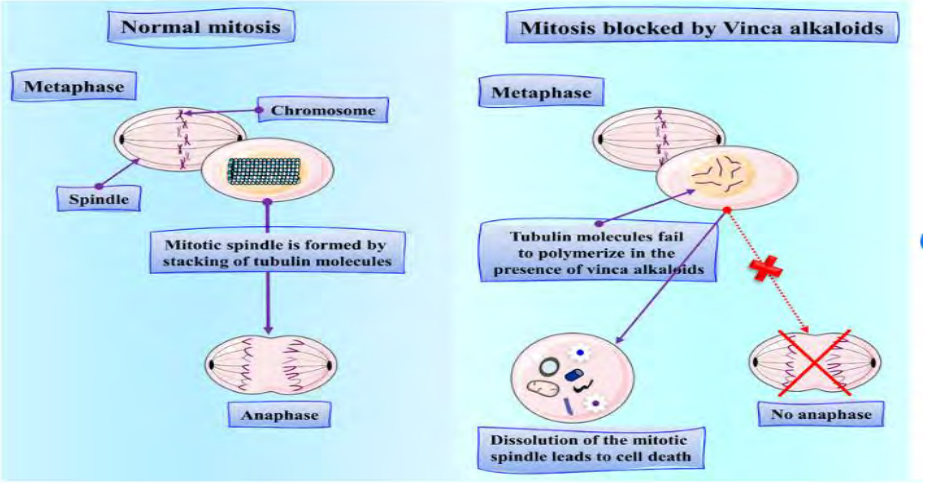

Figure 12: Mechanism of action of Vinca alkaloids(Kousar et al., 2022)

This graphic demonstrates the distinction between normal mitosis and its disruption by Vinca alkaloids, a class of anti-cancer agents include vinblastine and vincristine.

The left side illustrates the phases of standard mitosis, with particular emphasis on the metaphase and anaphase stages. In metaphase, chromosomes align along the cell's equatorial plane, and the mitotic spindle develops. The mitotic spindle is a structure composed of tubulin molecules that aggregate to form fibers (spindle fibers). These fibers connect to the chromosomes and separate them during the subsequent phase, anaphase, guaranteeing that each new cell receives the appropriate number of chromosomes(Dadashpour & Emami, 2018b)

The graphic on the right illustrates the effects of introducing Vinca alkaloids. These pharmaceuticals inhibit the aggregation of tubulin molecules necessary for the formation of spindle fibers, which are essential for the separation of chromosomes. In the absence of spindle fibers, chromosomes are unable to split correctly, resulting in the cell being arrested in metaphase. Consequently, the cell is unable to progress to anaphase, resulting in the disintegration of the mitotic spindle and eventually leading to cell death. This mechanism is particularly crucial in cancer therapy, since it inhibits the proliferation of rapidly dividing cancer cells.

Table 1: Utilization and mode of action of vinca alkaloids in different types of cancer

Vinca	Application in Cancer Treatment	Side effects	Reference
Vinblastine	Neoblastoma, Ewing's sarcoma, breast cancers, non-Hodgkin's and hodgkin's lymphomas, leukemia, this includes germ cell tumors, small-cell lung cancer, and testicular cancer.	Nausea, emesis, alopecia, weariness, constipation, oral lesions, anorexia, and abdominal discomfort.	(Patel et al., 2021)
Vincristine	Philadelphia-negative acute lymphoblastic leukemia, B-cell lymphoma, metastatic melanoma, and estrogen-receptor negative. Types of cancer include breast, glioma, and colorectal. NOL Hodgkin's lymphoma.	Peripheral neuropathy, constipation, alopecia, lethargy, and bone marrow suppression, resulting in an elevated risk of infections, anemia, and hemorrhage.	(Patel et al., 2022)
Vindesine	The following cancers may develop in children: malignant melanoma, acute lymphocytic leukemia, blast crisis chronic myeloid leukemia, metastatic colorectal cancer, and carcinomas of the breast, kidneys, and oesophagus.	Tiredness, constipation, nausea, vomiting, hair loss, and bone marrow suppression, which raises the risk of bleeding, and infections.	(Patel et al., 2021)
Vinorelbine	cancers of the breast and non-small cell lung varieties, lymphomas (both Hodgkin's and non-Hodgkin's), and cancers of the ovaries.	Exhaustion, constipation, alopecia, peripheral neuropathy, and bone marrow suppression.	(Patel et al., 2022)
Vinflunine	Metastatic breast carcinoma, non-small cell lung carcinoma.	Fatigue, nausea, constipation, anemia, neutropenia, thrombocytopenia, mouth sores, hair loss,	(Patel et al., 2022)

		hypertension and many more.	

2.4 Anticancer mechanism of Taxanes (Taxol Alkaloids)

The modified diterpene pseudoalkaloid Taxol was initially identified as a product of the Pacific yew tree and it was discovered that the distinct method of action of this chemical inhibits the proliferation of neoplastic cells by stabilizing microtubules. Additionally, because of their effectiveness on distinct molecular targets, first-generation Taxanes such as paclitaxel use as strong anticancer medicines in the treatment of refractory ovarian cancer, metastatic breast and lung malignancies and Kaposi's sarcoma(Ye et al., 2021).

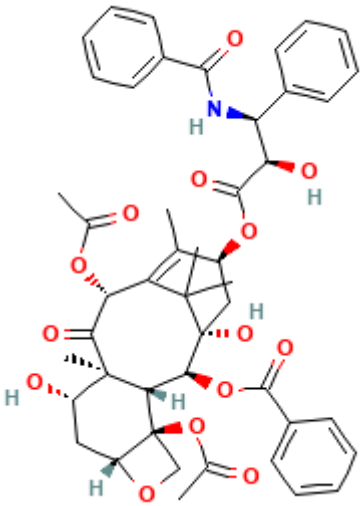

Figure 13: Paclitaxel structure(Jain et al., 2019)

Paclitaxel was first isolated from the bark and leaves of T. canadensis and yew and it was utilized to treat a range of malignancies by binding to b-tubulin in the microtubule lumen which reduced microtubule dynamics and stopped the cell cycle in the M phase. Docetaxel or Taxotere is a second-generation semisynthetic taxanes that was developed in 1992 as a result

of the distinct action of Taxol which is derived from T. baccata. It is used in anthracycline-resistant advanced breast cancer, pancreatic, prostate, and lung cancer regimens. Furthermore, docetaxel and paclitaxel are frequently used alone or in combination with other anticancer medications that stop mitosis and promote cell death but the toxicity profiles of the two taxanes differ from one another (Patel et al., 2022)

Paclitaxel therapeutic use in cancer- cancers of the breast, ovaries, lungs, bladder, prostate, melanoma, the stomach, and Kaposi's sarcoma

Docetaxel therapeutic use in cancer- Oncological malignancies affecting the breast, non-small cell lung, advanced stomach, head and neck, and metastatic prostate.

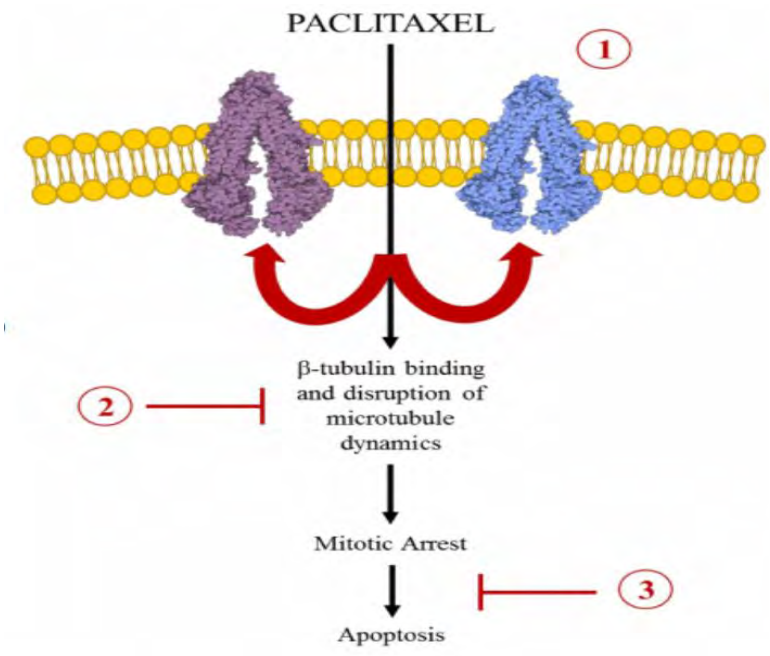

Figure 14: Mechanism of action of paclitaxel(Barbuti & Chen, 2015)

Paclitaxel functions by targeting microtubules, a crucial component of the cell's architecture composed of tubulin proteins, which are vital for cell division. Microtubules are typically dynamic entities that perpetually undergo growth and shrinkage. This dynamic characteristic

is essential during mitosis, namely in facilitating the separation of chromosomes into two daughter cells(Patel et al., 2022)

The cell gets immobilized in the mitotic phase, a condition known as mitotic arrest. When a cell cannot advance via mitosis, it initiates a self-destruction mechanism known as apoptosis or programmed cell death. This is especially significant in cancer therapy, since it inhibits the fast and uncontrolled proliferation of cancer cells, resulting in tumor reduction.

- Paclitaxel interacts with β-tubulin, stabilizing microtubules and impairing their typical dynamic functionality.
- Mitotic arrest transpires when microtubules fail to execute their function of segregating chromosomes, resulting in the cell's cessation of division.
- The failure to execute mitosis induces apoptosis, resulting in the extinction of the cancer cell.

Paclitaxel is useful in treating a number of cancers, including breast, ovarian, and lung cancer, by inhibiting cell proliferation and inducing apoptosis. It is especially beneficial in quickly proliferating cancer cells, which depend significantly on continual and expedited mitosis (Patel et al., 2021)

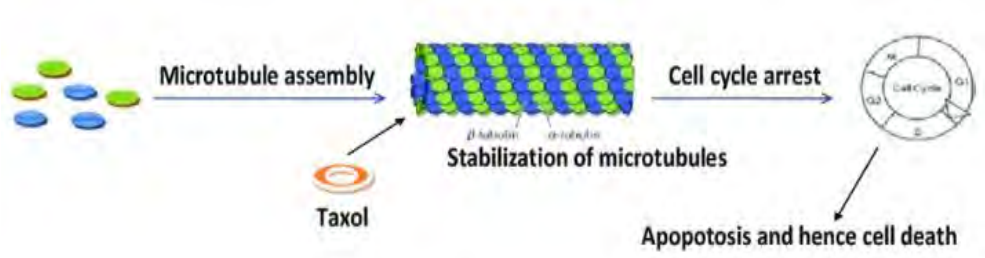

Figure 15: Mechanism of Action by Taxol(Ballout et al., 2019)

This image above demonstrates the mechanism by which Taxol inhibits cell division, eventually resulting in programmed cell death, or apoptosis.

Cells need a component known as microtubules to facilitate division during mitosis. Microtubules consist of proteins, namely α-tubulin and β-tubulin, which polymerize form elongated fibers essential for the segregation of chromosomes into two daughter cells. Typically, microtubules exhibit dynamic behavior, continually assembling and disassembling to facilitate the cell's progression through different phases of division.

Taxol disrupts this mechanism by attaching to and stabilizing the microtubules. Taxol inhibits the normal disassembly of microtubules, producing them hard and fixed in position. This stabilization inhibits the microtubules from executing their essential role, which is crucial for proper cell division. Consequently, the cell gets immobilized in the division process, referred to as cell cycle arrest(Ye et al., 2021)

When a cell fails to finish division, it initiates a self-destruction process known as apoptosis. This mechanism results in cellular apoptosis, which is the desired effect of chemotherapeutic agents such as Taxol, particularly in oncological therapy. Taxol inhibits the fast proliferation of cancer cells, hence limiting tumor development and diminishing the dissemination of cancer. In short, Taxol stabilizes microtubules, resulting in cell cycle arrest and inducing apoptosis, therefore efficiently eliminating cancer cells and halting their unchecked proliferation (Ballout et al., 2019).

Chapter03

Synthesis and SAR of Select Alkaloids

3.1 Synthesis of Indole

An indole is a mixture of aromatic-heterocyclic molecules in which two or three pyrrole ring locations are fused with a benzene ring and they are not fundamental in nature chemically. The water-soluble hypervalent iodine (III) reagent PISA (phenyliodonio) sulfamate efficiently synthesizes many indoles via a C-H amination of 2-alkenylanilines, leading to an aryl migration/intramolecular cyclization cascade with remarkable regioselectivity.

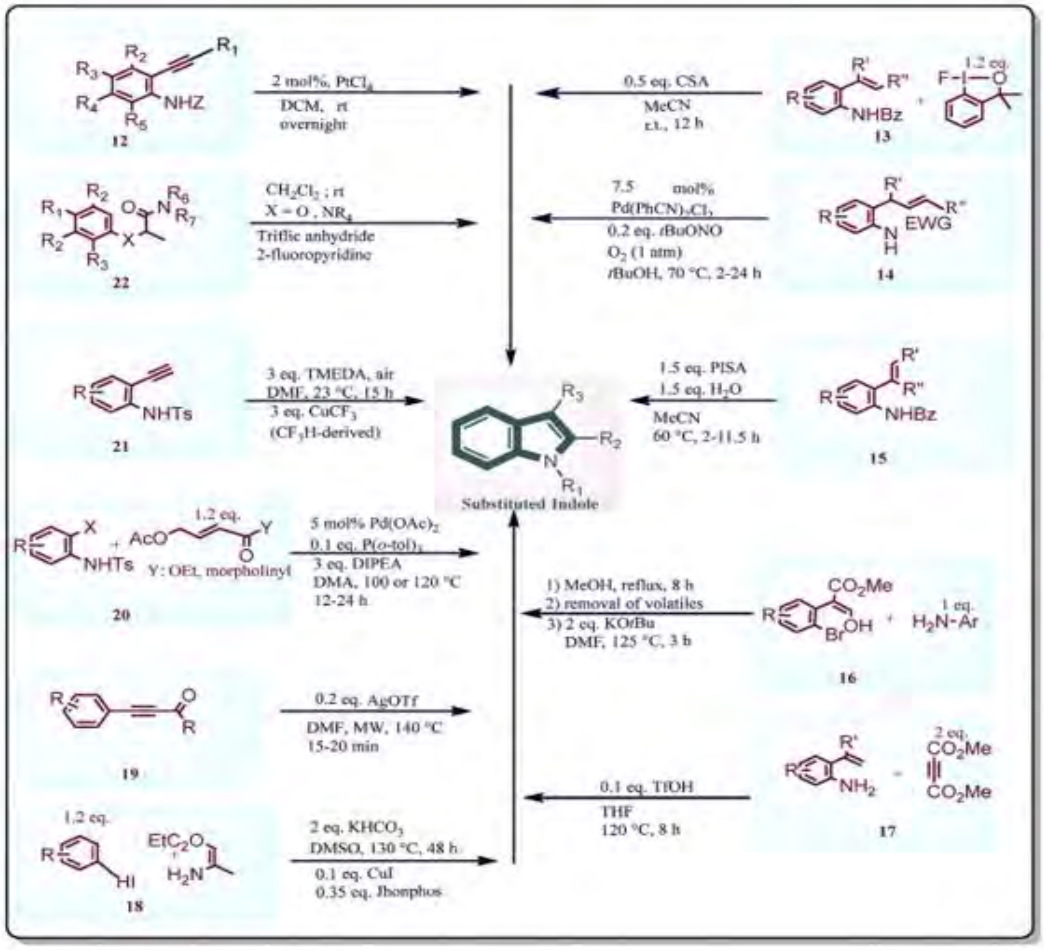

Figure 16: Illustration of a novel green chemical process for synthesizing indole derivatives (Dhiman et al., 2022).

Substituted indoles are organic molecules with many uses, especially in medicines, and this picture explains how to synthesize them in an easy-to-follow manner. The substituted indole structure, a nitrogen-bonded six-membered ring, is the building block of the synthesis reaction. The objective is to alter this structure by substituting R1, R2, and R3 with new or different chemical groups at various places. The figure shows many ways to make these variants by varying the initial ingredients, reagents, and reaction circumstances.

Primary Resources:

Twelve, eighteen, and nineteen are among the chemicals used as building blocks in the synthesis process. The structural and functional group diversity among these compounds allows for a wide range of potential end uses.

In response:

An arrow in the figure signifies each reaction stage. The addition of reagents, or targeted compounds, to the raw materials constitutes this stage. Extreme care is used to regulate the temperature, duration, and presence of catalysts in these processes. Chalcone (Palladium (II) chloride), KOFtBu, and TIOH are a few examples of these reagents. These molecules are able to undergo the transformations necessary for their synthesis into more complex forms because of these substances.

Conditions for Reactions:

The reaction conditions, including solvents (MeCN, DCM) and temperatures (e.g., 120°C, 125°C), are also listed in the graphic. For the reaction to go well and establish the structure of the end product, certain parameters are critical.

Reaction Pathways

Every route in the schematic culminates in a distinct modified indole molecule. Presented here are some visuals:

1. Beginning with chemical 12: This chemical undergoes a reaction with PdCl2 in DCM at ambient temperature. This method ultimately yields compound 13, with an R1 substitution at the nitrogen atom of the indole structure.

2. Beginning with molecule 19: This molecule reacts with Pd (OAc)2 and other reagents under regulated circumstances. The reaction yields compound 15, with distinct substitutions at the R2 and R3 locations of the indole framework.

3. Compound 17 method: This method encompasses many stages, using MeOH for reflux, followed by the incorporation of KOFtBu and DMF to provide compound 17, which has distinct functional groups linked to the indole core.

The ultimate products of each route are substituted indoles with various groups affixed at the R1, R2, and R3 sites. The modified indoles, including 13, 14, 15, and 17, exhibit varied characteristics owing to their distinct chemical groups. This synthesis's versatility enables scientists to customize indole molecules to fulfill particular requirements, whether for research or pharmaceutical development. This synthesis process demonstrates the diversity of chemical events in generating substituted indoles with diverse functional groups. Chemists may manipulate the structure of indole products by using diverse starting materials, reagents, and reaction circumstances, rendering them appropriate for several purposes (Dhiman et al., 2022).

3.2 Specific activity analysis of trimethoxy phenyl-based indole compounds

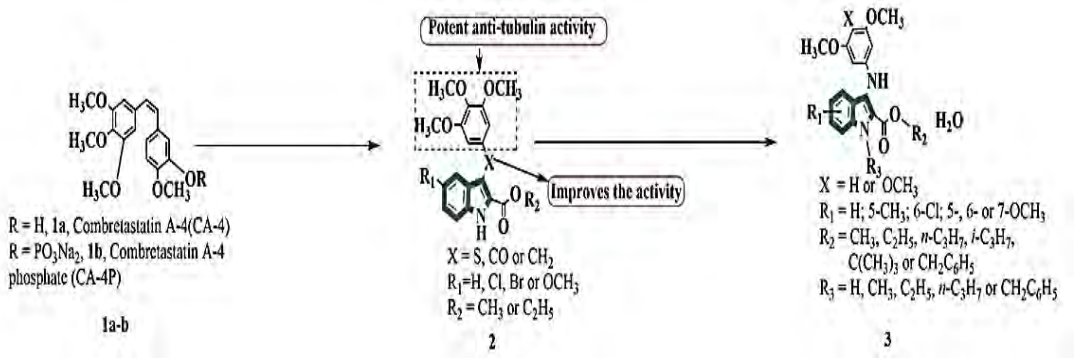

Figure 17: SAR of trimethoxy phenyl-based indole derivatives (Dhiman et al., 2022).

The illustration above demonstrates the use of SAR to enhance the efficacy of Combretastatin A-4 (CA-4), a recognized anti-cancer agent. The objective is to augment its efficacy in suppressing tubulin, a crucial protein implicated in cell division. The compound's efficacy against cancer cells is enhanced by a series of chemical changes.

The first compound in the SAR process is Combretastatin A-4 (CA-4), denoted as compound 1a. This chemical has shown significant anti-tubulin activity, indicating its ability to inhibit tubulin function, which is essential for the division and dissemination of cancer cells. Nonetheless, CA-4 has several limitations:

- Limited aqueous solubility: CA-4 has low solubility in water, complicating its practical use in a medicinal context.
- Possible adverse effects: Despite CA-4's significant efficacy, it may also impact healthy cells, resulting in toxicity.

The solubility problem is resolved by the phosphate derivative combretastatin A-4 phosphate (CA-4P) (compound 1b), which increases the chemical's suitability for therapeutic application. Yet this is only a first phase, requiring more adjustments to enhance overall efficacy. The SAR process starts at 1a-b, since these preliminary molecules, albeit useful, may be refined for enhanced biological activity, improved solubility, and reduced side effects. Structure-Activity Relationship (SAR) elucidates the structural components of CA-4 that enhance its efficacy, enabling precise changes (Dhiman et al., 2022).

The remaining phase of SAR involves changing the fundamental structure of CA-4 to synthesize compound 2. Scientists present a novel heterocyclic ring (in green) that incorporates nitrogen (N). This enhancement introduces two significant advancements:

- Enhanced anti-tubulin activity: The novel ring shape interacts more efficiently with the tubulin protein, perhaps inhibiting it more robustly or selectively, hence increasing its capacity to impede cancer cell proliferation.
- Increased specificity: By modifying X, R1, and R2 within the structure, researchers may alter the compound's physiological behavior.

- X may represent sulfur (S), carbonyl (CO), or methylene (CH2). These groups may influence the drug's affinity for tubulin or alter its metabolic processing inside the body.
- R1 (H, Cl, Br, OCH3) facilitates changes on the aromatic ring, perhaps affecting the compound's interaction with tubulin or improving the drug's stability.
- R2 (CH3, C2H5) may alter hydrophobicity, influencing the drug's cellular permeability.

The concluding phase of the SAR process yields compound 3, which incorporates further alterations to enhance the chemical's capabilities.

The X, R1, R2, and R3 groups have been optimized-

- X: Either methoxy (OCH3) or hydrogen (H), which both alter the compound's interaction with tubulin and may make it more soluble.
- R1: Selectivity and tubulin binding may both be improved by benzene ring modifications.
- R2 and R3: These groups are enhanced for improved solubility, pharmacokinetics, and augmented efficacy.

This final product is the result of many SAR cycles. Researchers precisely calibrated the compound's chemical characteristics to optimize its therapeutic efficacy, guaranteeing effective interaction with tubulin, rapid cellular uptake, and safety for human use. At this juncture, SAR is essential since it facilitates the precise adjustment of the compound's attributes. The objective is to develop a chemical that inhibits the proliferation of cancer cells while exhibiting optimal efficacy in the body and minimum adverse effects (Dhiman et al., 2022).

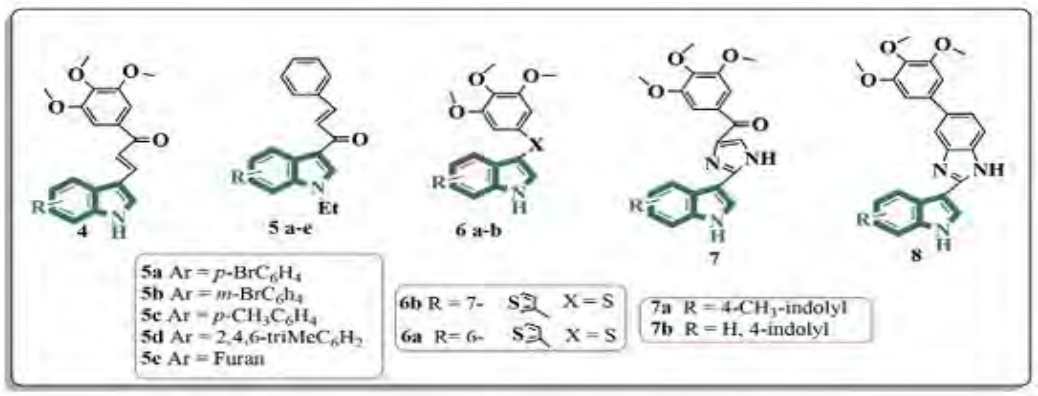

Figure 18: SAR of trimethoxy phenyl-based indole derivatives (Dhiman et al., 2022).

Compound 4 has a fundamental structure including a fixed heterocyclic ring (shown in green) and an ester group linked to the primary core. This chemical serves as the foundation for Structure-Activity Relationship investigations. The series 5a-e denotes alterations of this core, with variations in the aryl (Ar) group-

- (5a): A para-bromophenyl ring (p-BrC6H4) is the aryl group.
- (5b): A meta-bromophenyl ring (m-BrC6H4) is the aryl group.

- (5c): A para-methylphenyl ring (p-CH3C6H4) is the aryl group.
- (5d): The aryl group is bulkier due to the numerous methyl groups connected to it (2,4,6-triMeC6H2).
- (5e): The aryl group is an oxygen-containing ring with five carbon atoms, known as a furan ring.

The alterations to the aryl group (Ar) enable researchers to discern how the dimensions, electronegativity, and electron-donating or withdrawing characteristics of the substituents influence the compound's binding affinity to its target, such as an enzyme or receptor. Bromine (Br) atoms augment the compound's size and may improve its binding affinity via halogen bonds, whilst methyl groups (CH3) might modify the compound's hydrophobicity, hence affecting its interaction with the biological environment.

Compound 6a-b presents an alternative alteration in which the R group and the X position are modified.

- The R group has been attached to position 6 of the heterocycle.
- The R group has been attached to position 7 of the heterocycle.
- X in both examples is sulfur (S), which may augment the compound's lipophilicity, hence improving its capacity to traverse cell membranes.

This alteration emphasizes the arrangement of functional groups on the heterocyclic ring and their influence on the compound's biological activity. The placement of R (either at 6 or 7) might alter the molecule's compatibility with the binding site of its target, hence affecting its efficacy. The incorporation of sulfur may augment the molecule's binding interactions or modify its metabolic processes in the body, hence enhancing its pharmacokinetic profile (absorption, distribution, metabolism, and excretion).

Compounds 7a-b concentrate on altering the R group at the indole position:

- 7a: A 4-methylindolyl group is the R group.
- 7b: In the absence of the methyl substitution, the R group is a 4-indolyl group.

Compound 8 signifies an additional alteration with extra substituents on both rings.

The SAR analysis examines the impact of modifications to the indole group on the compound's biological characteristics.

- Incorporating a methyl group at position 4 (in 7a) may affect the compound's interaction with its biological target by altering its conformation or electrical characteristics.
- Eliminating the methyl group (as in 7b) enables a comparison to ascertain if the diminutive or more pliable structure enhances or diminishes activity.

Compound 8 elucidates the impact of simultaneous addition or modification of numerous functional groups on the compound's overall activity, solubility, and metabolic stability (Dhiman et al., 2022).

3.3 Synthesis of Phenastatin based indole derivatives

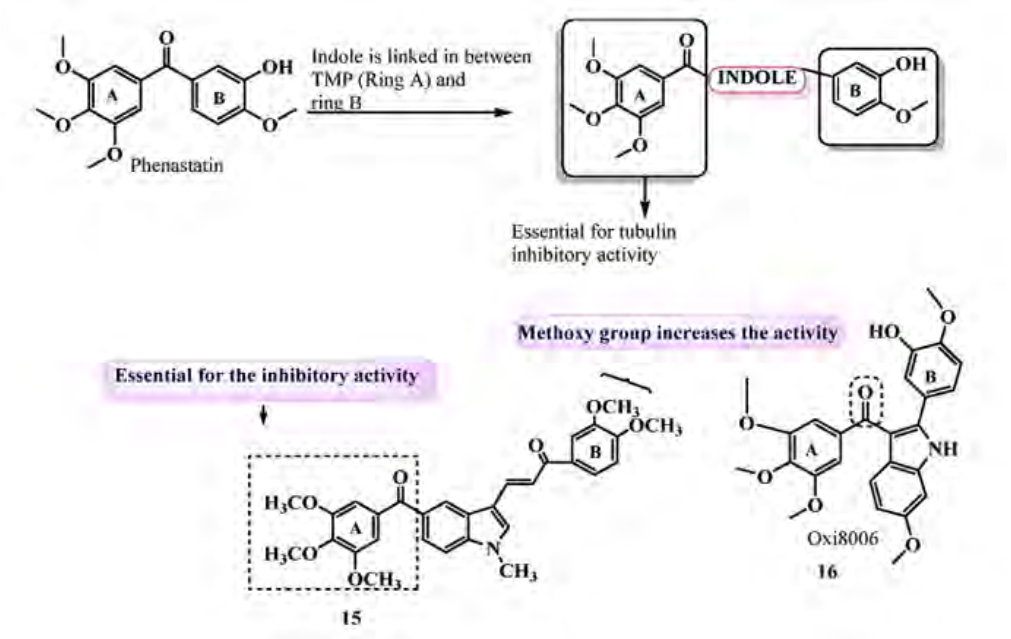

Figure 19: Phenastatin based indole derivatives 15 and 16 (Dhiman et al., 2022).

The tubulin inhibitory action of phenastatin is dependent on its basic structure, which has two rings connected by an indole scaffold: ring A, which contains a trimethoxyphenyl group, and ring B, which contains a hydroxyphenyl group. The trimethoxyphenyl group in ring A aids interaction with tubulin's hydrophobic pocket, while the hydroxyl group in ring B has the ability to create stabilizing hydrogen bonds. The ability of phenastatin to block tubulin polymerization, a target for cancer therapy, depends on its core structure.

Compound 15 enhances the structure by introducing a methoxy group (-OCH3), which is particularly connected to Ring A. The biological activity of the chemical is greatly increased by this addition.

- The incorporation of the methoxy group enhances the compound's efficacy in suppressing tubulin polymerization. The electron-donating properties of the methoxy group may augment interactions with the binding pocket on tubulin, hence enhancing the compound's binding affinity and overall efficacy.
- The trimethoxyphenyl group (TMP) is crucial for inhibitory activity because to its significant interactions with the hydrophobic areas of tubulin.

Compound 16 (Oxi8006) signifies a sophisticated alteration of the Phenastatin core, including more structural modifications. Both Ring A and Ring B contain many methoxy groups, and the overall structure grows more intricate with further functionalization.

- The methoxy groups of Oxi8006 boost the compound's tubulin-inhibitory activity, presumably owing to improved binding interactions.
- The increased complexity of Oxi8006 may enhance pharmacokinetic parameters, including solubility, stability, and cellular absorption, therefore making it a more potent therapeutic candidate.

The last phase of SAR demonstrates that scientists may enhance biological activity and drug-like features by further modifying the basic structure, achieving a balance between potency and better therapeutic attributes (Dhiman et al., 2022).

3.4 SAR of Cyclopregnane Alkaloids

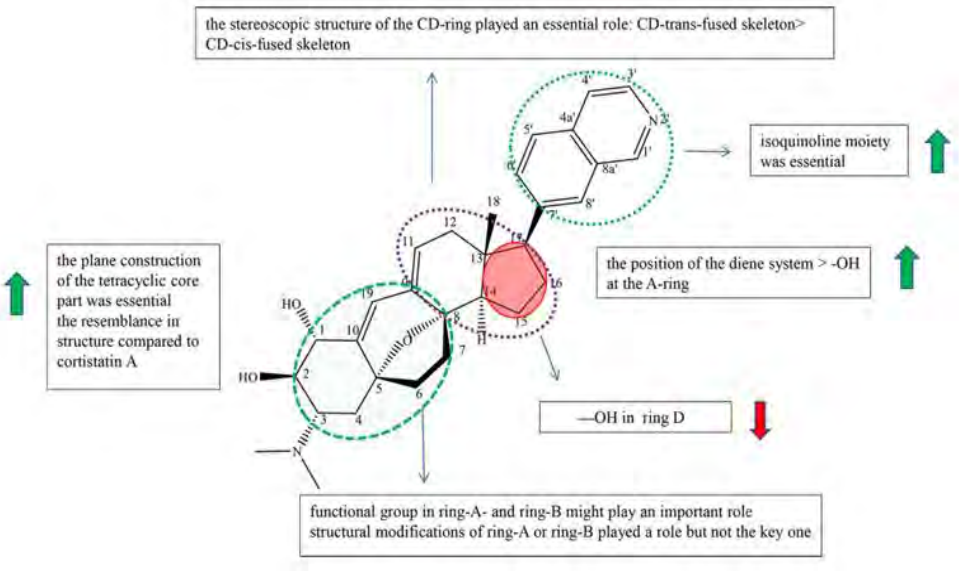

Figure 20: SAR of Cyclopregnane Alkaloids (Huang et al., 2021)

Cyclopregnane alkaloids' Structure-Activity Relationship (SAR) is a must-have for biology classes looking to identify active molecular components. These chemicals generally act as inhibitors of essential cellular processes, with their structural characteristics influencing their efficacy.

- ❖ Stereochemical Properties of the CD-Ring: The trans-fused skeleton is more active than the cis-fused skeleton, indicating that the stereochemistry of the CD-ring is important for activity. This spatial configuration is essential for the correct binding conformation to the biological target.

- ❖ The isoquinoline group is essential for the activity of the isoquinoline moiety. This structural unit probably interacts directly with biological targets, making it a crucial factor in the molecule's action.
- ❖ Hydroxyl Group and Diene System in the A-Ring: It is crucial for biological interaction that the hydroxyl group (-OH) and diene system (a pair of double bonds) be positioned on the A-ring. The molecule's binding affinity is enhanced by the hydroxyl group's ability to form hydrogen bonds.
- ❖ The planar tetracyclic core of the chemical guarantees the appropriate three-dimensional conformation required for efficacy. This core imparts stiffness and preserves structural resemblance to other physiologically active compounds, like cortistatins A.
- ❖ The hydroxyl group in Ring D is of lesser significance, suggesting that alterations in this region may not substantially influence the molecule's function.
- ❖ Despite their potential to impact activity, functional groupings on Rings A and B are not as important as the other attributes. Alterations in these rings may influence qualities like as solubility or bioavailability without significantly altering biological activity.

Recognizing the SAR of Cyclopregnane alkaloids facilitates the development of more efficacious pharmaceuticals by elucidating the structural characteristics essential for activity and those amenable to modification to enhance therapeutic attributes such as potency, specificity, and bioavailability (Huang et al., 2021).

Chapter 4

Total Synthetic method of Select Alkaloids

The synthesis of alkaloids is a multi-step process that requires precise control over chemical reactions to produce the desired complex structures. The following methods outline both classical and modern approaches. Each method has its own advantages and challenges, and recent advancements have helped improve efficiency and selectivity in alkaloid synthesis.

4.1 Diazene-Directed Assembly

A comprehensive approach to the directed and stereo controlled assembly of heterodimeric hexahydropyrroloindoles that are carbon-carbon linked is expounded. The sequential combination of complex amines as mixed diazenes, followed by the photochemical release of dinitrogen inside a solvent cage, facilitates the directed assembly of difficult C(sp(3))-C(sp(3)) and C(sp(3))-C(sp(2)) linkages (Movassaghi et al., 2011).

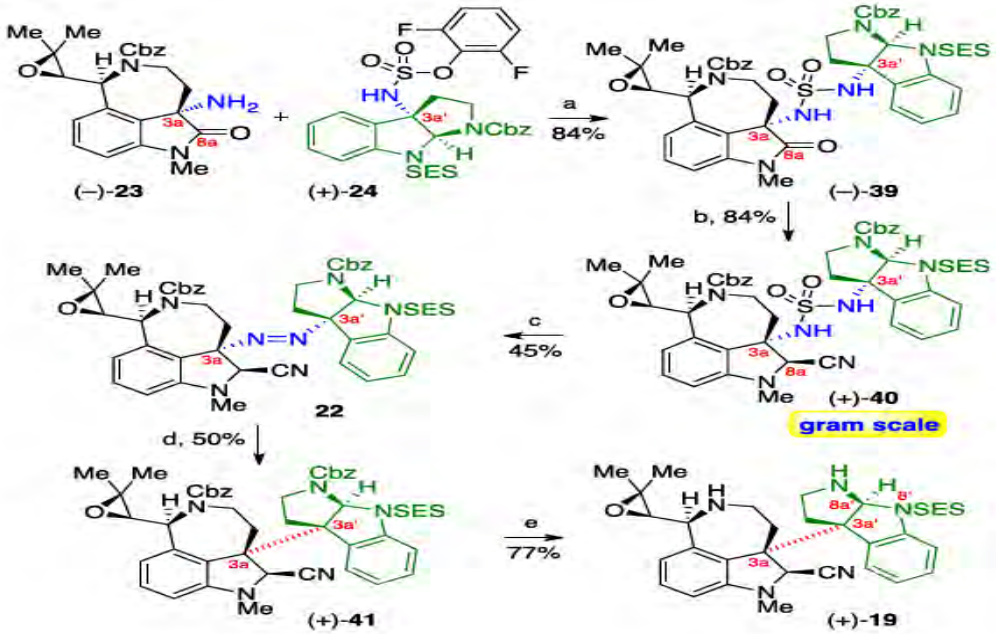

Figure 21: Applying Diazene to Direct Fragment Assembly for Heterodimer Synthesis (Pompeo et al., 2019).

Modern synthetic methods like Diazene Direct Fragment Assembly make it easy for scientists to precisely combine two separate molecular pieces into a single, complicated heterodimer. This technique relies on a diazene (a molecule with a nitrogen-nitrogen double bond, N=N) that functions as a reactive and selective linker between two distinct fragments. This image depicts a sequential process for heterodimer synthesis using Diazene Direct Fragment Assembly, demonstrating the amalgamation of two distinct molecular fragments (−)-23 and (+)-24 via a series of reactions to produce the final heterodimer product, (+)-19.

- Step a: The two fragments (−)-23 and (+)-24 are joined using a fluorosulfonate reagent, yielding compound (−)-39 with an outstanding 84% yield. This stage probably involves the production of diazene and a crucial connection between the two pieces.
- Step b: Compound (−)-39 is transformed into compound (+)-40. This reaction yields 84% and is conducted on a gram scale, illustrating its scalability.
- Step c: Additional chemical alteration of (+)-40 results in compound 22, yielding 45%. This phase may include the protection or deprotection of groups, which are prevalent techniques in multistep organic synthesis to regulate reactivity.
- Step d: Compound 22 is transformed into (+)-41, achieving a 50% yield, by an additional reaction step that may include cyclization or structural rearrangement, resulting in a more intricate scaffold.
- Step e: Ultimately, (+)-41 is converted into the target product (+)-19 with a yield of 77%, so concluding the synthesis. The final product maintains stereochemical control, as seen by the red bold bonds denoting precise 3D configurations at the critical stereocenters (3a and 8a).

The diagram demonstrates the accuracy and speed of the Diazene Direct Fragment Assembly method in the assembly of heterodimers, along with its precise stereo control and scalability at key stages

4.2 Quinoline alkaloid synthesis

This specific kind of alkaloid-carrying quinolone nucleus is exclusive to the bark of the Cinchona plant. On the other hand, many simple heteroaromatic quinolines have also been found in various marine sources. Two compounds were identified: 2-heptyl-4-hydroxyquinoline derived from a marine pseudomonad and 4, 8-quinolinediol derived from squid ink. Cinchonine, quinine, quinidine, and cinchonine are the main alkaloids in this category(Rasapalli et al., 2024).

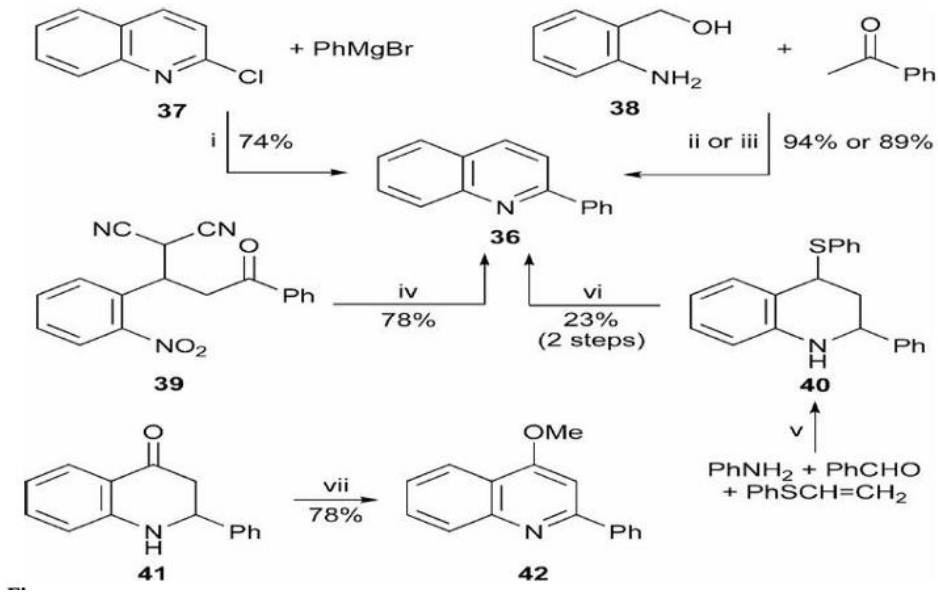

Figure 22: Quinoline alkaloid synthesis(Dumore et al., 2023)

This diagram illustrates the synthetic route for the production of quinoline alkaloids, beginning with simpler chemical entities and progressively constructing a more complex structure via many reaction stages-

- Step i: Compound 37 undergoes a reaction with phenylmagnesium bromide (PhMgBr) to generate compound 36, which has a 74% yield. A phenyl group (from PhMgBr) and the quinoline ring (from 37) establish a new bond in this step.
- Steps ii and iii: An alternative pathway utilizes compound 38, which combines with a phenyl aldehyde (PhCHO) and an additional reagent (acetophenone derivative) to give compound 36 with a very high yield of 94% or 89%, depending upon the specific circumstances used.
- Step iv: Compound 36 undergoes a chemical transition to create compound 39, achieving a 78% yield. This stage incorporates intricate substituents such as nitro (NO_2) and cyano (CN) groups into the quinoline structure.
- Step v: Compound 39 is then converted into compound 40 via two stages, achieving an overall yield of 23%. The reaction alters the structure by incorporating sulfur (S) and a novel phenyl group (Ph).
- Step vi: Compound 40 undergoes further processing to revert to compound 36, illustrating a technique for structural regeneration.
- Step vii: Ultimately, compound 41 is synthesized by a process involving compound 36, wherein an amine group (-NH) is introduced to provide a quinoline amide derivative. Compound 42 presents an alternate product with the addition of an O-methyl (OMe) group.

This graphic illustrates the transformation of a relatively simple precursor (37) into intricate quinoline derivatives (such as 41 and 42), which are classified as quinoline alkaloids. The process involves the incorporation of diverse functional groups and meticulous regulation of chemical processes to construct the ultimate structure(DeBono et al., 2015)

4.3 Retrosynthetic analysis of arbornamine (a monoterpene indole alkaloid)

Arbornamine (1) is a monoterpene indole alkaloid discovered in 2016 by Kam and colleagues, derived from the Malayan Kopsia arborea. It has a distinctive 6/5/6/5/6 "arbornane" framework that differs from the structures of the eburnane and tacaman groups.

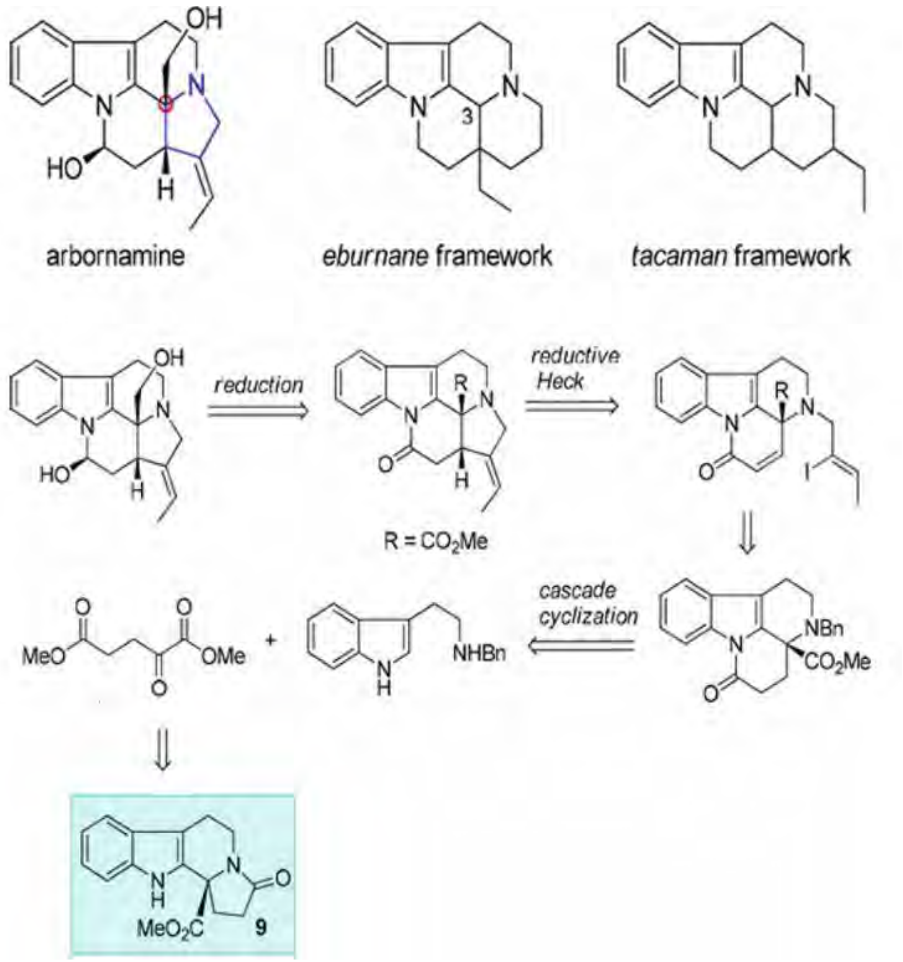

Figure 23: Synthesis of monoterpene indole alkaloid(Dumore et al., 2023)

This image illustrates the synthetic process for the production of monoterpene indole alkaloids, a category of intricate natural chemicals, via a sequence of meticulously coordinated events. The process starts with arbornamine, a molecule originating from the eburnane structure, which is typical of several indole alkaloids. The first phase is reduction, during which hydrogen is

introduced to the molecule, therefore activating it for further changes. Subsequently, the molecule experiences a reductive Heck reaction, a crucial process that forms a new bond and incorporates a methyl ester group (CO_2Me), hence enhancing structural complexity. In this phase, a nitrogen protective group (NBn) is included to stabilize the structure. In the concluding phase, two fundamental components (a methoxy compound and an indole derivative) are amalgamated, resulting in the synthesis of compound 9, which incorporates essential functional groups including an indole ring and an ester (MeO_2C) (García Maza et al., 2024)

4.4 Biosynthetic pathway of tropane alkaloid

Tropane alkaloid synthesis involves producing compounds with a characteristic tropane ring system, found in plants like those in the Solanaceae family. These alkaloids, including atropine, scopolamine, and cocaine, have significant effects on the nervous system and are used in medicine as anticholinergics, anesthetics, and stimulants (Dumore et al., 2023).

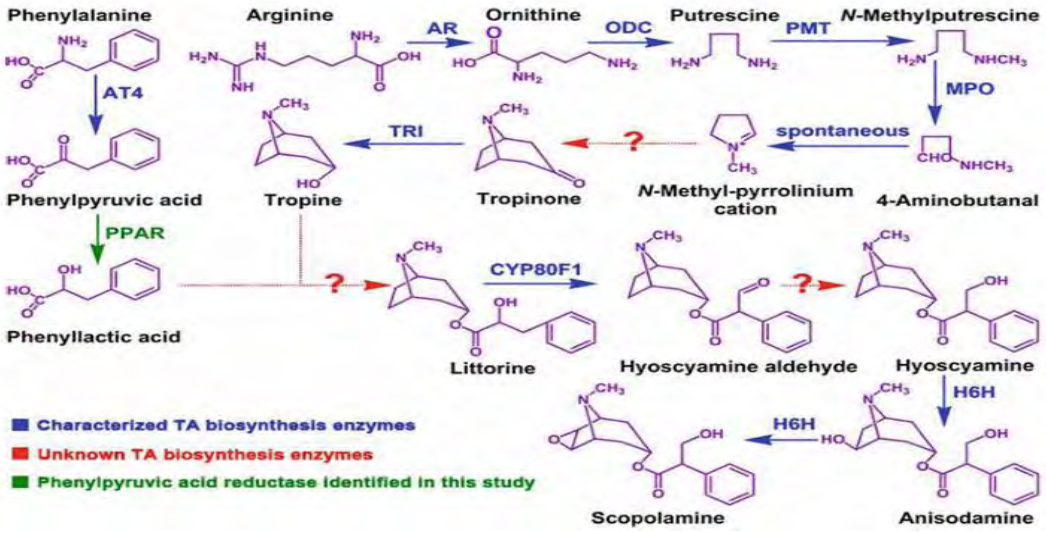

Figure 24: Tropane alkaloid synthesis(Dumore et al., 2023).

This diagram demonstrates the manufacture of tropane alkaloids (TAs) from the amino acids phenylalanine and ornithine. Initially, the enzyme AT4 transforms phenylalanine into

phenylpyruvic acid. At this juncture, phenylpyruvic acid may either proceed along the tropane alkaloid production route or be converted to phenylactic acid by the action of the enzyme PPAR. In the primary TA route, phenylpyruvic acid is converted into tropine by the action of TRI. Concurrently, arginine participates in the process via ornithine, which is transformed into putrescine by the enzyme ODC (ornithine decarboxylase). Putrescine is then methylated by PMT to produce N-methylputrescine, which undergoes further transformations to provide the N-methylpyrrolinium cation, ultimately resulting in the synthesis of tropinone. The red arrows with question marks denote phases for which the relevant enzymes remain unidentified, while the blue arrows signify well-characterized processes. Green emphasizes the recently discovered PPAR enzyme that plays a role in the reduction of phenylpyruvic acid, marking a significant improvement in the comprehension of this biosynthetic process (Mayer et al., 2020).

Chapter 5: Discussion

This paper examines current advancements in common alkaloids with anticancer effects and the associated obstacles. Numerous alkaloids have synergistic effects on cancer cells and reduce adverse effects when co-administered with chemotherapy agents, making combination therapy the optimal approach for practical use. Nevertheless, the majority of alkaloids have restricted solubility in water and low bioavailability, complicating their delivery to the tumor site. This study describes current advancements in the synthesis and structure-activity relationships (SARs) of many prevalent natural alkaloids exhibiting anticancer effects. Despite their potential, various obstacles exist regarding their progress and clinical use. Combining alkaloids with traditional pharmaceuticals could overcome resistance processes and enhance therapeutic effects.

Substituted indoles are chemical compounds having many applications, particularly in pharmaceuticals. The synthesis method involves a sequence of chemical events to produce diverse indole derivatives from several starting components. The substituted indole comprises a nitrogen-bonded six-membered ring, and the objective is to modify this structure by replacing R1, R2, and R3 with novel or distinct chemical groups. The synthesis process involves the incorporation of reagents, including Chalcone, KOFtBu, and TIOH, into the raw ingredients. The reaction parameters, including solvents and temperatures, are meticulously controlled to guarantee optimal reaction performance. The Structure-Activity Relationship (SAR) technique is used to improve the efficiency of Combretastatin A-4 (CA-4), a known anti-cancer drug, by augmenting its ability to inhibit tubulin, an essential protein in cell cycle.

The tubulin inhibitory activity of Phenastatin is attributed to its fundamental structure, which comprises two rings linked by an indole scaffold. The trimethoxy phenyl moiety in ring A engages with the hydrophobic pocket of tubulin, whilst the hydroxyl group in ring B forms

stabilizing hydrogen bonds. The compound's effectiveness in inhibiting tubulin polymerization, a target for cancer treatment, is contingent upon its core structure. The structure-activity relationship (SAR) of Cyclopregnane alkaloids is crucial for biology courses to discern active molecular constituents, since their structural attributes affect their potency. The stereochemistry of the CD-ring, isoquinoline moiety, hydroxyl group, and diene system is essential for binding affinity.

The synthesis of alkaloids is a complicated process requiring careful regulation of chemical processes to generate complex structures. Both classical and contemporary techniques have been designed to enhance efficiency and selectivity in this process. Contemporary synthetic techniques such as Diazene Direct Fragment Assembly enable researchers to merge two distinct molecular components into a singular, intricate heterodimer. This approach entails the synthesis of diazene, which serves as a reactive and selective connector between two separate pieces. The synthesis of quinoline alkaloids entails the creation of complicated quinoline derivatives, including quinoline amides and their derivatives. The primary alkaloids in this group are cinchonine, quinine, quinidine, and cinchonine. The procedure entails integrating many functional groups and carefully regulating chemical reactions to create the final structure.

Considering the complicated nature involved with natural alkaloid-based medicines, numerous critical research areas need prioritization –

- Clarification of Mechanisms: Although some alkaloids have significant anticancer properties, their exact mechanisms of action—especially in vivo—are little understood.
- Structural Optimization: Alkaloids with potential anticancer action need structural optimization to improve their solubility, bioavailability, and selectivity. Partly synthetic modification and biological transformation techniques have enhanced the medicinal potential of numerous alkaloids.

- Combination Therapies: Exploring the combined benefits of alkaloids with other chemotherapeutic drugs may provide more effective methods for treatment. Future research should concentrate on determining ideal combinations which utilize various cancer cell weaknesses.
- Innovations in Drug Delivery: Progress in nanotechnology and other drug distribution technologies provide promising solutions to the issues of inadequate solubility and bioavailability. Ongoing research into customized delivery systems is essential for guaranteeing that alkaloids get therapeutic concentrations at their tumor sites.
- Clinical studies: There is a need for more meticulously constructed clinical studies to thoroughly assess the safety, effectiveness, and thermodynamics of alkaloids in cancer therapy.

Alkaloids provide significant opportunity as anticancer drugs owing to their varied modes of action, capacity for structural alteration, and tendency for working together with other treatments.

Chapter 6: Conclusion

Cancer is a widespread affliction in both industrialized and developing countries, with anticancer pharmaceuticals being the most effective option owing to their adverse effects on non-target tissues. The therapeutic use of natural alkaloids is constrained by their suboptimal pharmacokinetic characteristics, inadequate solubility, and fast metabolism. Numerous compounds, such as berberine, have poor absorption, hence limiting their medicinal effectiveness. Semi-synthetic alterations of alkaloids have enhanced solubility and efficacy. Liposomes and dendrimers facilitate the encapsulation of alkaloids, enhancing their concentration at tumor locations while reducing systemic toxicity. The present study examines the progress in common alkaloids with anticancer properties and their related challenges. Alkaloids have synergistic effects on cancer cells and mitigate side effects when co-administered with chemotherapeutic drugs, making combination treatment the most effective strategy for practical use. Nonetheless, the majority of alkaloids exhibit limited solubility in water and reduced bioavailability, hindering their administration to the tumor location. A feasible strategy for alkaloid-derived pharmaceuticals is combinatorial treatment. Combination therapy renders alkaloids a viable option for practical use in cancer treatment, especially as supplements to existing chemotherapies. Structural alterations and improvements in drug distribution are being examined to address these issues. Substituted indoles are chemical entities having several uses, especially in the pharmaceutical sector. The synthesis of alkaloids is a difficult process requiring careful management of chemical reactions to produce intricate structures. Modern synthetic methods like Diazene Direct Fragment Assembly allow researchers to combine two separate molecular entities into a unified, complex heterodimer. The study highlights the need of clarifying the mechanisms of action of these substances and the potential advantages of combination treatments that use the capabilities of both natural and developed medications. In summary, while alkaloids offer considerable promise for cancer

treatment, it is crucial to tackle the issues of resistance, toxicity, and delivery to fully harness their potential in therapeutic applications. Subsequent research must emphasize structural optimization, novel delivery mechanisms, and extensive clinical trials to validate alkaloids as feasible cancer therapy alternatives. In conclusion, natural alkaloids serve as significant agents in cancer therapy, providing various modes of action and the possibility for precisely focused treatments. By tackling issues such as bioavailability and drug resistance via novel research, alkaloids can facilitate the development of safer, more effective cancer therapies in the future.

References

Ballout, F., Habli, Z., Monzer, A., Rahal, O. N., Fatfat, M., & Gali-Muhtasib, H. (2019). Anticancer Alkaloids: Molecular Mechanisms and Clinical Manifestations. *Bioactive Natural Products for the Management of Cancer: From Bench to Bedside*, 1–35. https://doi.org/10.1007/978-981-13-7607-8_1

Barbuti, A. M., & Chen, Z. S. (2015). Paclitaxel Through the Ages of Anticancer Therapy: Exploring Its Role in Chemoresistance and Radiation Therapy. *Cancers 2015, Vol. 7, Pages 2360-2371*, *7*(4), 2360–2371. https://doi.org/10.3390/CANCERS7040897

Dadashpour, S., & Emami, S. (2018a). Indole in the target-based design of anticancer agents: A versatile scaffold with diverse mechanisms. *European Journal of Medicinal Chemistry*, *150*, 9–29. https://doi.org/10.1016/J.EJMECH.2018.02.065

Dadashpour, S., & Emami, S. (2018b). Indole in the target-based design of anticancer agents: A versatile scaffold with diverse mechanisms. *European Journal of Medicinal Chemistry*, *150*, 9–29. https://doi.org/10.1016/J.EJMECH.2018.02.065

DeBono, A., Capuano, B., & Scammells, P. J. (2015). Progress Toward the Development of Noscapine and Derivatives as Anticancer Agents. *Journal of Medicinal Chemistry*, *58*(15), 5699–5727. https://doi.org/10.1021/JM501180V/ASSET/IMAGES/MEDIUM/JM-2014-01180V_0001.GIF

Dhiman, A., Sharma, R., & Singh, R. K. (2022). Target-based anticancer indole derivatives and insight into structure–activity relationship: A mechanistic review update (2018–2021). In *Acta Pharmaceutica Sinica B* (Vol. 12, Issue 7, pp. 3006–3027). Chinese Academy of Medical Sciences. https://doi.org/10.1016/j.apsb.2022.03.021

Dhyani, P., Quispe, C., Sharma, E., Bahukhandi, A., Sati, P., Attri, D. C., Szopa, A., Sharifi-Rad, J., Docea, A. O., Mardare, I., Calina, D., & Cho, W. C. (2022). Anticancer potential of alkaloids: a key emphasis to colchicine, vinblastine, vincristine, vindesine, vinorelbine and vincamine. *Cancer Cell International 2022 22:1*, *22*(1), 1–20. https://doi.org/10.1186/S12935-022-02624-9

Dumore, N., Girhepunje, N., Dumore, M., Danao, K., Dumore, N., Girhepunje, N., Dumore, M., & Danao, K. (2023). Methods of Alkaloids Synthesis. *Medicinal Plants - Chemical, Biochemical, and Pharmacological Approaches*. https://doi.org/10.5772/INTECHOPEN.111785

García Maza, L. J., Salgado, A. M., Kouznetsov, V. V., & Meléndez, C. M. (2024). Pyrrolo[2,1-a]isoquinoline scaffolds for developing anti-cancer agents. *RSC Advances*, *14*(3), 1710–1728. https://doi.org/10.1039/D3RA07047F

Huang, Y., Li, G., Hong, C., Zheng, X., Yu, H., & Zhang, Y. (2021). Potential of Steroidal Alkaloids in Cancer: Perspective Insight Into Structure–Activity Relationships. *Frontiers in Oncology*, *11*, 733369. https://doi.org/10.3389/FONC.2021.733369/BIBTEX

Jain, S., Chandra, V., Kumar Jain, P., Pathak, K., Pathak, D., & Vaidya, A. (2019). Comprehensive review on current developments of quinoline-based anticancer agents. *Arabian Journal of Chemistry*, *12*(8), 4920–4946. https://doi.org/10.1016/J.ARABJC.2016.10.009

Kousar, R., Naeem, M., & Arshad, A. (2022). Exploring the anticancer activities of novel bioactive compounds derived from endophytic fungi: mechanisms of action, current challenges and future perspectives. In *Article in American Journal of Cancer Research* (Vol. 19). www.ajcr.us

Kurek, J., & Kurek, J. (2019). Introductory Chapter: Alkaloids - Their Importance in Nature and for Human Life. *Alkaloids - Their Importance in Nature and Human Life*. https://doi.org/10.5772/INTECHOPEN.85400

Lu, J. J., Bao, J. L., Chen, X. P., Huang, M., & Wang, Y. T. (2012). Alkaloids Isolated from Natural Herbs as the Anticancer Agents. *Evidence-Based Complementary and Alternative Medicine*, *2012*(1), 485042. https://doi.org/10.1155/2012/485042

Mayer, S., Keglevich, A., Für, C. S., Bölcskei, H., Ilkei, V., Keglevich, P., & Hazai, L. (2020). Results in Chemistry of Natural Organic Compounds. Synthesis of New Anticancer Vinca Alkaloids and Flavone Alkaloids. *Chemistry 2020, Vol. 2, Pages 714-726*, *2*(3), 714–726. https://doi.org/10.3390/CHEMISTRY2030046

Movassaghi, M., Ahmad, O. K., & Lathrop, S. P. (2011). Directed heterodimerization: Stereocontrolled assembly via solvent-caged unsymmetrical diazene fragmentation. *Journal of the American Chemical Society*, *133*(33), 13002–13005. https://doi.org/10.1021/JA2057852/SUPPL_FILE/JA2057852_SI_001.PDF

Patel, A., Vanecha, R., Patel, J., Patel, D., Shah, U., & Bambharoliya, T. (2021). Development of Natural Bioactive Alkaloids: Anticancer Perspective. *Mini-Reviews in Medicinal Chemistry*, *22*(2), 200–212. https://doi.org/10.2174/1389557521666210712111331

Patel, A., Vanecha, R., Patel, J., Patel, D., Shah, U., & Bambharoliya, T. (2022). Development of Natural Bioactive Alkaloids: Anticancer Perspective. *Mini Reviews in Medicinal Chemistry*, *22*(2), 200–212. https://doi.org/10.2174/1389557521666210712111331

Pompeo, M. M., Cheah, J. H., & Movassaghi, M. (2019). Total Synthesis and Anti-Cancer Activity of All Known Communesin Alkaloids and Related Derivatives. *Journal of the American Chemical Society*, *141*(36), 14411–14420. https://doi.org/10.1021/JACS.9B07397/SUPPL_FILE/JA9B07397_SI_004.CIF

Rasapalli, S., Huang, Y., Sammeta, V. R., Alshehry, R., Anver, F., Golen, J. A., Krishnamoorthy, S., & Chavan, S. P. (2024). Diversity oriented total synthesis (DOTS) of pyridoquinazolinone

alkaloids and their analogues. *Tetrahedron Chem*, *9*, 100062. https://doi.org/10.1016/J.TCHEM.2024.100062

Rawat, A., & Vijaya Bhaskar Reddy, A. (2022). Recent advances on anticancer activity of coumarin derivatives. *European Journal of Medicinal Chemistry Reports*, *5*, 100038. https://doi.org/10.1016/J.EJMCR.2022.100038

Shaik, B. B., Katari, N. K., & Jonnalagadda, S. B. (2022). Role of Natural Products in Developing Novel Anticancer Agents: A Perspective. *Chemistry & Biodiversity*, *19*(11), e202200535. https://doi.org/10.1002/CBDV.202200535

Sun, J., Zhan, X., Wang, W., Yang, X., Liu, Y., Yang, H., Deng, J., & Yang, H. (2024a). Natural aporphine alkaloids: A comprehensive review of phytochemistry, pharmacokinetics, anticancer activities, and clinical application. *Journal of Advanced Research*, *63*, 231–253. https://doi.org/10.1016/J.JARE.2023.11.003

Sun, J., Zhan, X., Wang, W., Yang, X., Liu, Y., Yang, H., Deng, J., & Yang, H. (2024b). Natural aporphine alkaloids: A comprehensive review of phytochemistry, pharmacokinetics, anticancer activities, and clinical application. *Journal of Advanced Research*, *63*, 231–253. https://doi.org/10.1016/J.JARE.2023.11.003

Wang, Y., Liu, Y., Du, X., Ma, H., & Yao, J. (2020). The Anti-Cancer Mechanisms of Berberine: A Review . *Cancer Management and Research*, *12*, 695–702. https://doi.org/10.2147/CMAR.S242329

Ye, H., Wang, L., Ma, L., Ionov, M., Qiao, G., Huang, J., Cheng, L., Zhang, Y., Yang, X., Cao, S., & Lin, X. (2021). Protein kinases as therapeutic targets to develop anticancer drugs with natural alkaloids. *Frontiers in Bioscience-Landmark*, *26*(11), 1349–1361. https://doi.org/10.52586/5028