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The Role of Chemistry in Cancer Chemotherapy: A Mini Review

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1. Introduction

Cancer is a collective term used to describe a wide range of diseases that cause abnormal cells to grow, divide, and spread rapidly, resulting in the formation of a primary tumor which invades and destroys surrounding tissues. Cancer is still one of the most aggressive and deadly diseases, accounting for one in seven deaths worldwide. It is responsible for more deaths worldwide than AIDS, TB, and malaria put together. Cancer is one of the most difficult diseases to treat and the global cancer burden continues to rise at an alarming rate as a result of population growth and ageing in most of countries.

Cancer treatment is based on surgery, radiotherapy, chemotherapy, immune therapy, and targeted therapy. Chemotherapy can be used for curative or life-extending purposes or to reduce symptoms (palliative chemotherapy). It belongs to a group of medical disciplines specifically dedicated to the treatment of cancer through pharmacotherapy (termed as medical oncology). Cancer chemotherapy is the treatment of disease with a drug or combination of drugs. The aim is to inhibit the proliferation of tumor cells by effectively targeting fast-dividing cells while leaving the host cell unharmed or at least recoverable.

2. Brief history of chemotherapy

Chemotherapy is one of the oldest forms of cancer treatment. Ancient Egyptians used compounds from barley, pigs' ears, and other compounds to treat cancers of the stomach and uterus. During World War I German introduced chemical warfare, among which mustard gas was particularly devastating. World War II raised concerns about the return of chemical warfare. Serious research into chemotherapy began with the discovery that soldiers exposed to sulphur mustard suffered from lower white blood cells count. This discovery led to the development of nitrogen mustard, which is similar to sulphur mustard but less toxic, for treatment of patients with

lymphoid leukemia (high white blood cells count). Nitrogen mustards developed as a chemical modification of sulfur mustard gas are still chemically useful today.

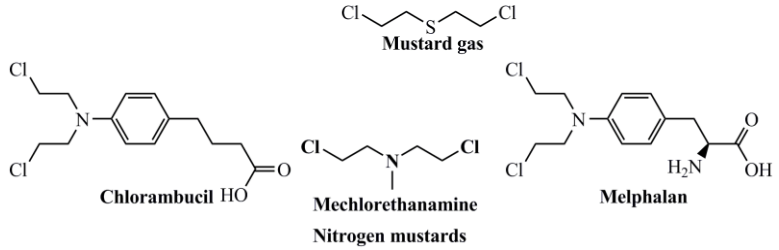


Fig. 1: **Mustard gas and Nitrogen mustards**

Nitrogen mustard and other mustard gas derivatives are able to alkylate molecules such as protein, DNA, and RNA and hence are named as alkylating agents. Tetrazines and cisplatin are other examples of alkylating agents that are used as chemotherapeutic agents.

In the early 1940s, another approach to chemotherapy was proposed by a Harvard Medical School pathologist, Sidney Farber. Farber was interested in the anticancer potential of folic acid, an essential vitamin in the metabolism of DNA, in leukemia patients. Faber, and his colleagues, Heinle, and Welch, developed a number of folate analogs like aminopterins or amethopterins (now better known as methotrexate), which were in fact antagonistic to folate and block the activity of enzymes that needed folate to function. By 1948, these folate analogs were the first drugs in the world to induce remission in children suffering from acute lymphoblastic leukemia, demonstrating the potential of antifolate therapy to restore bone marrow function.

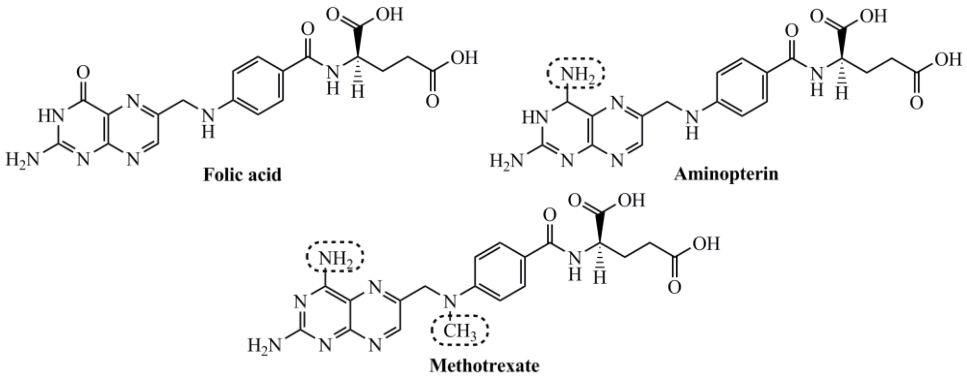


Fig. 2: **Folate analogs**

In the early 1950s, Burchenal, with the help of Farber, Hitchings and Elion, developed two drugs: 6-thioguanine and 6-mercaptopurine, which are able to inhibit purine ring synthesis. Both of these drugs were highly effective against acute leukemia.

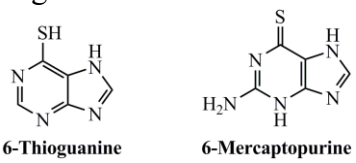
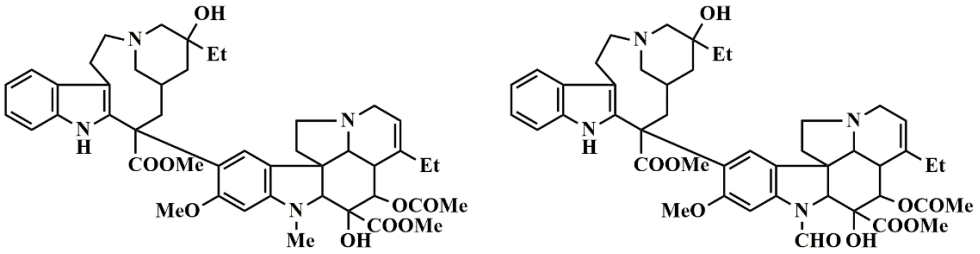


Fig. 3: Drugs effective against acute leukemia

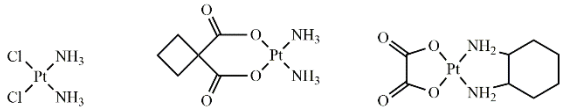
In the late 1950s, the natural products group of the Eli Lilly Company announced that the plant alkaloids extracted from the Madagascar periwinkle plant (*Vinca rosea*) inhibited the growth of tumor cells, leading to the introduction of these alkaloids as anti-cancer agents in the 1960's. For example, vinblastine is used for the treatment of Hodgkin's disease, while vincristine is used in the treatment of pediatric leukemia. These drugs act as antitumor agents due to their ability to inhibit microtubule polymerization.



Vinblastine **Vincristine**

Fig. 4: Vinca alkaloids, anticancer agents used in the 1960's

Rosenberg and colleagues introduced cisplatin in 1965 as the first inorganic metal complex to be used as an anti-tumour agent in cancer. Since then, several other platinum-based or metal-containing complexes (e.g., Ruthenium, Gold, Titanium, Copper, Iron, Rhodium, Vanadium, and Cobalt) that are less toxic and selectively target tumour cells have been proposed.



Cisplatin **Carboplatin** **Oxaliplatin**

Fig. 5: **Platinum based antitumor compounds**

The combination of drugs with various mechanisms of action has led to further improved patient survival and a decrease in mortality rates that have decreased every year since 1990. The decline in death rates has been attributed to the both early detection and chemotherapy.

3. Chemistry's role

Almost every aspect of chemotherapy involves chemistry in some way. For example, the two most commonly used drugs in cancer therapy are Asparaginase, an enzyme made from the bacterium (Escherichia coli), and Doxorubicin, an antibiotic made from the soil fungus (Streptomyces). Both drugs were originally found in nature but were most likely refined in a laboratory. Chemists were able to replicate and produce these enzymes and bacteria in a much simpler way to develop them for use in medicine. Without chemistry, they would never have been possible to treat cancer.

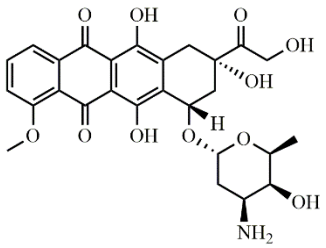


Fig. 6: Doxorubicin, a chemotherapeutic drug of anthracycline and antitumor antibiotic family

Chemistry plays an extremely important role in drug development in cancer therapy. The first step in drug development involves identifying natural or synthetic compounds that show anticancer activity. Many natural products are used as pharmaceuticals after isolation, purification, and determination of their structure. Natural products have been a useful class of structurally diverse anticancer drugs for decades. Paclitaxel (Taxol) is one naturally occurring cancer drug used to treat many types of cancer, including ovarian, breast, lung, cervical, and pancreatic cancer.

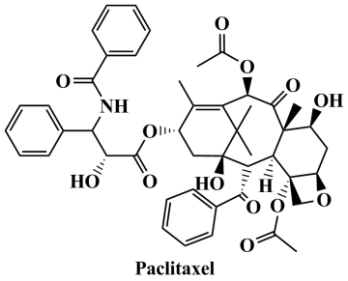


Fig. 7: Paclitaxel, chemotherapy medicine first isolated from Pacific yew

Synthetic chemistry is an important part of expanding the range of naturally occurring drugs that are available in very small amounts. Developing semisynthetic and synthetic strategies may have a big impact on understanding the biological activity of these rare natural products. Paclitaxel is a drug derived from the bark of the slow growing tree *Taxus brevifolia*. The commercial marketing of paclitaxel was delayed due to the need for large-scale procurement of this compound, which can decimate the tree. The total synthesis of the compound taxol has long been a subject of interest in the synthetic chemistry world. This has led to the formation of the esterified taxol derivative (docetaxel), which is made from the esters of the 10-deacetyl bactatin III. Docetaxel is derived from the readily available and renewable leaves of the *Taxus baccata*.

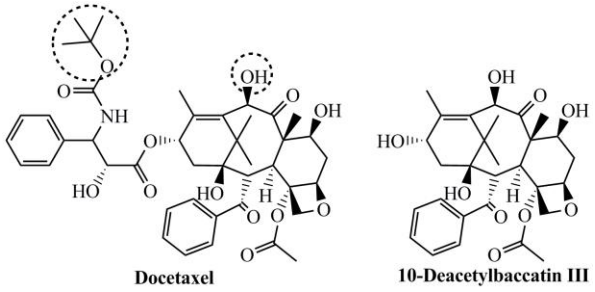


Fig. 8: Docetaxel, an esterified taxol derivative and its precursor 10-deactyl baccatin III

The alkylating agent Trabectedin was originally obtained by partial synthesis of cyanosafrancin B, a metabolite of the micro-organism of *Pseudomonas frutescens*.

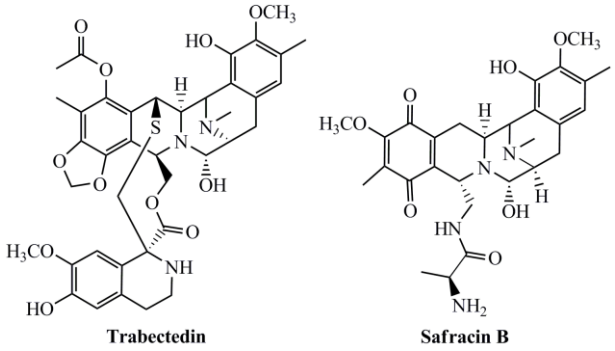


Fig. 9: Trabectedin, a partially synthesized alkylating agent and its precursor Safracin B

The success of this approach in the development of a feasible approach to total chemical synthesis for the bioactive molecule allowed further structure-activity relationship studies (SARs) and lead optimization. The SAR study of the original lead, methyl 5-tert-butyl-3- phenyl-3-thiophene-2-carboxylate, revealed that the optimized lead was 30 times more potent than the original lead. This second generation of lead was ultimately optimized to allow the production of Sorafenib, also known as Nexavar, which is currently on the market for the treatment of some forms of cancer.

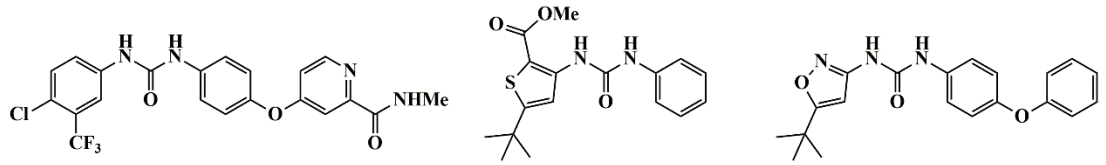


Fig. 10: Sorafenib, its original lead and optimized lead

Synthetic chemistry has also been widely used to alter drug leads to enhance the effectiveness or safety of existing drugs used for cancer treatment. For example, Aminopterin, which is structurally related to folic acid, inhibits the enzyme dihydrofolate reductase by competing for the binding site and blocks tetrahydrofolate synthesis. It is a predecessor of Methotrexate, an inhibitor of dihydrofolate reductase that blocks thymidine synthesis.

Molecular modifications can also be used to overcome drug resistance and solubility as well as metabolic limitations. For example, 5-hydroxy-pyridine-2-carboxaldehyde thiosemicarbazone (5-HP), the first Heterocyclic thiosemicarbazone (HCT) to undergo clinical trials demonstrated a wide range of antitumor activity in transplanted animal models. However, it did not show any activity in solid tumors due to its rapid metabolism (*via* formation and subsequent elimination of the *O*-glucuronide conjugate). 3-aminopyridine-2-carboxaldehyde thiosemicarbazone (Triapine) has been designed to avoid this metabolic fate by minimizing the formation of the *O*-glucuronide conjugate.

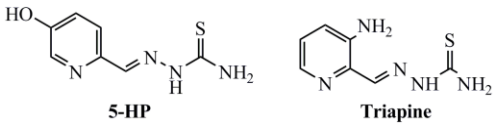


Fig. 11: Heterocyclic thiosemicarbazones that demonstrated antitumor activity

Various HCTs are synthesized with modifications to heterocyclic rings, thiosemicarbazone side chain and variations to ring substituents. However, due to their inability to be solubilized in aqueous solutions, these HCTs and their metal complexes have poor *in vivo* activity. Efforts have been made to improve water solubility and biological activity, as well as to reduce drug toxicity. This has led to the development of a series of *N*(4) substituted thiosemicarrbazones with the thiosemicarbazone moiety attached to an amide carbamide.

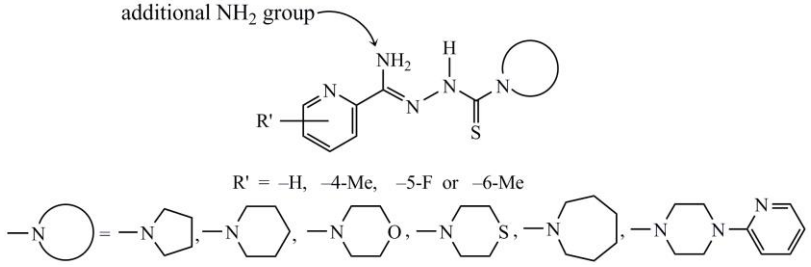


Fig. 12: Some 2-Pyridineformamide Thiosemicarbazones

The anticancer activity can be improved by synthesizing some new molecules based on active "pharmacophore" models. (A pharmacore is the part of the molecule that contains the important organic functional groups that interact directly with the active site of the receptor and thereby provides the biological activity of interest).

In recent years, macrocycles have become well-known in cancer therapy for their ability to encapsulate various anticancer drugs, either by host-guest complexation or by self-assembly, resulting in multiple benefits. In many cases, anti-cancer drugs based on the macrocycles have demonstrated more robust anticancer activity than their free drug analogues, likely due to improved permeation and retention effects. Knowing the three-dimensional structure of the target macromolecule allows small molecules to be designed in a rational manner, mimicking the stereochemical properties of the functional domains of the target molecule. A total synthesized drug Halaven (Erbulin mesylate), for example, is a simplified analogue of macrocyclic ketone halichondrine B, a potent cytotoxic compound. Originally Halichondrine B was isolated from a marine sponge, *Halinchondrio okadai*.

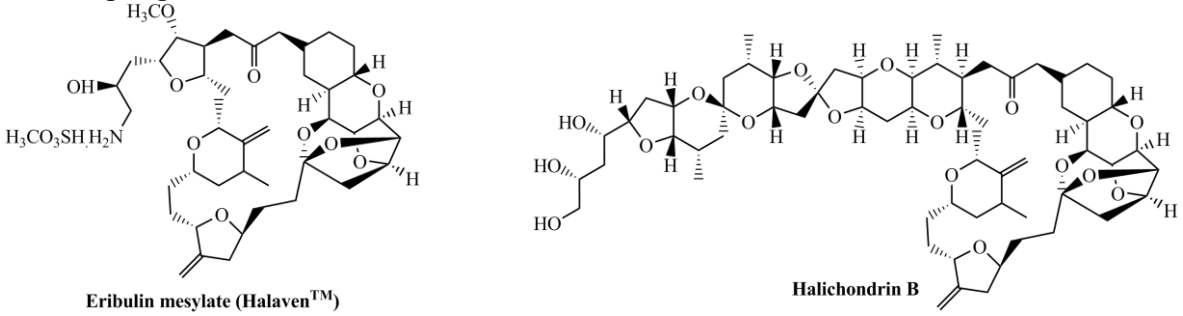
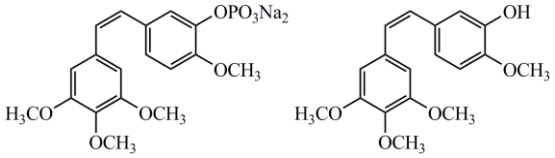


Fig. 13: Microcycles (Supramolecules) having ability to encapsulate various anticancer drugs

Chemistry has also enabled significant progress in the development of prodrugs. Combretastatin A4 phosphate, for example, is a water-soluble Prodrug (a drug that does not have a pharmacological active ingredient that is metabolized to an active substance by the body), derived from *Combretum caffrum*.



Combretastatin A4 phosphate **Combretastatin A4**

Fig. 14: Prodrugs derived from *Combretum caffrum*

Chemistry has also played an important role in the development of anticancer agents, such as contrast agents used in magnetic resonance imaging (MRI) and CT scans.

4. Summary

Chemistry has played a key role in the development and prevention of some of the most common human cancers. Since the early days of cancer therapies, chemistry has played a variety of roles in drug discovery and development. It has been widely used to alter drug leads, particularly natural ones, and to address the problem of often limited natural product availability through the development of semisynthetic or synthetic approaches. Many of today's therapeutic products are synthetic analogs of natural products. These analogs can be designed to augment supply, enhance pharmacophore understanding, enhance solubility, reduce cost, enhance potency or selectivity, and/or explore biological activity. Chemistry has also enabled significant advances in the development of prodrugs and related targeted approaches (e.g., antibody coupled drugs, photoactive agents, etc.). As cancer research advances, chemistry will continue to play an essential role in the search for new drugs to help treat patients.

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