

Review Article

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Development of heterocyclic-based anticancer agents: A comprehensive review

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Abstract: This review article summarizes the role of heterocyclic compounds as anticancer drugs used against various human cancers, including doxorubicin, cisplatin, paclitaxel, and resveratrol, which are among the most effective therapeutic agents. Chemotherapy, a treatment modality, exerts its effects on tumor cell DNA and often involves the use of low-molecular-weight medicines to selectively target and destroy cancer cells. However, systemic chemotherapy is associated with several side effects, such as nausea, vomiting, myelosuppression, and cardiotoxicity. Cancer remains one of the most prevalent and lethal diseases, characterized by uncontrolled cell division and abnormal cell growth driven by multiple genetic mutations. The etiopathogenesis of cancer is complex, but significant advancements have been made in treatment, particularly with the discovery of anticancer drugs, including cytotoxic chemotherapy, hormonal agents, and targeted therapies. Anticancer drugs are widely employed for the treatment of various cancers, such as breast, cervical, uterine, and kidney cancers. These drugs are classified into several categories, including alkylating agents, antimetabolites, antibiotics, and topoisomerase inhibitors. Among these, numerous heterocyclic compounds have shown promising anticancer properties. The goal of this review is to compile information on heterocyclic compounds used as anticancer drugs, highlighting their positive effects and therapeutic targets in cancer treatment and chemoprevention.

Keywords: heterocyclic compounds, mechanisms, medicinal chemistry, anticancer agents, biological activity, chemotherapy, cytotoxic

1 Introduction

Heterocyclic compounds have shown a significant potential as anticancer agents. These compounds are organic compounds that contain at least one heteroatom, such as nitrogen, oxygen, or sulfur, in their cyclic structure [1–3]. Several families of heterocyclic compounds have been extensively studied for their anticancer properties [4,5]. Cancer is the world's second-deadliest disease, characterized by the loss of growth control in one or more cells, resulting in a solid mass of tumor-related cells or even liquid cancer such as blood or bone marrow-related cancer [6,7]. Many protein-coding genes, such as growth factors, growth factor receptors, antiapoptotic proteins, transcription factors, and tumor suppressors, are involved in most malignancies. In addition, there are some factors, such as tobacco, alcohol, and environmental toxins, that raise the risk of cancer [8,9]. According to the World Health Organization, the number of cases increased dramatically in 2018; there will be 18.1 million new cases of this disease and 9.6 million fatalities [10]. The most common types of cancer in men worldwide in terms of the number of new cases are cancers of the lung, prostate, colorectal, stomach, and liver cancer, while the most common types among women are breast, colorectal, lung, cervical, and thyroid cancers [11,12]. By 2030, the global death toll from this devastating disease is anticipated to rise to 21.6 billion [13]. Therefore, the advancement of research aimed at improving cancer therapy has increased, as a result of which new developments have occurred depending on the method of treatment. However, the primary treatments were surgery, chemotherapy, radiotherapy, hormonal therapy, and immune therapy. Chemotherapy uses medicines of lower molecular weight to kill tumor cells, or at least their proliferation is limited [14].

Anticancer drugs can be divided into different categories according to antimetabolites, antitubulin agents,

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DNA-interactive agents, and other mechanisms involving hormones, monoclonal antibodies, molecular targeting agents, and other biological agents [15,16]. Anticancer medications that stop cancer cells from dividing and proliferating have a low selectivity for cancer cells. Cytotoxic medicines with high potency work on both cells and organs in cancer cells and healthy living cells. That makes healthy living cells susceptible to the anticancer drug's cytotoxic action affects DNA synthesis [17]. In addition, the use of large anticancer drug dosages through chemotherapy as well impacts patients' immunity by influencing the body's bimolecular protection system. However, the irrational use of unreasonable drugs is a significant health issue in medical practice today. This in turn leads to numerous consequences including, but not limited to, ineffective diagnosis, excessive prescription of especially antimicrobials and injections, creation of antibiotic resistance, adverse effects, and economic burden [18]. In this review, we will focus on the most common heterocyclic compounds that are discovered as antitumors until 2024.

2 Classification of anticancer drugs

Anticancer drugs are primarily classified into different groups based on their action mechanisms: chemotherapy, hormonal therapy, and targeted drugs (Figure 1).

2.1 Chemotherapy drugs in cancer treatment

Chemotherapy, a critical tool in cancer treatment, has been in use since the 1940s, starting with nitrogen mustard-based

drugs. It remains a central component of oncology, often combined with other therapeutic strategies. Chemotherapy works through monoclonal antibodies and small molecules that target proteins within tumor cells and disrupt DNA processes, effectively hindering cancer cell growth and survival.

Widely regarded as a frontline defense against cancer, chemotherapy utilizes a diverse range of antineoplastic drugs designed to address specific cancer types. These drugs are categorized based on their mechanisms of action and molecular targets, enabling more precise and effective treatment approaches (Figure 2).

2.1.1 Alkylating agents

Alkylating agents are the most widely used anticancer drugs, and they are essential components of combination chemotherapy [19]. These agents could cause direct DNA damage by introducing methyl or other alkyl groups into their nucleotide bases [20]. These are small molecules that can form adducts by covalently binding an alkyl group to electron-rich nucleophilic moieties and thus have a cytotoxic influence on cells engaged to DNA molecules [21]. In addition to deactivating cell respiration and intermediate metabolism by protein and enzyme alkylation, alkylating agents cause a reduction in DNA synthesis, genetic mutations, and chromosomal aberrations [22]. Melphalan, cyclophosphamide (CP), dacarbazine, procarbazine, temozolomide (TMZ), chlorambucil, and ifosfamide (IFO) are examples of anticancer drugs that contain alkylating agents (Table 1).

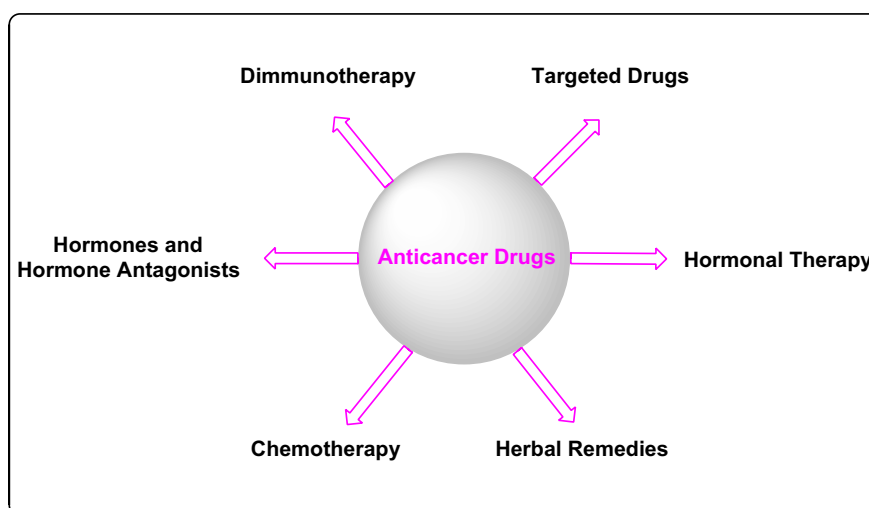


Figure 1: Anticancer drug categories.

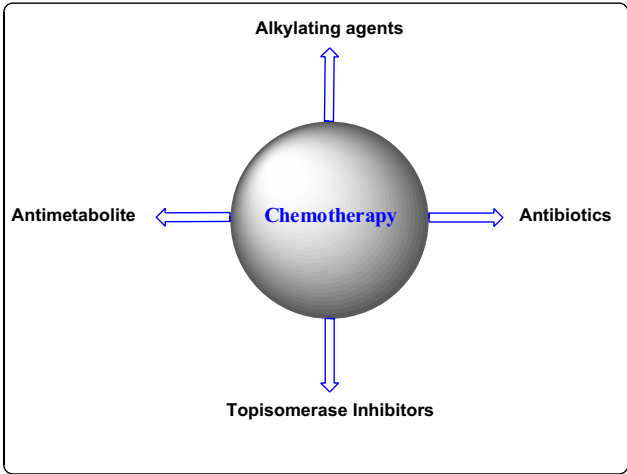


Figure 2: Chemotherapy drugs.

2.1.1.1 Nitrogen mustards

Nitrogen mustard-based substrates are cytotoxic organic compounds with chloroethylamine functional groups. It is considered a type of DNA bifunctional alkylating agent. During cell division, alkyl groups are transferred to DNA in the N-7 position of guanine, according to the chemical structure (Figure 3). DNA strand breaking and cross-linking of such two strands are all possibilities, as shown in Figure 4.

2.1.1.1.1 CP

CP is a nitrogen mustard-containing compound, which could be inefficient, primarily in the liver, when metabolic activation is negatively affected. It is activated by hepatic

transformation to form 4-hydroxycyclophosphamide, which breaks down into the ultimate alkylating agents [23,24]. The active metabolites of CP alkylate cellular macromolecules form covalent bonds that impede their separation. The most critical target is probably DNA, as alkylation limits cell division and disrupts gene expression. Following CP treatment, lymphocyte count and function are significantly reduced [23]. The mechanism of CP synthesis involves interfering with the replication of DNA, resulting in ribonucleic acid (RNA) formation. The effective metabolite of CP is phosphor amide mustard, which is produced by liver enzymes such as cytochrome P-450 during the metabolism of the drug in the body. This metabolite was created only in cells with low activity levels of aldehyde dehydrogenase. The phosphor amide metabolite at the guanine N-7 position forms cross-linkages within and between adjacent DNA strands, which results in the apoptosis of cells [25]. These types of drugs can be given either orally or parenterally. However, it is more common in rheumatology (intravenous administration). CP is an effective immunosuppressant and is, therefore, widely used for bone marrow transplantation and autoimmune disease treatment [26]. CP pharmacokinetics studies in kidney failure have generated contradictory findings. To date, scientists have not found any improvements in the presence of hepatic or renal sufficiency, which led to no dose adjustment in case of kidney failure, whereas others have reported substantially reduced drug clearance in the case of extreme renal insufficiency [27–29]. Myelosuppression is typically dose-limiting toxicity; escalation beyond this dosage range is restricted by cardiac toxicity. Synergistic hematopoietic toxicity may occur with concomitant use of

Table 1: Alkylating agent drugs

Alkylating agents	Drugs	Uses
Nitrogen mustards	CP	Lymphoma, leukemia Hodgkin's disease, multiple myeloma (MM), sarcoma, lung, testicular, prostate, breast, lupus vasculopathy and ovarian carcinoma, rheumatoid arthritis
	Chlorambucil	Non-Hodgkin's lymphomas, Hodgkin's, chronic lymphocytic leukemia (CLL)
	IFO	Breast cancer, lung cancer, cancer of the head and neck, cervical cancer and Ewing sarcoma
	Melphalan	Germ cells, breast cancer, lung cancer of the head and neck, cervical cancer, and Ewing sarcoma
	Mechlorethamine	Hodgkin's disease, and in the topical treatment of mycosis fungoides and other lymphomas
Other alkylating agents	TMZ	Metastatic melanoma, malignant melanoma, and primary brain tumor
	Procarbazine	MM, multiform glioblastoma and Hodgkin lymphoma, and CNS malignancies
	Chlorozotocin	Neuroendocrine tumors, pneumonitis, hormone-sensitive cancers, such as ovarian, prostate, breast, and endometrium
Alkyl sulfonates	Busulfa	Chronic myelocytic leukemia and polycythemia vera
Nitrosoureas	Carmustine	Pancreatic metastatic islets, cellular carcinoma
	Lomustine	Hodgkin's disease, lung and brain tumors, MM, melanoma, and brain tumors
Ethylenimine derivative	Thiotepa	Adenocarcinoma of the breast and ovary, urinary bladder carcinoma, and urinary bladder carcinoma
Triazines	Dacarbazine	Metastatic malignant melanoma, Hodgkin's disease, sarcoma, neuroblastoma, neuroendocrine brain tumors and primary tumors

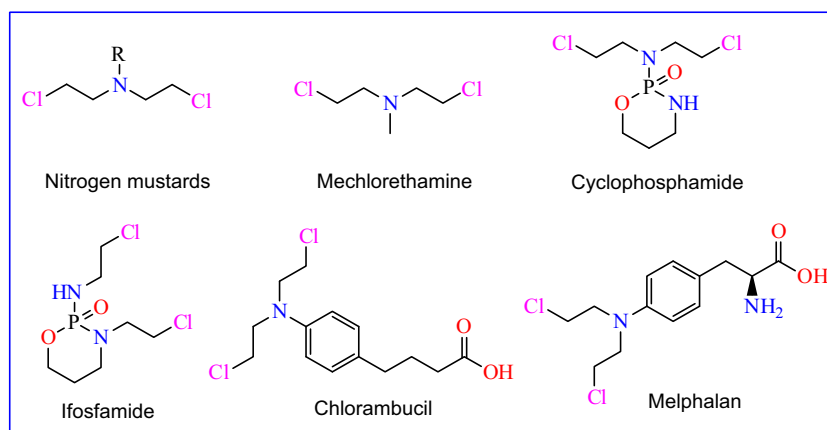


Figure 3: Alkylating agent drugs (nitrogen mustards).

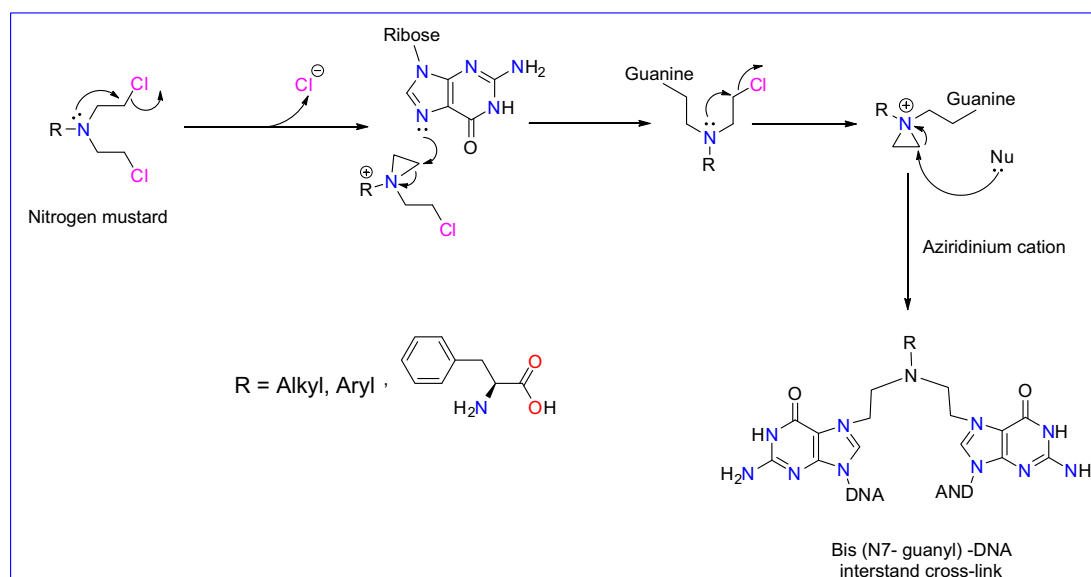


Figure 4: Nitrogen Mustard mechanism of action.

allopurinol [30]. According to the Food and Drug Administration (FDA) agency in 1995, CP was approved to be a valuable drug for consumption [31,32]. From that time, CP started to be one of the most common medicines to treat tumor malignancies such as MM and breast cancer. Besides, it can be used in the treatment of various rheumatic diseases, including scar pemphigoid (also known as pemphigoid mucous membrane), juvenile dermatomyositis and soft tissue sarcoma, and thrombocytopenic purpura refractory therapy [33–35]. In contrast, the side effects of CP use are nausea, vomiting, amenorrhea, ovarian failure, sterility, cardiotoxicity, and immunosuppression, which is associated with an increased risk of secondary malignancy infection. Resistance mechanisms are similar to those of other mustards but also include increased expression of aldehyde

dehydrogenase, which leads to enzymatic detoxification of the drug [36].

2.1.1.1.2 Chlorambucil

Chlorambucil belongs to the nitrogen mustard group of alkylating agents, which also form DNA cross-linking scaffolds. In 2013, the FDA approved chlorambucil in combination form as a therapy for patients with previously untreated CLL [37]. The mechanism of action for chlorambucil is similar to that of CP but relatively slow [17]. CLB's mechanism of action has been explored in many tumor cell models. The agent hydrolyzes quickly and has a half-life of 30 min in water and 42 min in blood [23]. Passive diffusion was found to be the mechanism of drug uptake in rat Yoshida ascites sarcoma

cells [24] and mouse models. CLB and other nitrogen mustards form DNA crosslinks and monoadducts in several cell types. DNA crosslinks may limit replication in growing cells, while DNA monoadducts may contribute to the agent's cytotoxicity by inhibiting transcription [38]. This compound is used for patients with non-Hodgkin's lymphomas, Hodgkin's disease, non-Hodgkin's lymphomas, and CLL [39–42]. The therapeutic use of this drug's effectiveness is limited by toxic effects such as bone marrow suppression, anemia, and a weakened immune system. It also causes nausea, myotoxicity, and neurotoxicity, as well as secondary cancers [43].

2.1.1.1.3 IFO

IFO is a nitrogen mustard compound, which differs from CP in the location of chloroethyl moiety. It is commonly used as a racemic mixture intravenously to produce the active cytotoxic metabolites, which are activated by the liver cytochrome P450 microsomal system [44]. IFO was approved as an official drug in 1988 by the FDA agency [45]. The mechanism of action of IFO involves its metabolites by CYP450 enzymes in the liver. These effective metabolites (the derivatives of phosphor amide mustard and acrolein) bind to DNA and inhibit the synthesis of modified DNA. There are two types of mechanisms for IFO: first, it forms an intrastrand cross-linking reaction with DNA to generate the modified one, which causes cell damage; and second, it contributes to the apoptosis of the damaged cells. These active metabolites upregulate the reactive oxygen species, resulting in irreparable damage to DNA and ceasing the formation of proteins [46]. IFO has many major toxic side effects: hemorrhagic cystitis is responsible for the dose-limiting toxicity. However, the drug itself is not specifically harmful to kidneys, but its metabolite chloro-acetaldehyde *in vitro* and *in vivo* is harmful to renal tubular cells [47]. This type of drug is specifically recommended for patients with persistent cancers of the germ cells, breast cancer, lung cancer, cancer of the head and neck, and cervical cancer [48,49]. Cancer treatment with alkylating DNA agents, like IFO, can lead to gonadal toxicity, ovarian failure, and reduced fertility, leading to premature menopause due to numerous electrophilic aldehydes that result from chemotherapy [50,51].

2.1.1.1.4 Melphalan

Melphalan is an anti-cancer drug that prevents cancer cells in the body from growing and spreading. It has been an effective treatment for MM, also known as phenylalanine mustard and phenylalanine melphalan [52,53]. The mechanism of action of Melphalan, as a peptide–drug combination: the

compound's high lipophilicity allows for fast diffusion across the neoplastic membrane. The peptidase enzyme found in the cell acts on the peptide–drug combination, releasing the alkylating moiety from the carrier. The nitrogen mustard moiety enters the nucleus, which leads to DNA crosslinking.

Furthermore, Melphalan has been utilized in the treatment of MM since the 1960s [54]. In 2016, in the United States, this drug was not licensed for use as a high-dose conditioning therapy prior to hematopoietic progenitor (stem) cell transplantation in MM patients [55]. The mechanism of action is similar to bifunctional alkylating agents; its cytotoxicity seems to be linked to the degree of its DNA cross-linking. These covalent bonds bend DNA's double helix, causing cytotoxicity and interfering with the polymerases' ability to function, presumably by binding guanine at the N7 position. In addition, these adduct cell apoptosis can be caused by deletions, strand scissions, and the development of open rings. Thus, it is an efficient treatment against resting and rapidly dividing tumor cells [56,57]. In addition, Melphalan was utilized orally for MM, ovarian, and breast carcinomas and is used in treatment regimens in bone marrow transplantation at high dosages [58,59]. However, it has many side effects, such as nausea, diarrhea, vomiting, and ulcers in the mouth. Therefore, to decrease the microsites, the patients were recommended to consume ice chips to maximize circulation of blood to the oral mucosa and to improve drug distribution to the region, often referred to as cryotherapy [60].

2.1.1.1.5 Mechlorethamine

Mechlorethamine was the first nitrogen mustard drug used in clinical practice and the progenitor of antineoplastic alkylating agents, also known as chlormethine. It is readily and unimolecularly converted at physiological pH to a relatively stable aziridinium ion as a free base to turn the interaction of biomolecules into accessible nucleophilic centers. It was approved by the FDA in 1949 [61]. Mechlorethamine reacted with N-7 to create an interstrand cross-link of two separate guanines in DNA. The formation of the ammonium ion N-7 makes the guanine more acidic and thus tends to alter the balance in favor of the enol tautomer. In addition, N-7 alkylated guanosine is susceptible to hydrolysis and forms a basic guanosine [62]. Mechlorethamine is also utilized in the therapy of Hodgkin's disease systemically and in the topical treatment of mycosis fungoides and other lymphomas [63]. Vomiting and nausea are the most common side effects of mechlorethamine; it typically begins within 30 min of injection and lasts for 8 h, as reported [64].

2.1.1.2 Other alkylating agents

2.1.1.2.1 TMZ

TMZ has been used as a standard anti-cancer drug for glioblastoma, often in conjunction with radiotherapy (Figure 5) [65]. It is a convenient oral drug adjunct that penetrates the blood–brain barrier [66]. In 1999, the FDA approved this drug for patient remediation with primary brain tumors [67]. The mechanism of TMZ metabolism includes DNA damage and repair. Under physiological conditions, TMZ is metabolized to MTIC, which is subsequently converted to its active form, a methyl diazonium ion. The electrophilic methyl diazonium ion functions as a methyl donor, donating its methyl group to negatively charged DNA to form DNA adducts. This alkylating activity occurs primarily at N7 of guanine, O3 of adenine, and O6 of guanine, and if left unrepaired, causes incorrect base pairing and causes breaking of the single and double-stranded DNA and the key endogenous DNA repair [68]. The cytotoxicity of TMZ is regulated by the addition of methyl groups to guanine at the N7 and O6 sites and adenine at the O3 site to genomic DNA. During subsequent DNA replication, alkylation of the O6 site on guanine leads to the addition of thymine instead of cytosine opposite methyl guanine, and this may result in cell death [69]. Adding TMZ to the standard treatment protocol was considered a significant advance in GB therapy [70]. TMZ is also utilized in the treatment of metastatic melanoma and is often utilized in the treatment of malignant melanoma. Few respiratory side effects were reported, mainly pharyngitis, infection of the upper respiratory tract sinusitis, and cough [71].

2.1.1.2.2 Procarbazine

Procarbazine is a moderate inhibitor of monoamine oxidase (MAOI), which was approved by the Food and Medications for therapy in 1969 (Figure 5) [72]. PCB is a prodrug, and its hepatic metabolism plays a significant role in the production of active metabolite species. Chemical breakdown and microsomal oxidation are two potential activation mechanisms. It

is converted to azoprocabazine by microsomal cytochrome P-450 oxidoreductase or mitochondrial MAOI enzymatic conversion. AzoPCB may be metabolized further through unknown mechanisms. [73]. To generate cytotoxic responses, procabazine must first be metabolically activated. The mechanism of action of procabazine is through *trans* methylation of the methionine group to t-RNA, which is blocked by the drug procabazine and leads to triggers the cessation of protein synthesis. It can also directly target DNA by targeting the sulfahydrate protein groups found in the residual protein that are closely bound to DNA [74]. Procarbazine is utilized in Hodgkin's lymphoma, non-lymphoma, Hodgkin's brain tumors, melanoma, lung cancer, and MM [75]. Acute side effects of Procarbazine include nausea at large doses; nausea and vomiting can develop leukopenia, and thrombocytopenia develop hematologic toxicity within 3–4 weeks of administration [76].

2.1.1.2.3 Chlorozotocin

Urea is a type of alkylating agent used to treat neuroendocrine tumors (Figure 5). Several cases of moderate pneumonitis were associated with its use, which was managed by discontinuation of the drug and administration of corticosteroids [77].

2.1.1.2.4 Steroidal hormones

Steroids have been commonly used for drug delivery because they bind selectively to steroid hormone receptors located on the cancer cells' surface [78]. Moreover, studies have shown that tumor growth and proliferation in certain forms of cancer, such as breast cancer, are directly linked to steroidal hormones. The chemical bonding of an alkylating chemical to steroidal nuclei as a carrier molecule was a promising strategy for increasing the absorption of nitrogen mustard into these hormone-sensitive tumors [79,80]. The significance of steroid hormones in the prevention and treatment of hormone-sensitive organisms' cancers such as ovarian, prostate, and breast with endometrium. Steroids have shown that steroidal–mustard conjugates are more effective, selective, and less toxic [81].

2.1.1.3 Alkyl sulfonates

Alkyl sulfonates are a kind of alkylating agent, which are mainly used to treat neoplastic diseases. These modes of action all involve reactive amine alkylation on DNA. It is most efficient in rapidly proliferating tissues, which partially account for their immunosuppressive effects, as shown in Figure 6 [82].

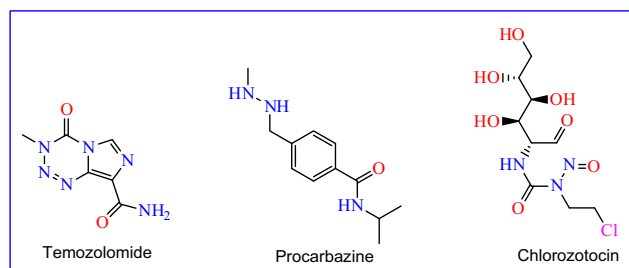


Figure 5: Other alkylating agents.

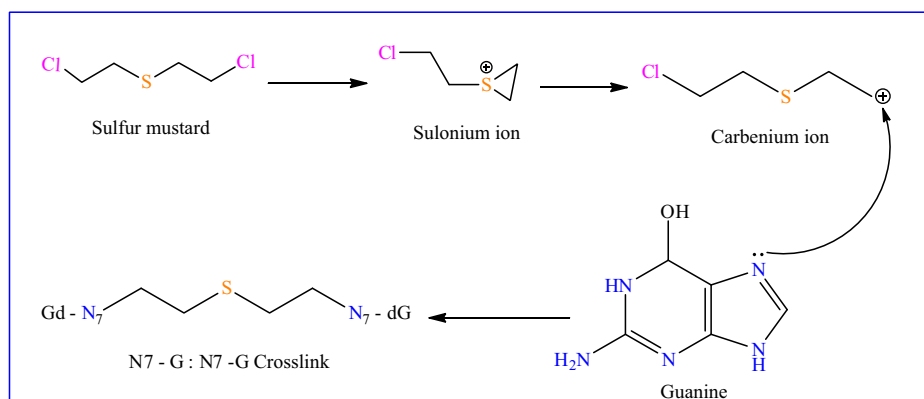


Figure 6: Mechanism of action of alkyl sulfonates.

2.1.1.3.1 Busulfan

Busulfan is an alkylating agent used to treat myeloproliferative neoplasms (MPNs). It was utilized in a number of hematopoietic conditioning regimens, system cell transplantation hematopoietic cell transplantation (HCT), and in the control of chronic myelogenous leukemia in 1953 [83,84]. Furthermore, in 1999, Busulfan was approved by the FDA for the treatment of chronic myeloid leukemia (CML). It interacted with the protein during the hydrolysis process. The methane sulfonates are released, and carbonium ions are formed. DNA is alkylated by carbonium ions, resulting in the intervention of DNA replication and transcription of RNA. Its alkylation mechanism of action establishes an intrastrand crosslink between guanine and adenine [85]. It is also utilized as a conditioning agent in pediatrics and adults in conjunction with CP or clofarabine prior to bone marrow transplantation. However, it suppresses bone marrow in the same way as other antineoplastic alkylating medicines. Busulfan, on the other hand, can cause myelosuppression to last a long time [86].

2.1.1.4 Nitrosoureas

The nitrosourea drug is a class of nitrogen mustard-linked DNA and is considered the chemotherapeutic agent most widely used in the treatment of malignant PBT (Figure 7). It is an extremely lipid soluble, non-ionized, cell-cycle-non-specific agents that easily cross the blood-brain barrier. It spontaneously decomposes into two active intermediates, a group of isocyanates and chloroethyl diazohydroxide [87]. Their mechanism of action is established on the formation of diazohydroxide under basic conditions, which in turn generates a reactive for alkylation (Figure 8).

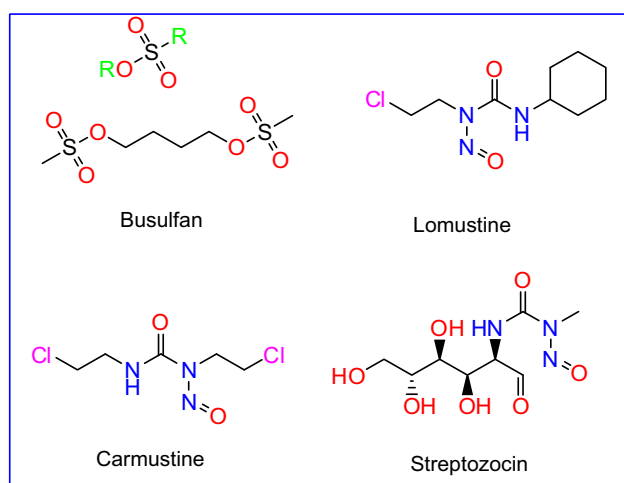


Figure 7: Alkyl sulfonates and nitrosoureas drug.

2.1.1.4.1 Lomustine

Lomustine is an oral chemotherapeutic efficient, highly lipid-soluble, and enters cells by passive diffusion. Lomustine spontaneously decomposes into a reactive center to cross-link DNA alkylation, DNA–DNA, and DNA–protein under aqueous conditions and at physiological pH [88]. In 1976, the FDA approved it for the treatment of certain diseases. Lomustine undergoes inclusive hepatic metabolism, mainly through cyclohexyl ring hydroxylation, to form metabolites of alkylating activity, which is at least equivalent and are believed to play a significant role in cytotoxic activity [89]. Nitrosourea subclass, 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU, lomustine) is most widely used against lymphoma and mast cell tumors due to its possibility to pass through the blood-brain barrier. CCNU is most often used alone or in multi-agent protocols for brain tumors [24,90]. Myelosuppression with acute neutropenia followed by thrombocytopenia is the primary dose-limiting toxicity [91].

2.1.1.4.2 Carmustine

Alkylating nitrosourea is commonly utilized for treating malignancies. Since systemic administration of nitrosoureas was poorly successful in treating high-grade glioma, carmustine wafers were designed to deliver high local drug concentrations. In particular, carmustine was successful by alkylating DNA and RNA [92]. It has a low molecular weight, is extremely lipophilic, and penetrates deep into the central nervous system blood–brain barrier easily owing to its medicinal lipophilic nature [93]. The main action mechanism for this family drug is by binding to DNA and alkylation of DNA nitrogen bases in the duplex. However, several studies have confirmed that carmustine prevents cancer cell growth. The essential processes such as replication, transcription, and DNA translation are inhibited by the alkylation of DNA [94,95]. Carmustine is commonly used to treat various forms of human cancers, including glioblastoma, brainstem glioma, astrocytoma, metastatic brain tumor leukemia, and medulloblastoma [96,97]. Delayed myelosuppression, interstitial pneumonia, and platelet count are almost common, and severe disadvantages of carmustine might even be nausea and vomiting [98,99].

2.1.1.4.3 Streptozocin

Streptozocin (also known as streptozotocin) is an alkylating nitrosourea agent known to be absorbed into cells by the GLUT2 protein expressed by glucose to cause cell harm [100]. STZ is also a powerful alkylating agent used to methylate DNA directly and is extremely genotoxic [101]. It was approved by the FDA in 1982 and is used to treat metastatic cancers of pancreatic islets of Langerhans [102]. Streptozocin does not cross the blood–brain barrier quickly, nor is it highly myelosuppressive. *Streptomyces achromogenes*, which are especially toxic to the pancreatic beta cells producing insulin in mammals. It is used as a chemotherapeutic medication in the medical sector to treat some Langerhans islets cancers and a singular antineoplastic agent used to treat pancreatic metastatic islets cellular carcinoma [103]. Streptozocin is unique in its attraction to pancreatic islet cells. Because it is a vesicant, it should be given intravenously with caution. It is one of the most emetic agents, necessitating a large amount of antiemetic premedication. The side effect of this drug is the possibility to be toxic and thereby cause renal and hepatic failure [104,105].

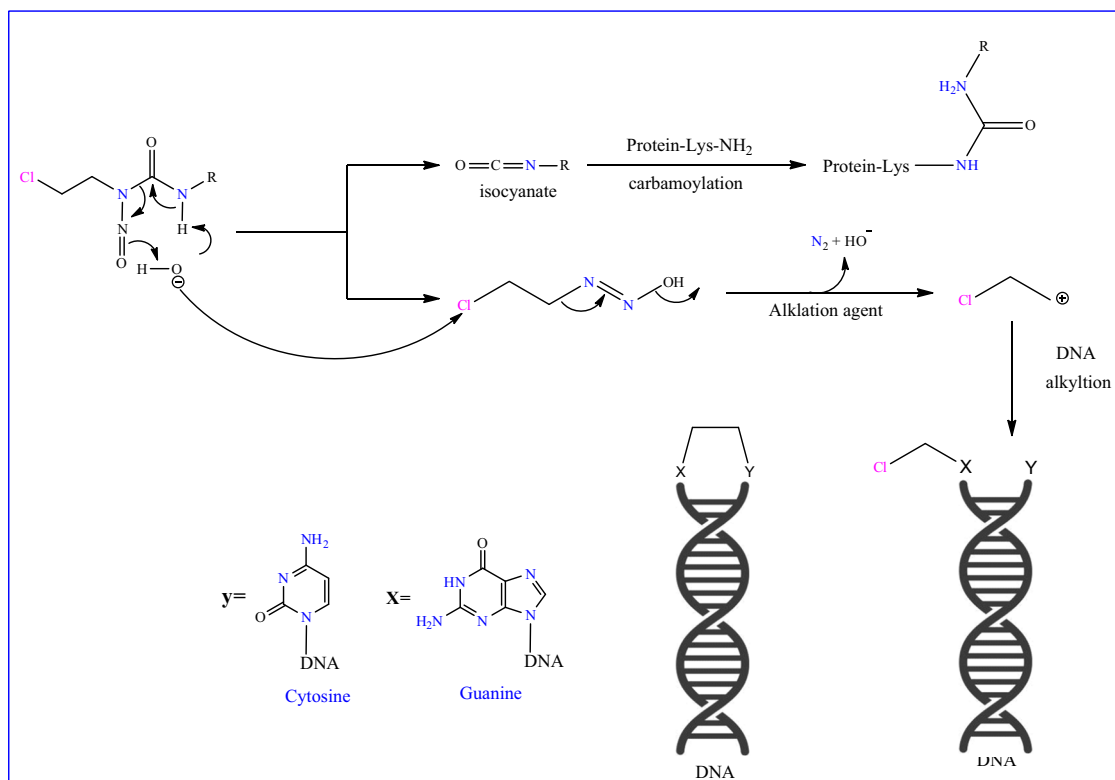


Figure 8: Mechanism of action of nitrosourea.

2.1.1.5 Ethylenimine derivative

Ethylenimine is also called aziridine, which is made from ethylenimine. It is a three-pointed ring made up of two carbon atoms and one nitrogen atom, such as Thiotepa (Figure 9).

2.1.1.5.1 Thiotepa

Thiotepa is the first chemotherapeutic agent contra NMIBC FDA-approved. It is a nonspecific alkylating agent with low molecular weight (189 kDa) chemically used for nitrogen mustard [106]. According to routes, Thiotepa is a polyfunctional alkylating chemical, and it can generate crosslink reactions with DNA molecules. The aziridinyl groups' mechanism draws a proton from the N7 guanine of DNA and performs a ring-opening reaction via nucleophilic attack [107]. The exact method by which they have anticancer properties is uncertain. However, they are categorized as alkylating agents, and it is assumed that they work by crosslinking DNA double-helix strands to halt tumor growth. This prevents the strands from uncoiling and separating, which is required for DNA replication. Cancer cells can no longer divide and die as a result [81]. Their toxicity appears to be dose-dependent, as there is a lesser likelihood of leucopenia. A leukocyte and platelet count should be acquired before each treatment because it is the system that is responsible for much toxicity. In 1994, thiotepa was approved by the FDA for the treatment of breast cancer, ovarian cancer, and bladder cancer. After that, it was used as a conditioning treatment prior to hematopoietic stem cell transplantation in 2007 [108]. Thiotepa has been utilized to treat a variety of neoplastic diseases, the most common of which are adenocarcinoma of the breast and ovary, urinary bladder carcinoma, and intracavitary effusions caused by diffuse or localized neoplastic diseases of various serosal cavities [109]. Acute side effects of thiotepa are similar to other alkylating agents like nausea, vomiting, diarrhea, alopecia, mucositis, bone marrow suppression, and rash, and uncommon but potentially serious adverse events involve severe myelosuppression, severe infections, sepsis, bleeding, and embryo-fetal toxicity [110].

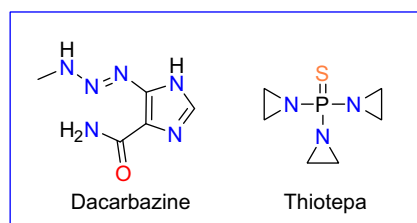


Figure 9: Ethylenimine derivative and Triazine drugs.

2.1.1.6 Triazines

Triazine derivatives, particularly 1,2,4-triazine derivatives, have been identified as new antitumor agents. These compounds exhibit potent cytotoxic activities with fewer side effects [111].

2.1.1.6.1 Dacarbazine

Dacarbazine was used widely as a chemotherapeutic agent in the triazine family as an alkylating agent. A chemotherapeutic drug for the treatment of melanoma was approved by the FDA in 1975 [112,113]. Dacarbazine influences cells through three pathways as follows: carbon ion alkylation, metabolic inhibitory effects against DNA and RNA synthesis, and protein alkylating sulfhydryl groups [114]. DTIC was highly efficient and developed for clinical use. Therefore, it is used in the treatment of metastatic malignant melanoma and Hodgkin's disease. Additionally, DTIC has moderate efficiency in sarcoma therapy, neuroblastoma, neuroendocrine brain tumors, and primary tumors [115]. The main side effects of dacarbazine include nausea and vomiting, which are common. This agent has been linked to mild bone marrow suppression. Patients taking moderate to soaring doses of DTIC also exhibit photosensitivity responses [116].

2.1.2 Antimetabolites

Antimetabolites are among the oldest and the first effective chemotherapeutic agents discovered. It is comparable to chemicals necessary with proper metabolic efficiency but is dissimilar enough to disrupt normal cell functions when antimetabolites are integrated into RNA and DNA during the S phase of cell growth; they cause cell death or block enzymes involved in nucleic acid creation. Because cells in the S phase are more sensitive to antimetabolites DNA synthesis, toxicity is prevalent in any tissue, for example, bone marrow and gastrointestinal tract tissues. This drug classification is described in Table 2 and contains antifolates and antipyrimidines "5-fluorouracil, capecitabine, eniluracile, hydroxyurea," and antipurines "6-mercaptopurine, 6-thioguanine" methotrexate, pemetrexed" [117].

2.1.2.1 Folic acid analogues

The synthesis of folates plays a crucial role in RNA and DNA structures. Analogues of folate are also known as antimetabolites, which are considered the most used drug for cancer treatment. Since cancer cells have an aberrant proliferation compared to their normal counterparts, DNA and

Table 2: Antimetabolite drugs

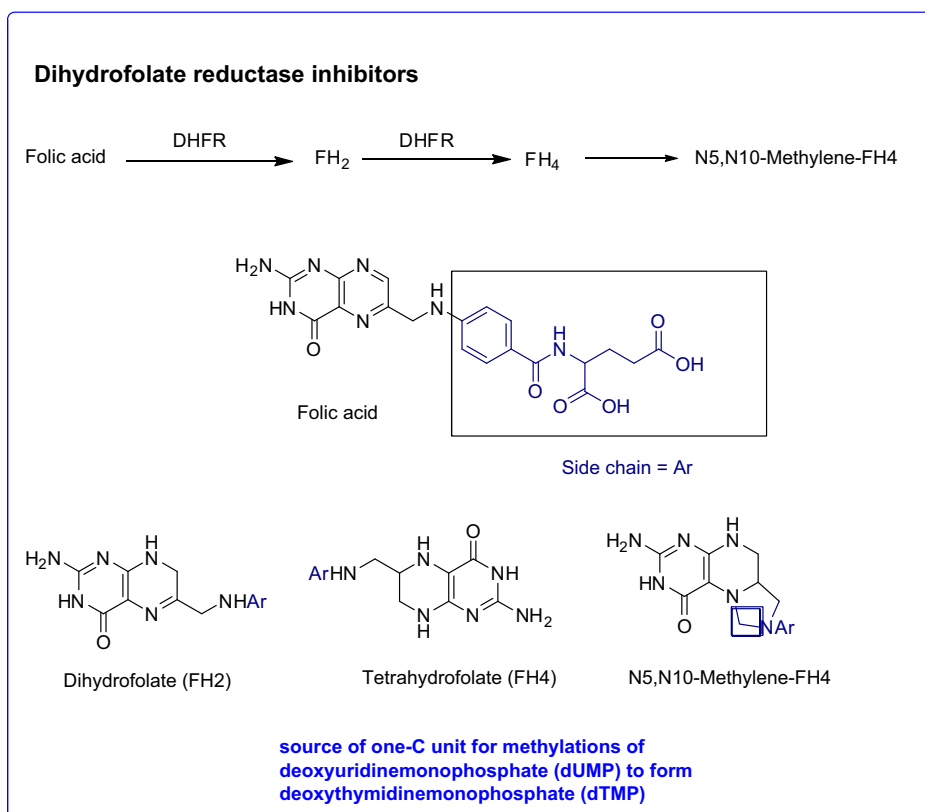
Antimetabolites	Drugs	Use
1. Folic acid analogues	Methotrexate Pemetrexed	Leukemia: lymphocytic leukemia, acute lymphoid leukemia, and acute and CML Non-small cell lung cancer, and treatment for lung, colon, pancreatic, breast, bladder, head and neck, and cervix and gastric cancers
2. Pyrimidine analogues	Fluorouracil Capecitabine Cytarabine Gemcitabine	Breast, stomach, pancreatic, head and neck, esophageal, gastric, colorectal, and anal cancers Colon cancer and breast and gastric cancer Lymphoma and leukemia Solid tumor pancreatic cancer
3. Purine analogues	Mercaptopurine and thioguanine Fludarabine Pentostatin Cladribine Clofarabine Nelarabine	Hematological malignancies, chronic inflammatory diseases, and transplantation acute leukemia in oral chemotherapy CLL, hairy-cell leukemia, and non-Hodgkin's lymphomas Hairy cell leukemia and T cell lymphoma Hairy cell leukemia and acute myeloid for leukemia Refractory acute myeloid and lymphoblastic leukemia Relapsed and refractory T-ALL

RNA synthesis inhibition is a very effective anticancer therapy strategy [118] (Figure 10).

2.1.2.1.1 Methotrexate (MTX)

Antifolate compounds are potent and well-characterized compounds, which imitate folic acid as they have an

additional methyl group at N10" (Figure 10). MTX is a folic acid antimetabolite that works by being competitively bound to the dihydrofolate reductase enzyme. MTX was approved in the United States in 1953 and in 1972 by the FDA to treat psoriasis [119,120]. It inhibits the formation of purines and pyrimidines in the cells and it could also inhibit the synthesis of DNA but may also interfere with

**Figure 10:** Mechanism of action of folic acid analogues.

protein synthesis that blocks the conversion of certain amino acids [121]. This inhibition results in diminished dihydrofolate conversion for tetrahydrofolate and impaired thymidic acid synthesis. Deficiencies of such acids hinder the synthesis of DNA and RNA [122]. MTX shows a toxic effect profile against normal proliferating tissues such as bone marrow and intestinal tissue to broaden the treatment efficacy to competitively inhibit intracellular MTX transport in tissues close to blood vessels; high doses of MTX are usually followed by low doses of leucovorin (5-formyl-THF) [123]. MTX is approved to treat all cases of leukemia, acute lymphocytic leukemia, acute lymphoid leukemia in childhood, and CML. Also, it is a common medication used to treat pain lymphoid leukemia in childhood [124,125]. In fact, the side effects of MTX appeared in bone marrow and gastrointestinal mucosa [126].

2.1.2.1.2 Pemetrexed

Pemetrexed was authorized as an FDA drug for the first time in 2004 for nonresectable pleural mesotheliomas in conjunction with cisplatin. It works as a cell cycle-specific and antimetabolic anticancer medication that blocks folic acid metabolism (Figure 11). Also, it works on the inhibition of enzymes, implicates purine and pyrimidine metabolism, and impairs the synthesis of RNA and DNA in tumors [127,128]. Reduced folate carrier (RFC) and folate receptor-a allow pemetrexed to enter cells (FR-a) and are intracellularly polyglutamated. Polyglutamation leads to a significant increase in pemetrexed's affinity for enzymes involved in folate metabolism and a decrease in its affinity for RFC and FR. This process results in a prolonged intracellular lifespan of the drug [129]. Furthermore, pemetrexed is shown officially for the treatment of non-small cell lung cancer, whether locally advanced or metastatic, and for lung treatment, colon, pancreatic, breast, bladder, head and neck, and cervix and gastric cancers [130]. The most common side effects of this drug are

diarrhea, mucositis, rash, tiredness, and myelosuppression. Therefore, recently published results confirmed to reduce myelosuppression and mucositis. Folic acid (1 mg daily) and vitamin B12 (1 mg injectable every 8 to 10 weeks) supplementation were prescribed [131].

2.1.2.2 Pyrimidine analogues

Pyrimidine antimetabolites that interfere with the synthesis of nucleic acids are known as analogues (Figure 12). They are hydrophilic molecules, in general, which require specialized membrane transporters for cell entry. Therefore, by the intracellular enzyme phosphorylation, such as deoxycytidine, the kinase will transform these drugs into active metabolites. Their antiproliferative effect is achieved through incorporation into DNA, resulting in chain termination and suppression of DNA composition (Figure 13) [132].

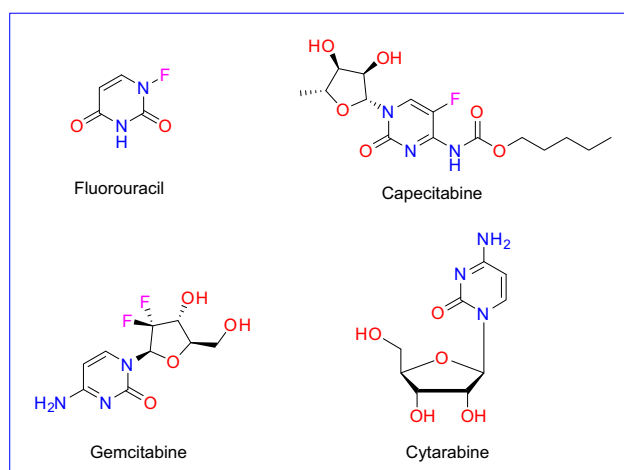


Figure 12: Pyrimidine analogues.

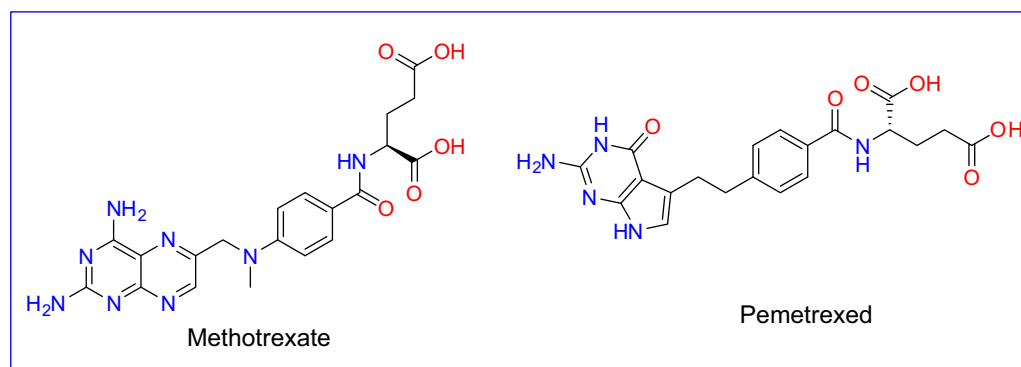


Figure 11: Folic acid analogues.

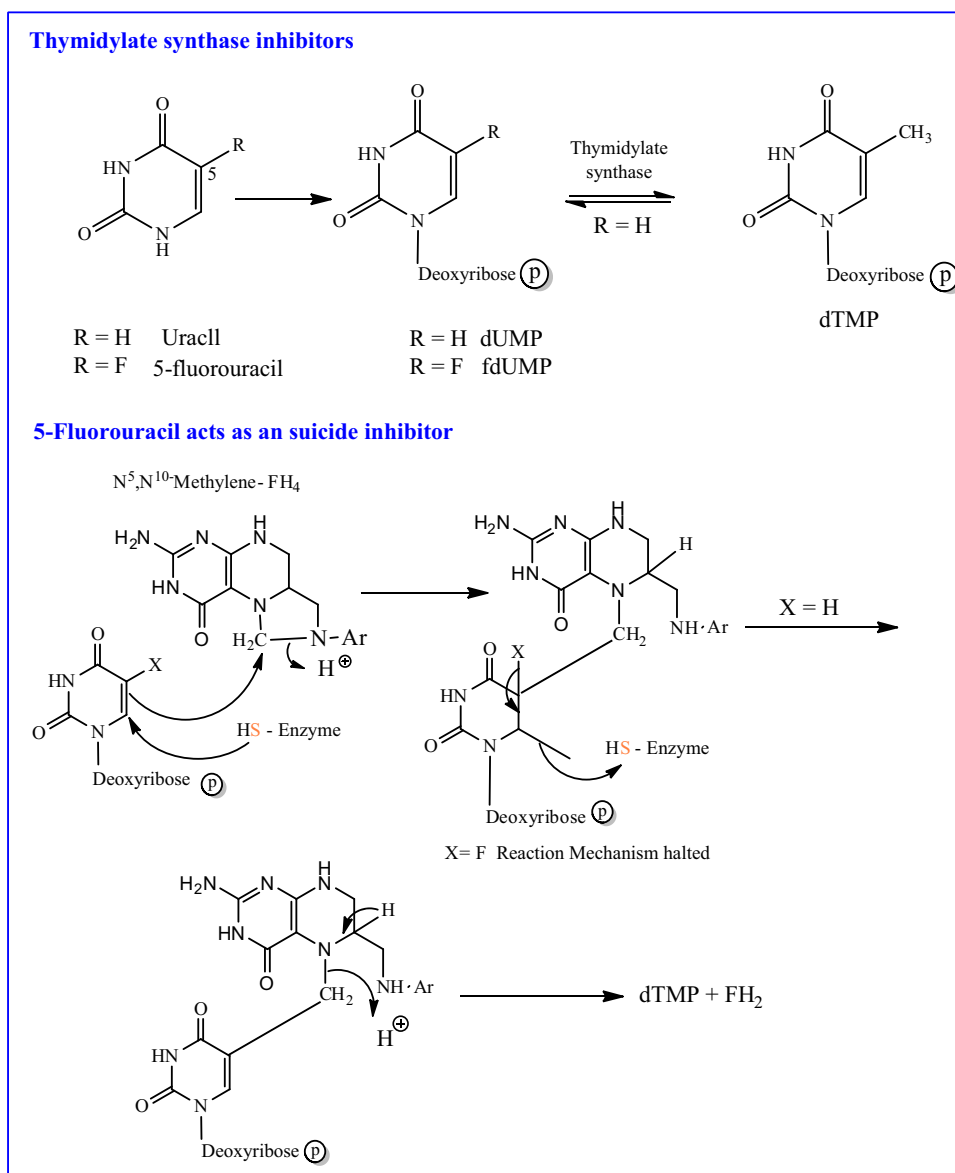


Figure 13: Mechanism of action of pyrimidine analogues.

2.1.2.2.1 Fluorouracil

The use of 5-fluorouracil (5-FU) as an anticancer agent in the United States was licensed for medical use in 1970 to treat breast cancer, colorectal cancer, stomach cancer, pancreatic cancer, head and neck, esophageal, gastric, colorectal, and anal cancers. Although the exact act mechanism of the drug is still to be fully known, it involves blocking the thymidylate synthase (TS) enzyme, resulting in a loss of phosphorylated deoxythymidine and a toxic accumulation of deoxyuridine [133,134]. It is an anti-cytotoxic but also an anti-neoplastic cell from the type of anti-metabolites, a natural pyrimidine base that is employed in the production

of nucleic acids [135]. 5-FU is transformed into various active metabolites like fluorodeoxyuridine monophosphate (FdUMP), fluorouridine triphosphate (FUTP), and fluorodeoxyuridine triphosphate (FdUTP). It plays an important role in biological activities such as disrupting RNA synthesis and exerts anticancer influence through TS inhibition [136]. These formulations are all administered through the intravenous route. The main problem with this administration is that healthy tissues are exposed to harmful chemotherapeutic agents [137]. 5-FU was used in treatment protocols for breast, stomach, and pancreatic cancers [138]. Severe side effects of this drug in patients who receive it intravenously to treat malignant neoplasms include loss of appetite, nausea, fatigue, a metallic taste, and ulcers [139].

2.1.2.2.2 Capecitabine

Capecitabine is an antimetabolite 5-FU prodrug and was approved in 2001 for metastatic colon therapy [140]. Capecitabine is commonly used as a monotherapy for palliative chemotherapy in inoperable patients. Capecitabine is hydrolyzed in the liver and gradually transformed into the effective 5-FU drug. This drug is active as a single agent, but it can also be combined with other cytotoxic agents, including oxaliplatin, irinotecan, taxane, or cisplatin [141,142]. In its mechanism of action, thymidylate phosphorylase converts capecitabine to 5-FU. TS is inhibited by 5-FU, which leads to the inhibition of the development of thymidine monophosphate needed for *de novo* DNA synthesis. In many tumor cells and hepatocytes, high thymidylate phosphorylase levels are observed, making these cells more vulnerable to toxicity [143]. Capecitabine is currently being utilized in conjunction with preoperative radiotherapy, postoperative adjuvant therapy, or in conjunction with other chemotherapy agents that are effective against some cancer types [144]. However, capecitabine has been recorded by 5-FU to be used as a treatment for colon cancer and advanced breast and gastric cancers. Capecitabine's side effects include stomatitis, extreme diarrhea, and minor nausea and vomiting. In addition, extreme "hand-foot syndrome," "palmar/plantar erythrodysesthesia," and other dermatology benefits have been noted [145].

2.1.2.2.3 Cytarabine (CBN)

CBN is a structural analogue of pyrimidine and purine bases, and its functional role is to inhibit unchecked cancer cell growth by interfering with cell DNA synthesis [146]. It was approved by the FDA in 1969 as a potent drug of antileukemic substance [147]. The mechanism of action of this drug is that it is converted into a triphosphate inside the cell and competes to integrate itself into the DNA with cytidine. CBN's sugar moiety hinders the molecule's rotation within the DNA. Through the S steps of a cell cycle, DNA replication stops, giving it a particular medication for quickly proliferating cells like cancer cells. The replication and repair of DNA also stops because CBN inhibits DNA polymerase [148]. This drug is recommended for patients intravenously and it is quickly eliminated from the plasma with a half-life of 5–20 min, and the blood is delaminated in the liver [149]. CBN treats CNS disease with systemic because of the height-dose therapy; CBN can pass through the blood–brain barrier to reach cerebrospinal fluid concentrations between 40 and 50% of plasma concentrations [150]. CBN is also effective in treating acute lymphocytic leukemia, and it can be used in both children and adults to treat relapses of acute lymphocytic leukemia. In the treatment of non-Hodgkin lymphomas, Ara-Cis is used in conjunction

with other agents. In terms of treatment of solid tumors, Ara-C is not especially useful [151]. CBN can also be used to treat other forms of lymphoma and leukemia [152]. Therefore, myelosuppression is the main side effect of this drug. In fact, high doses cause nausea and vomiting, mucositis, diarrhea, keratoconjunctivitis, and cerebellar toxicity [153].

2.1.2.2.4 Gemcitabine

Gemcitabine is a deoxycytidine analogue, which is helpful for treating several forms of solid tumors. It is an effective candidate for combination therapy and the combination of gemcitabine and DNA-damaging drugs such as alkylating agents and platinum complexes [154]. Gemcitabine was approved by the FDA in 1996 to treat advanced pancreatic cancer [155]. The mechanism of action of gemcitabine is that it mostly has anticancer properties and influences interfering with DNA synthesis. It possibly integrates its metabolites into DNA, thus abrogating successful DNA synthesis. In addition, it inhibits TS, the primary enzyme in the thymidine *de novo* production pathway. The alternative route to the thymidine salvage pathway represents the basis for tissue absorption of FLT [18F] [156]. Gemcitabine is an approved medicine for pancreatic cancer and lung cancer, with an objective response rate of 23.8% [157]. The commonly recorded side effects are bone marrow suppression, liver and renal issues, nausea, fever, rash, shortness of breath, and hair loss [158].

2.1.2.3 Purine analogues

Purine analogues are the most common class of heterocyclic compounds containing nitrogen, which play a crucial role in a wide range of living organisms' functions, as shown in Figure 14.

2.1.2.3.1 Mercaptopurine and thioguanine

6-Mercaptopurine and (thiopurines) are immunosuppressive drugs that have shown benefit in the maintenance of remission in both CD and UC [159]. 6-MP was first approved for medical use in the United States in 1953 [160]. Mercaptopurine's key mechanism of action is that 6-MP thiopurines need intracellular activation to exert cytotoxicity, catalyzed by multiple enzymes. Thiopurine drugs' cytotoxic effects are achieved by various mechanisms: incorporation of thio-deoxyguanosine triphosphate and thioguanine triphosphate into DNA and RNA, respectively, inhibition of *de novo* purine synthesis by methyl mercaptopurine nucleotides, inhibition of Rac1 inducing apoptosis, and inhibition of Rac1 inducing apoptosis. It is utilized mainly in relation

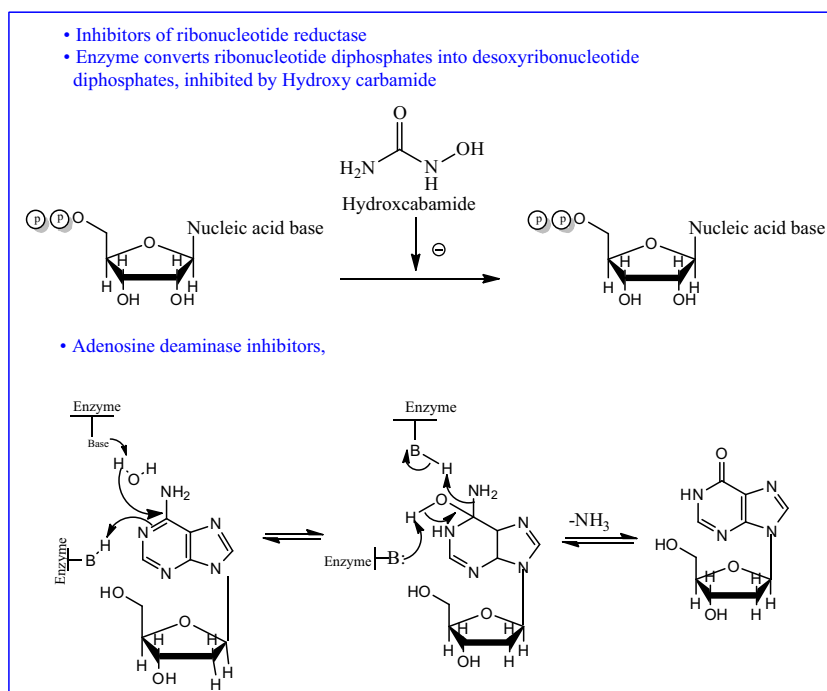


Figure 14: Mechanism of action of purine analogues.

to the remediation of leukemia, autoimmune disorders, and solid tumors. 6-MP is the most prescribed drug for acute lymphoblastic leukemia (ALL). Common side effects include rashes, flu-like symptoms, bone marrow suppression, hepatotoxicity, pancreatitis, nausea and vomiting, and bone marrow suppression. 6-MCP is commonly utilized to treat hematological malignancies, chronic inflammatory diseases, and transplantation acute leukemia in oral chemotherapy [161,162]. Some dose- and metabolism-dependent toxicity, such as leukopenia, thrombocytopenia, and malignancy, are linked to thiopurine methyltransferase (TPMT) deficiency. Other hypersensitivity reactions include rash, fever, arthralgia, pancreatitis, hepatitis, nausea, non-pancreatic stomach discomfort, and diarrhea [163].

2.1.2.3.2 Fludarabine

Fludarabine is a type of purine analogue that is the most widely used as a chemotherapeutic agent for B-cell CLL treatment dysfunction [164]. F-ara-ATP is the active metabolite in charge of the mechanism of action. This is due to competition with the naturally occurring metabolite deoxyadenosine triphosphate (dATP). The inclusion of a thymidylate in the template strand leads F-ara-ATP to compete with dATP for incorporation. The DNA polymerases are stopped or paused at the exact place in the DNA strand when a single F-ara-A molecule is integrated into it. Fludarabine's inhibitory property makes it a chain terminator

[164,165]. Hairy-cell leukemia, non-lymphomas, Hodgkin's, and Waldenström's macroglobulinemia are among the cancers that can be treated with this drug [166]. Fludarabine side effects include nausea, diarrhea, fever, rash, and dyspnea, as well as the development of myelosuppression. Fludarabine can cause cardiac and hematologic toxicity, as well as pain, paresthesia, visual disturbance, vomiting, anorexia, chills, and diaphoresis [167].

2.1.2.3.3 Pentostatin

Pentostatin is a purine analogue that induces T-cell apoptosis through adenosine deaminase inhibition. It is used as part of the conditioning regimen in HCT [168]. Pentostatin and related compounds, which are of particular interest in lymphoproliferative treatment, primarily target proliferative lymphocytes [169]. The key mechanism of pentostatin includes the inhibition of adenosine deaminase (ADA), causing dATP pools to accumulate, inhibiting ribonucleotide reductase, and changing the pools of other deoxynucleotides. High amounts of dATP, an inhibitor of RNR, the enzyme that removes the 2'-hydroxy group of the ribose ring during DNA modification, occur from accumulation. Hairy-cell leukemia, B-cell CLL, Waldenström's macroglobulinemia, T-cell leukemias, cutaneous lymphomas, lymphomas, glucocorticoid-refractory acute, and chronic graft-versus-host disease have all been treated with pentostatin [170]. The main toxicities of pentostatin involve myelosuppression, nausea and vomiting,

immunosuppression, acute renal failure, keratoconjunctivitis, fever, and elevations of liver function enzymes that have been recorded in higher doses. Neurologic toxicity, including somnolence, seizures, and coma, rarely appears in patients receiving standard-dose treatment [171].

2.1.2.3.4 Cladribine

Cladribine, or 2-CdA, is an analogue of purine that is resistant to ADA activity. Cladribine agent builds up in the lymphoid cells, likely because they are abundant in the deoxycytidine kinase enzyme [172]. Approved by the FDA in 1993 for medical use, this type of drug works primarily by incorporating itself into DNA as a fake nucleotide. This integration inhibits DNA strand elongation, DNA polymerase, and ribonucleotide reductase. Besides, when given as a single agent by continuous intravenous infusion, 40–90% of patients who underwent main therapy had significant responses (for 5–7 days, a 2-h daily infusion or subcutaneous bolus injections are used) [173]. Cladribine is most widely used for treating hairy cell leukemia and acute myeloid leukemia. Myelosuppression is the primary dose-limiting toxicity [174].

2.1.2.3.5 Clofarabine

Clofarabine is a purine analogue, which inhibits the enzyme ribonucleotide reductase and DNA synthesis [175]. It is analogous to cladribine as the hydrogen in the purine's 2-position is substituted with chlorine. In addition, DNA strand elongation is inhibited by triphosphate metabolites and ribonucleotide reductase is inhibited, decreasing the deoxynucleotide pools required for DNA synthesis [176]. Clofarabine is a drug that is used to treat acute myeloid and lymphoblastic leukemia that has relapsed or become resistant to other treatments [143]. Clofarabine was approved as an FDA drug for medical use in 2004. Clofarabine is recommended in pediatric patients with recurrent refractory lymphoblastic. Severe myelosuppression has been described as a dose-limiting adverse effect, including neutropenia, anemia, and thrombocytopenia. Therefore, the risk of serious infection could be increased, and non-hematological adverse dose-limiting effects, including rashes, reversible hyperbilirubinemia, and increased aminotransferase activity, have been identified [177,178].

2.1.2.3.6 Nelarabine

Tetrahydrofuran-3,4-diol is a prodrug of the deoxyguanosine analogue 9-beta-D-arabinofuranosylguanine (Ara-G). It is considered a purine nucleoside analogue that is good for

T cells. Ara-G triphosphate is then converted, accumulates preferentially in lymphoblasts, and inhibits DNA replication [179]. It reduces deoxynucleotide pools, which are required for DNA synthesis by inhibiting ribonucleotide reductase, and triphosphate metabolites are incorporated into DNA, where they inhibit strand elongation. In 2005, the FDA organization approved it for medical use. T-cell acute lymphoblastic leukemia (T-ALL) and T-cell lymphoblastic lymphoma are both treated with nelarabine (T-LBL) [180]. After infusion, nelarabine can be administered intravenously and is rapidly converted to Ara-G in the plasma by adenosine deaminase [179]. The active metabolite Ara-G has a half-life of 3 h, while nelarabine has a half-life of 30 min [171]. Some of the negative side effects include extreme sleepiness, seizures, peripheral neuropathies, cough, dyspnea, as well as paralysis, exhaustion, bone marrow suppression, and gastrointestinal and respiratory symptoms are the main side effects [181] (Figure 15).

2.1.3 Antibiotics

Antibiotics are generally used to inhibit cell division in chemotherapy and chemotherapeutic agents for microorganism-inserted cancer. Some of them introduce direct DNA damage and use antitumors to specifically inhibit topoisomerase II (Figure 16). They bind to DNA mainly through intercalation and obstruct DNA and RNA [182]. In 1940, Waksman and Woodruff discovered and published the first anticancer antibiotic (Actinomyces antibiotic "actinomycin D), which was extremely toxic to animals. Furthermore, Waksman and Woodruff subsequently proved the successful use of antibiotics in some childhood tumors in 1941. This was the beginning of the use of antibiotics in cancer chemotherapy, and since then, numerous natural or synthetic antibiotics have been used in cancer care. Some common antibiotic drugs are summarized in Table 3 [117,183,184].

2.1.3.1 Dactinomycin (actinomycin D)

Dactinomycin is a crystalline antibiotic, which is made up of two symmetric polypeptide chains attached to a central phenazone ring because of *Streptomyces parvulus* fermentation [185]. In early 1942, actinomycin was discovered and emanated from Selman Waksman's pioneering work on soil microorganisms [186,187]. Dactinomycin was approved by the FDA in 1964 for medicinal use. The mechanism(s) of action of the drug is through the inhibition of RNA (RNA polymerases; transcription) and DNA-dependent synthesis by its non-covalent interaction with unique DNA motifs

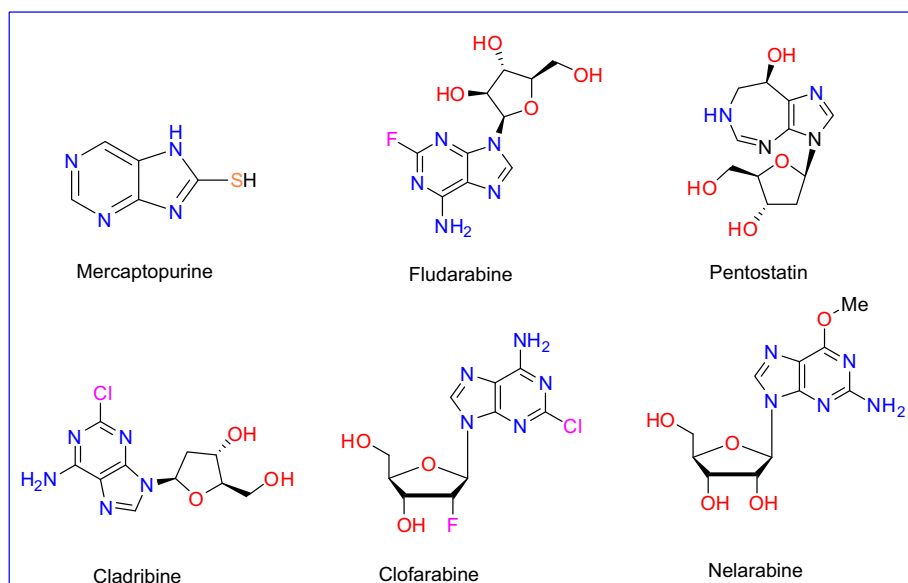


Figure 15: Mercaptopurine derivatives.

near transcriptional complexes. The minor grooves of DNA are bound to the DNA–RNA polymerase sites and have an “interfacial” (intercalator, noncovalent) action [188]. Dactinomycin is the most common treatment for pediatric tumors like Ewing sarcoma, Wilms tumor, and embryonic rhabdomyosarcoma. It has a significant role in the treatment of testicular tumors in choriocarcinoma, and its dose-limiting toxicity in mucositis and vein extravasation causes extreme necrosis of the tissue [189,190].

2.1.3.2 Bleomycin (BLM)

Bleomycin (BLM) is also known as Blenoxane. It is commonly used as an antibiotic glycopeptide antitumor generated by the *Streptomyces* bacterium. Similar to those obtained with radiotherapy, BLM induced breaks in DNA [191]. Bleomycin was first approved by FDA in 1973 [192]. The mechanism of action of bleomycin includes free radical induction. Bleomycin forms the Fe(II) complex, which is oxidized to Fe(III). This causes free radicals to reduce oxygen, which causes single-

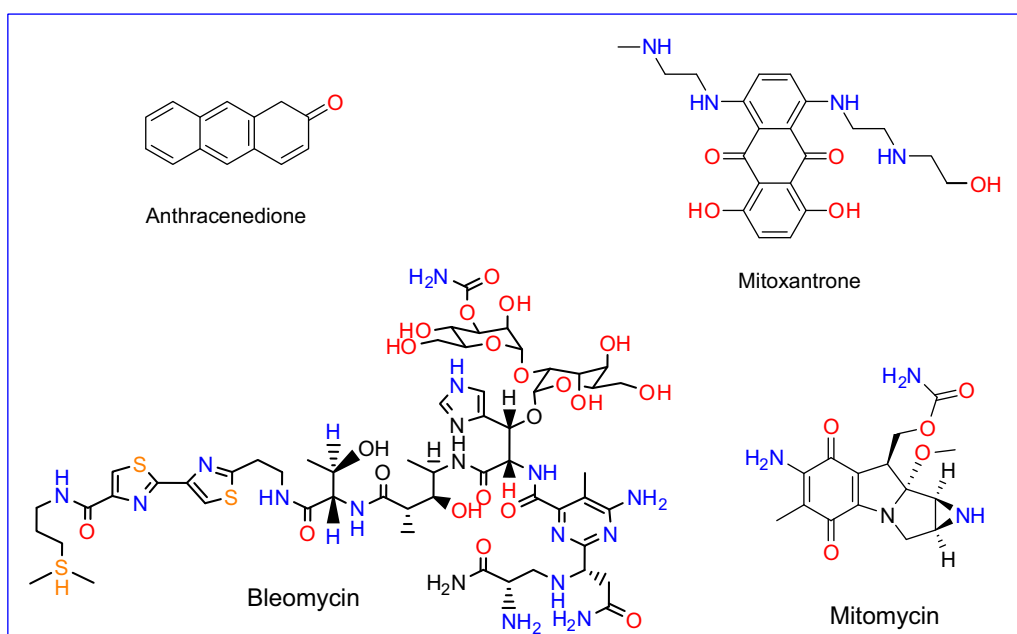


Figure 16: Antibiotic drug structures.

Table 3: Antibiotics drugs

Antibiotics	Drugs	Use
Dactinomycin	—	Pediatric tumors, such as Wilms tumor, Ewing sarcoma, embryonal rhabdomyosarcoma, testicular tumors, and choriocarcinoma
Anthracedione	—	Prostate cancer, which is reticent to hormonal therapies, lymphomas, and multiple sclerosis relapse-remitting, acute leukemias
Bleomycin	—	Hodgkin's lymphoma, head and neck penile cancer, testicular cancer, cervical and vulvar squamous cell carcinomas
Mitomycin	—	Solid tumors
Anthracyclines	Mitoxantron	Myelogenous leukemia and acute lymphocytic leukemia
	Doxorubicin	Acute leukemia, lymphoma, cancer of the liver, breast, and ovaries, Kaposi's sarcoma, and cancer of the bone
	Epirubicin	Breast cancer, gastric and esophageal malignancies, and soft malignancies tissue sarcomas
	Idarubicin	Lymphoma

and double-strand breaks in cellular DNA, leading to damaged cells becoming genomically unstable. It also prevents the angiogenesis of tumors [193]. Bleomycin removal correlates well with patients with renal impairment and should be given in lower doses based on their creatinine clearance. BLM is inactivated in the tissues by bleomycin hydrolase. In addition, tissues that lack this enzyme are more sensitive to the toxic influences of the drug, such as the lungs and skin [194]. It is recommended for palliative treatment of Hodgkin's lymphoma, head and neck penile cancer, testicular cancer, and cervical and vulvar squamous cell carcinomas [195,196]. Bleomycin is easily cleaned out of the lungs, spleen, and kidney blood and concentrated in the liver and epithelial tissues. Approximately 80% is excreted within 24 h in the urine [197]. The major important toxic influences of bleomycin are included in the lungs and skin [198].

2.1.3.3 Mitomycin

Mitomycin is one of the common drugs derived from *Streptomyces caespitosus*. It was approved by the FDA in 2002. It inhibits DNA synthesis after intracellular activation by responding to DNA similar to alkylating agents. Mitomycin inhibits DNA synthesis and cross-links DNA at the O6 N₂ positions of guanine and the N₆ position of adenine [199]. This drug is utilized for the treatment of solid tumors; Mitomycin C has a cumulative and dose-dependent effect. When Mitomycin is used by itself, the occurrence of nephrotoxicity is less than 1%; however, in conjunction with 5-FU, nephrotoxicity occurs more frequently [200]. It has been used as a cytotoxic and is active against several tumors, esophagus, and bladder, including breast, stomach, and non-small cell lung cancer [108]. Side effects involve skin irritation (dermatitis) and ocular irritation because of contact or toxic contact conjunctivitis, headaches, nausea, dizziness, and hair and menstrual alterations [201].

2.1.3.4 Mitoxantrone

Mitoxantrone is a synthetic antibiotic commonly utilized as a chemotherapy medication for solid tumor therapy [202]. It is a medication accepted by the US FDA to treat adult acute myeloid leukemia in 1987. It was used for treatment of worsening relapsing-remitting multiple sclerosis in 2000 [203]. The mechanisms of action of this drug involve intercalation with the DNA molecules, which in turn induces by inhibiting topoisomerase II, and it disrupts single- and double-stranded DNA and decreases DNA repair. Mitoxantrone greatly inhibits the development of macrophages as well as B and T lymphocytes. Other cells are also killed, and migration of the activated leukocytes is suppressed, such as antigen-presenting cells [204]. Mitoxantrone greatly inhibits the development of macrophages in addition to B and T lymphocytes. Other cells are also killed, and migration of activated leukocytes is suppressed, such as antigen-presenting cells. Mitoxantrone is widely used to treat prostate cancer; it is resistant to hormonal therapies, lymphomas, and multiple sclerosis relapse-remitting acute leukemia [205]. There are three essential side effects of mitoxantrone, such as serious leukopenia, cardiac toxicity, and acute myelogenous leukemia. Furthermore, patients treated with mitoxantrone often run a high risk of opportunistic infections [204,206].

2.1.3.5 Anthracyclines

Anthracyclines are part of many procedures that are used to treat pediatric cancer. According to most groups' oncology treatment classes, the hematologic toxicity of anthracycline agents is equivalent to their cardiotoxicity, and they have been utilized in different hematological and solid tumor malignancies (Figure 17) [207]. However, hematological toxicity, alopecia, and cardiotoxicity are the main side effects to be considered for these types of drugs [208].

2.1.3.5.1 Daunorubicin

Daunorubicin is just a cytotoxic antibiotic produced with anthracycline by *Streptomyces peucetius* subsp. It received approval from the FDA in the United States in 1998. The antitumor effects of daunorubicin are back to intercalation by multiple mechanisms affecting both anti-mitotic and anti-cytotoxic activities. It functions by intercalating the DNA base pairs to uncoil the DNA double helix and inhibit the topoisomerase II enzyme, resulting in single- and double-strand breaks, thereby inhibiting the synthesis of DNA and RNA. Daunorubicin also inhibits the function of the polymerase enzyme that dysregulates gene expression, leading to free radical DNA damage and eventually leading to apoptosis, mitochondrial injury, and programmed death of cells [209]. This drug is being used to treat solid tumors that develop in the breast bile ducts, endometrial tissue, the esophagus, and the liver, acute myelogenous leukemia, and acute lymphocytic leukemia. The main route of removal is primarily through the bile duct, with some urine excretion [209,210]. Daunorubicin has some side effects, such as various skin and hypersensitivity reactions in addition to severe myelosuppression, and other adverse events that occurred frequently were nausea, neutropenia, stomatitis, rash, mucositis, vomiting, anemia, and neutropenia [211].

2.1.3.5.2 Doxorubicin (Adriamycin)

Doxorubicin is the most commonly utilized anthracycline antibiotic, and it has one hydroxyl group that distinguishes doxorubicin from daunorubicin [212]. It was the first FDA-confirmed anticancer nanomedicine for the treatment of certain forms of cancer in 1995. Intercalation into DNA and the inhibition of topoisomerase II activity tend to be its mechanism of action, thereby blocking DNA synthesis and giving rise to cytotoxic and apoptotic cell death [213]. Dox is used to treat a wide variety of human cancers, including acute leukemia, lymphoma, cancer of the liver, breast, and ovaries, Kaposi's sarcoma, and cancer of the bone [214]. Dose-dependent permanent side effects arise from Dox administration, some of which give rise to the development of cardiomyopathy, dyspnea, exercise intolerance, hepatotoxicity, and nephropathy [214].

2.1.3.5.3 Epirubicin (Ellence)

Epirubicin is a DNA-damaging anticancer drug. Consequently, epirubicin lowers mRNA due to better efficacy and fewer side effects, and it is favored over doxorubicin [106,215]. Epirubicin was confirmed by the FDA in 1999 to treat some types of cancer. The mechanism of action of Epirubicin is adoxorubicin drug resistance mechanisms P-gp and mutations in

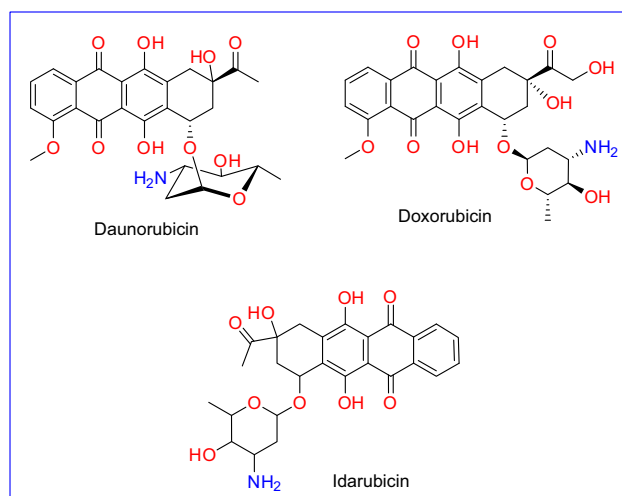


Figure 17: Anthracycline drug structures.

topoisomerase II are involved in drug resistance, analogues that cause DNA strand breaks due to damage caused by topoisomerase II or free radicals. Epirubicin is licensed for use in breast cancer patients and shows efficacy in both gastric and esophageal malignancies and soft malignancies. Tissue sarcomas are a primary target of treatment with epirubicin. Most of its metabolites are excreted via the biliary system [216,217]. However, severe side effects, including acute myelotoxicity and cumulative dose-related cardiotoxicity, have limited its clinical use [218].

2.1.3.5.4 Idarubicin

Idarubicin is a daunorubicin analogue that lacks the methoxy group on the C4 aglycone. It is an anthracycline that has a longer half-life than doxorubicin and is used to treat lymphoma. In preclinical studies, idarubicin demonstrated a better therapeutic index, particularly in terms of the rate of cardiotoxicity [219]. Idarubicin was FDA-approved for the treatment in 1990 [220]. This family of molecules' antitumor mechanism involves interactions with DNA in a variety of ways, including intercalation, DNA strand breakage, and inhibition of the topoisomerase II enzyme. Some antineoplastic drugs that contain saccharides include etoposide, a semisynthetic-d-glucopyranoside analogue of podophyllotoxin. This medication inhibits DNA synthesis by forming a topoisomerase II and DNA complex [221]. IDA, which is used in acute myelogenous leukemia and ALL treatment, is extremely lipophilic compared to DOX and DNR and is imported into cells faster than the anthracyclines described above [222]. Idarubicin can have severe blood and bone marrow disorder side effects such as myelosuppression, and gastrointestinal, dermatologic, cardiologic, hepatic, or renal complications [223].

2.1.4 Topoisomerase inhibitors

Topoisomerases have been regarded as important targets for therapeutic intervention due to their crucial role in DNA replication and recombination, as well as transcription and repair, as summarized in Table 4. These enzymes can change DNA architecture, which is important in the cell cycle.

2.1.4.1 Topoisomerase inhibitors of topoisomerase

The inhibitors of topoisomerase I and topoisomerase II compounds inhibit topoisomerase enzymes in the S stage of the cell cycle by altering the phosphodiester backbone of DNA strands to cause changes in the DNA structure. Classical examples of topoisomerase I inhibitors are camptothecins (CPTs), topotecan, and irinotecan derivatives inhibiting topoisomerase I, and topoisomerase II inhibitors are antitumor antibiotics (doxorubicin) [183]. Pemetrexed is one of the cytotoxic agents used most often in non-squamous NSCLC conditions [224].

2.1.4.2 Topoisomerase I (TOP1)

Topoisomerase I (TOP1) is an enzyme that is present in both prokaryotes and eukaryotes. TOP1 is an important enzyme in the mammalian system for normal development [225]. These enzymes are mainly responsible for relaxing supercoiled DNA positively and/or negatively. To form a 5'-phosphotyrosine intermediate, Topia enzymes cleave a single strand of supercoiled DNA transiently. These enzymes contain *E. coli* Top A, which relaxes negatively supercoiled DNA preferentially [226].

2.1.4.2.1 CPT

CPT is a quinoline alkaloid inhibitor specific to the cytotoxic TOP1 utilized in traditional Chinese medicine to treat cancer [227]. CPT inhibits DNA and RNA (including ribosomal RNA) synthesis and causes DNA harm. These scientists noted that during the S-phase of the cell cycle, CPT is the most potent and predicted that the DNA replication

fork could play a role in cell death induced by CPT. Later studies suggested that at both S and G2 levels, CPT stopped the cell cycle, which was needed for CPT cytotoxicity [228]. During the treatment of many cancers, including colorectal cancer, liver cancer, lung cancer, and bladder cancer, CPT is commonly used [229]. The use of CPT is restricted by disadvantages such as water insolubility, low target ability, and natural tissue toxicity. To avoid these drawbacks, lower molecular weight drugs are conjugated to create higher molecular weight polymers [230].

2.1.4.2.2 Irinotecan (Camptosar)

Irinotecan is one of the considered derivatives of water-soluble CPT, which also inhibits TOP1. It is transformed into an effective metabolite, SN-38, by carboxylesterases after administration [231]. Irinotecan was approved to treat cervical, lung, and ovarian cancers in Japan in 1994 as the first member of this drug community. Its use was authorized in Europe in 1995 and the USA in 1996 [232]. The ternary irinotecan-TOP1-nicked DNA complex turns off the nicked strand's relegation and prevents the release of topoisomerase. Collision with advancing replication forks of the shaped complex results in the formation of a lethal double-strand break (DSB). This leads to the fact that checkpoint signaling for DNA damage results in DNA replication failure, breaks of the DNA chain, and cell death [233,234]. This type of drug is recommended to be used in colorectal cancer patients, and in patients with lung cancers [235,236]. The much more common adverse effects of irinotecan use are diarrhea, vomiting, bone marrow suppression, and fever. Colitis, anaphylactic reaction, and thrombosis are other side effects that have been reported [237].

2.1.4.2.3 Topotecan (Hycamtin)

Topotecan is a semi-synthetic derivative that is structurally similar to CPT. It is an inhibitor of TOP1 and has demonstrated repeated disease as a single agent's activities and remains the only second-line agent that has been recommended by the FDA and can be used in patients with SCLC [235,238]. In 1996, the US FDA approved intravenous

Table 4: Topoisomerase inhibitor drugs of topoisomerase

Topoisomerase inhibitors	Drugs	Uses
Topoisomerase I	CPT	Liver cancer, lung, and bladder
	Irinotecan	Colorectal cancer patients and in patients of lung cancers
	Topotecan	Metastatic ovarian carcinoma, relapsed and refractory cervical cancer
Topoisomerase II	Etoposide	Small cell lung cancer and testicular cancer Hodgkin's and non-Hodgkin's lymphomas, gastric cancer

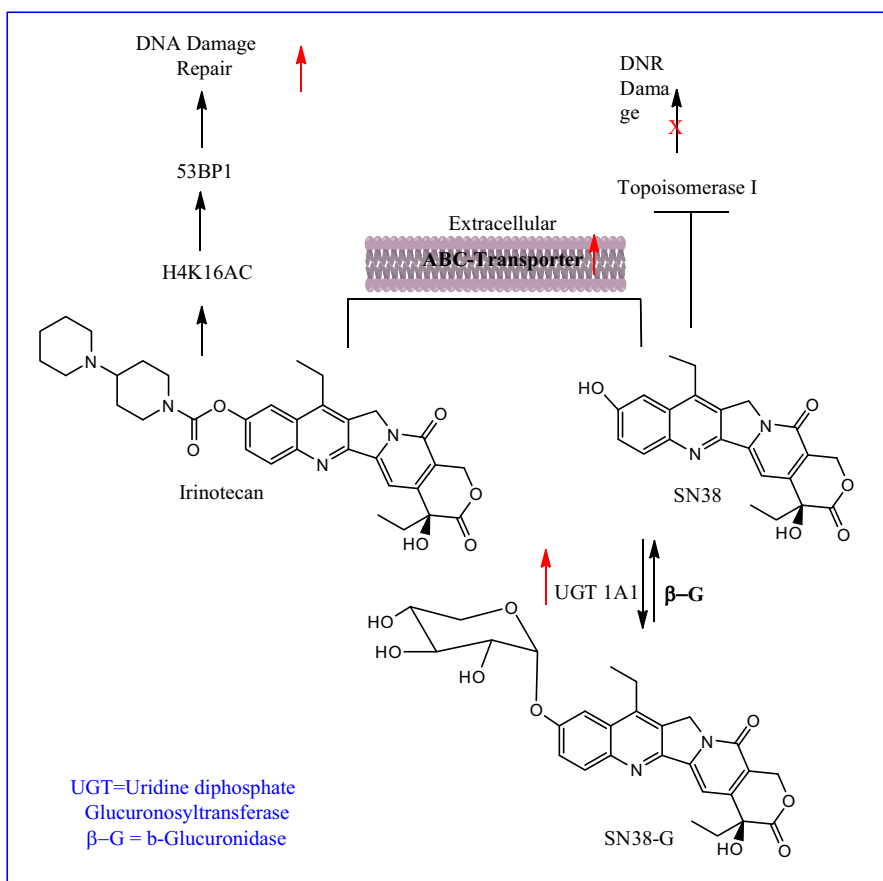


Figure 18: Mechanism of action and resistance of irinotecan to SN-38.

topotecan (IV) infusion for many forms of cancer, and its oral capsule formulation was approved in 2007 [239]. Topotecan's mechanism of action precludes topoisomerase from relegating split DNA strands caused by the collision of DNA replication forks with a ternary complex of TOP1, DNA, and topotecan, resulting in DNA damage. Topoisomerase inactivation causes apoptosis and cell death, as shown in Figure 18 [240,241]. Topotecan is approved as a second-line treatment in case of cell lung cancer, as well as for metastatic ovarian carcinoma, relapsed, and refractor cervical cancer [238]. Toxicities regarding topotecan involve bone marrow suppression, diarrhea, nausea, constipation) stomatitis, and fatigue [143].

2.1.4.3 Topoisomerase II

Type II DNA topoisomerases (TOP2), Class II topoisomerase enzymes, are responsible for resolving DNA topological problems (Figure 19). Enzymes tackle DNA topological challenges by causing transitory double-stranded breaks in critical biological processes, including transcription, replication,

recombination, DNA repair, chromatin remodeling, chromosome condensation, and segregation [242].

2.1.4.3.1 Etoposide (Etopophos)

Etoposide is a variety of alkaloids produced from the plant etoposide *Podophyllum peltatum* mandrake plant in the late S and G2 stages of the cell cycle; it has cell cycle-specific action [213]. It was approved by the FDA and consumed as a cancer therapy in 1983 [243]. The action mechanisms of the etoposide cell cycle are predominantly in the later S and G2 phases. DNA unwinding replication is aided by topoisomerase II. It produces and repairs double-stranded DNA breaks during the replication process. Etoposide binds to topoisomerase II in a reversible manner, preventing it from repairing double-stranded DNA breaks. The etoposide–topoisomerase II complex initiates a mutagenesis and cell-death pathway in tumor cells with higher levels of topoisomerase II enzymes, which is more efficient in tumor cells, as shown in Figure 20 [244]. Etoposide is used to treat various cancers, which include small cell lung cancer and testicular cancer, and often a bone marrow conditioning

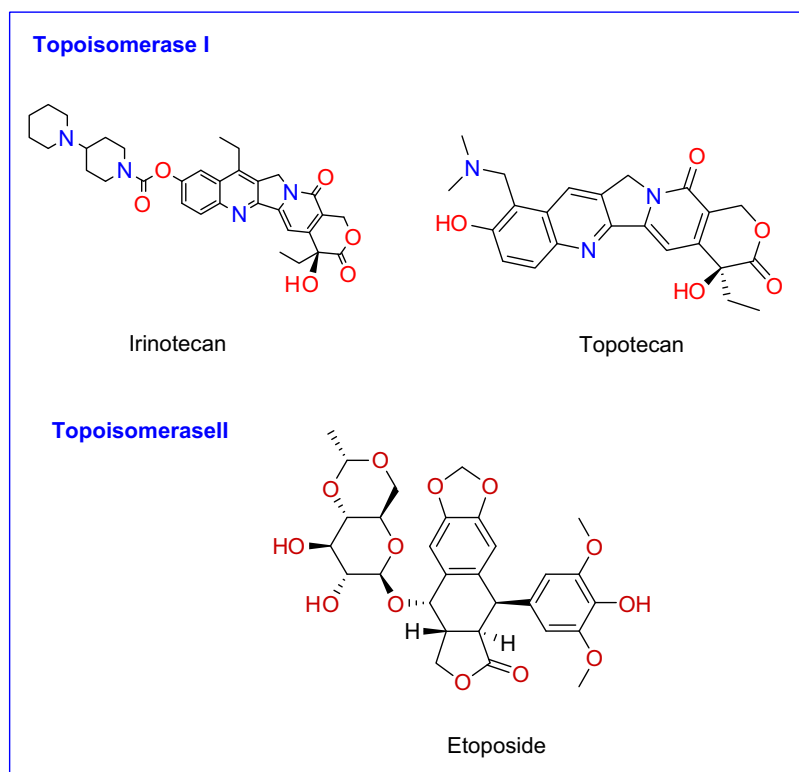


Figure 19: Topoisomerase drug structure.

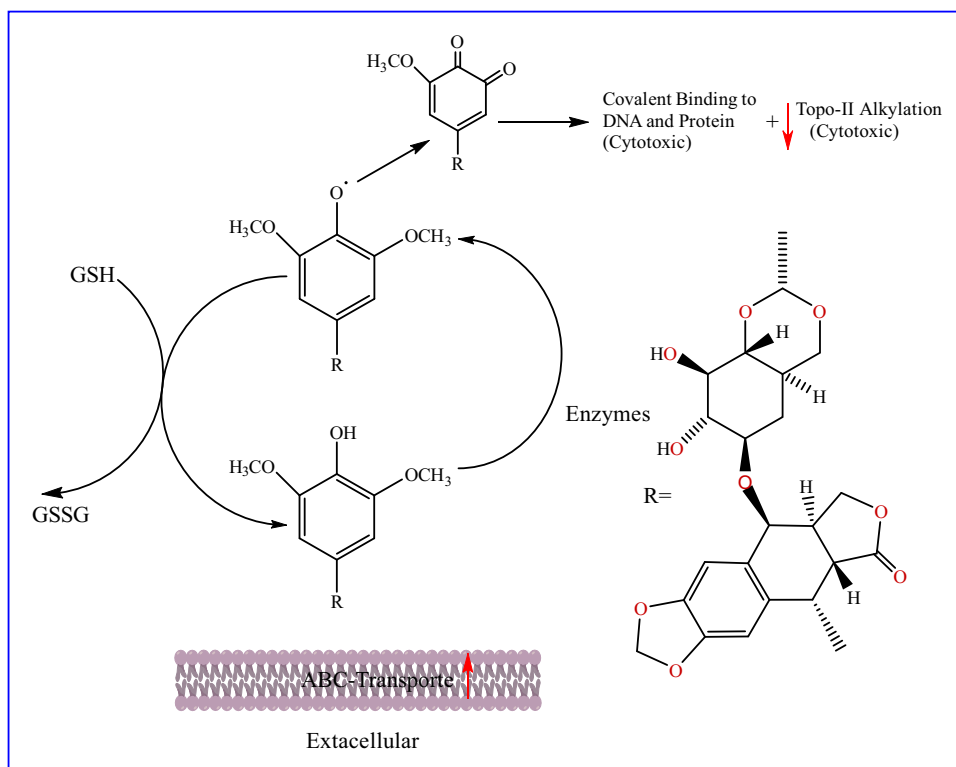


Figure 20: Mechanism of action and resistance of Etoposide.

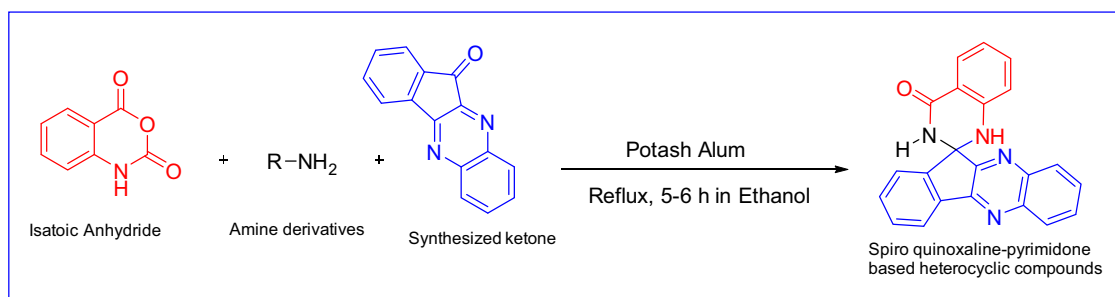


Figure 21: Spiro compounds as a potent anticancer agent.

agent in combination with other chemotherapeutic agents and Hodgkin's and non-lymphomas, Hodgkin's gastric cancer, and ovarian cancer [245,246]. The side effects of this drug include myelosuppression, anorexia, nausea/vomiting, alopecia, mucositis, diarrhea, fever, bronchospasm, hypersensitivity reactions, skin alterations in dyspnea, hypotension, and radiation recall [90].

2.1.5 Recent heterocyclic compound-based anticancer reactivity

Spiro heterocyclic compounds have crucial pharmacological biological and chemical properties such as antimicrobial, antiviral, psychotic, anti-inflammatory, and anticancer [247]. Sustainable protocols for the synthesis of novel spiro

quinoxaline-pyrimidone-based heterocyclic compounds were successfully developed. Due to the high demand for Spiro heterocyclic compounds, currently, they are used as potent inhibitors of the proliferation of cancer cell antibacterial applications [248–250]. Therefore, it is tremendously important to develop synthetic methodologies to prepare Spiro heterocyclic compounds. Bhupesh and co-workers confirm that the spiro quinoxaline-pyrimidone-based heterocyclic compounds (RD 1–RD 12) were synthesized by using mild conditions and characterized via NMR, IR, and mass analysis techniques [251]. It is important at this stage to discuss the preparation strategy of these valuable heterocyclic compounds. A multi-component reaction methodology was used; the crude product obtained was collected, followed by simple purification to get the desired product in powder form. A wide range of pharmaceutical

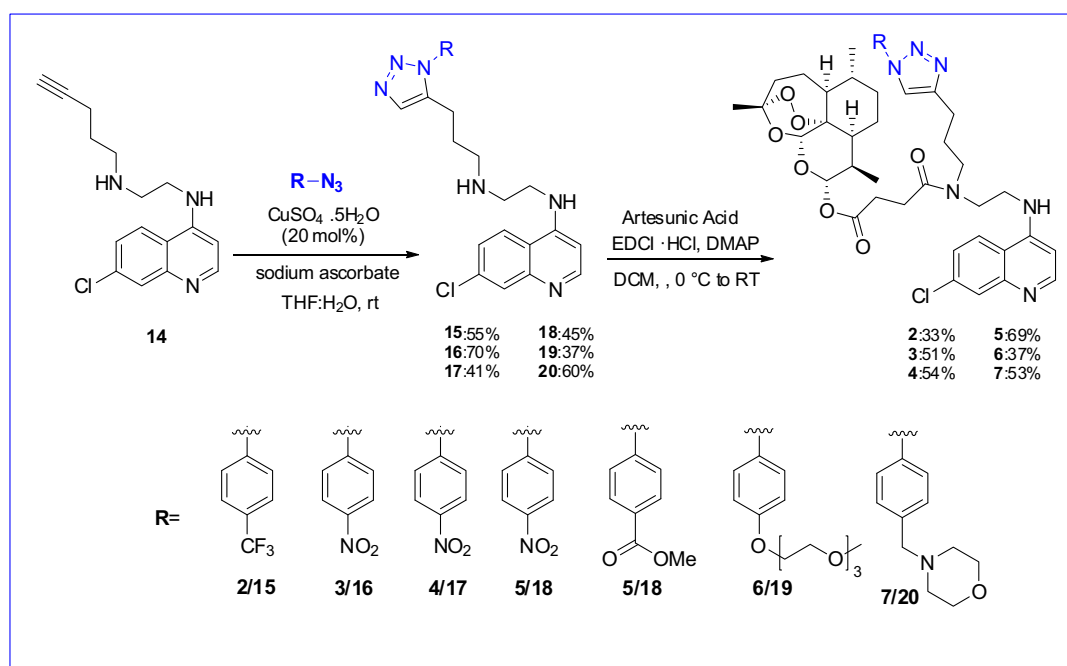


Figure 22: Synthesis route of peroxide-based hybrid compounds.

applications are used to demonstrate the potent activity of these compounds. A minimum inhibitory concentration was observed for all prepared spiro compounds toward bacteria by observing turbidity in the vial. In addition, various activities, such as the binding strength with DNA,

molecular docking study, and cytotoxicity assay, were carried out to evaluate the biological activity. These studies demonstrated that all the spiro compounds bind efficiently with certain receptors and may work as a potent anticancer agent (Figure 21).

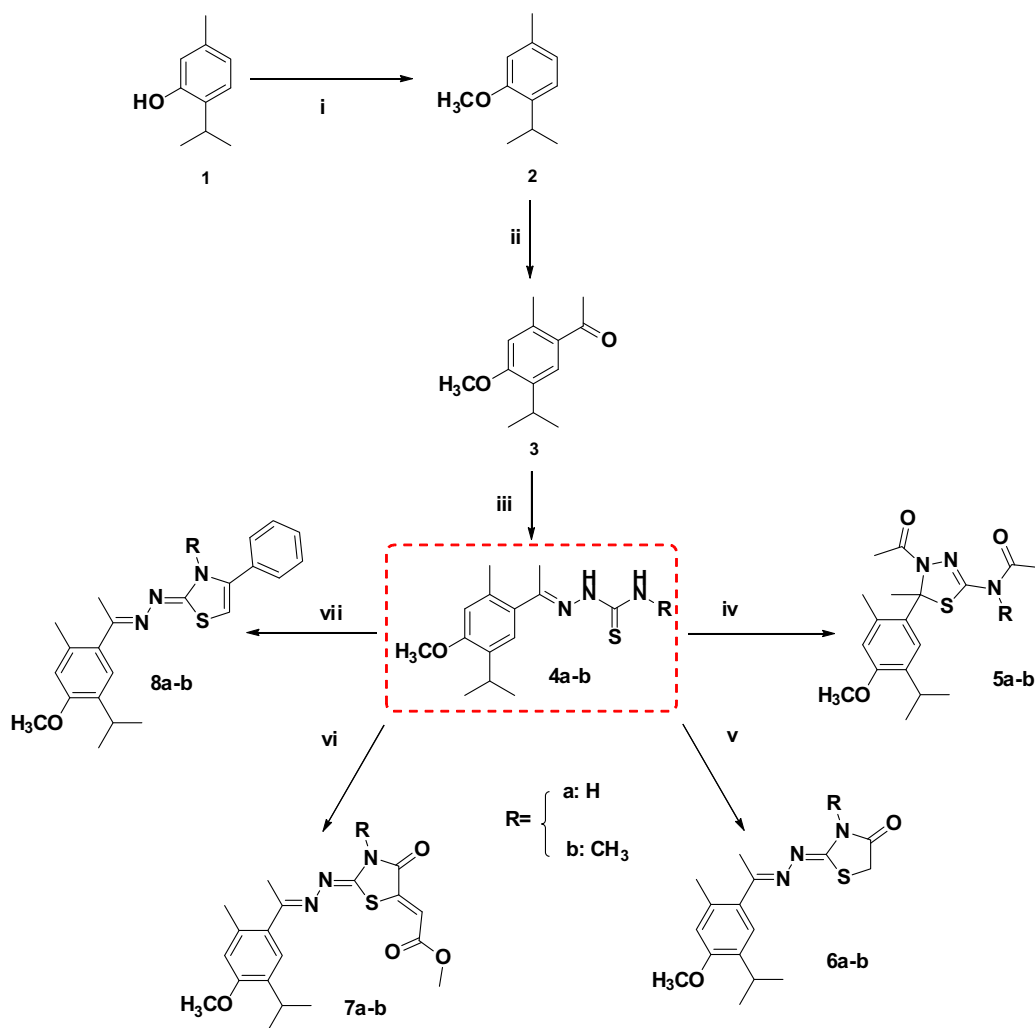
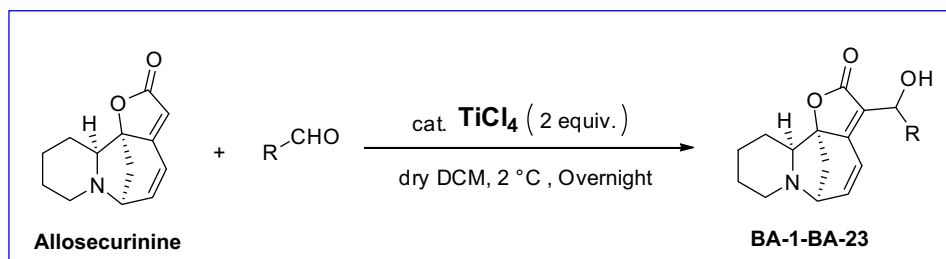


Figure 23: The synthetic procedures for the target thiosemicarbazones and their cyclization. Reagents and conditions: (i) CH_3I , K_2CO_3 , acetone, 12 h; (ii) AcCl , AlCl_3 , CH_2Cl_2 , 0°C , 2 h; (iii) Thiosemicarbazides, AcOH (few drops), EtOH , reflux, 12 h; (iv) Ac_2O , $\text{N}(\text{Et})_3$, CH_2Cl_2 , 5 h; (v) $\text{BrCH}_2\text{COOEt}$, sodium acetate, EtOH , reflux, 8 h; (vi) DMAD , sodium acetate, EtOH , reflux, 4 h; (vii) Phenacyl bromide, sodium acetate, EtOH , reflux, 4 h.



Scheme 1: Synthetic route of Allosecurinine derivatives.

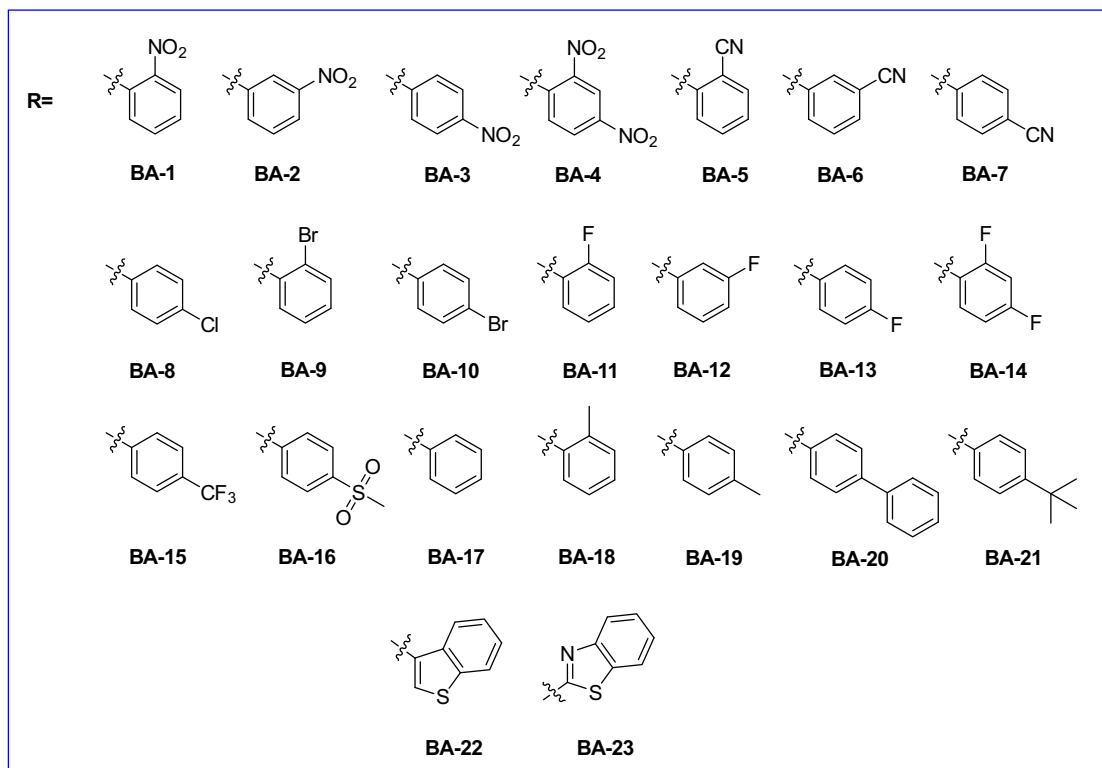
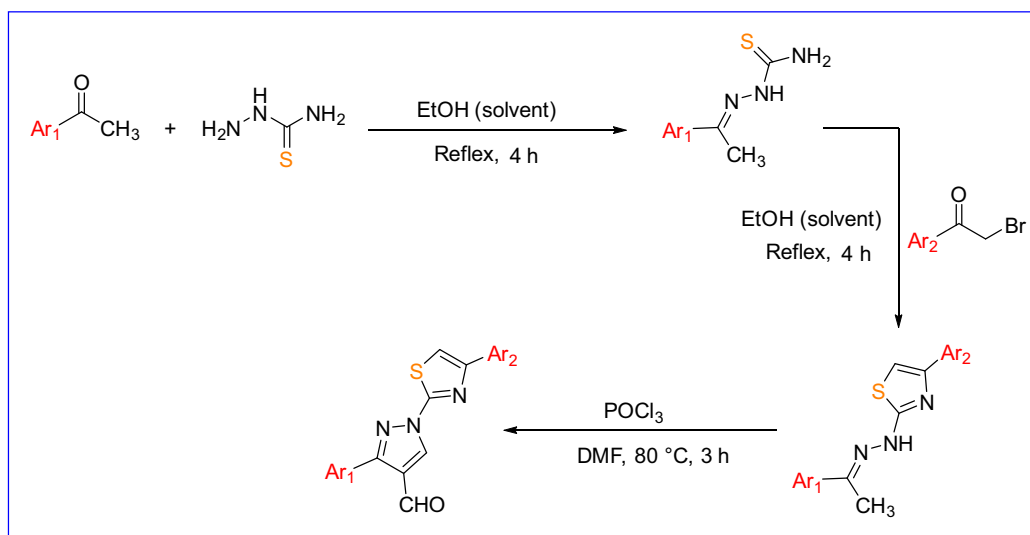


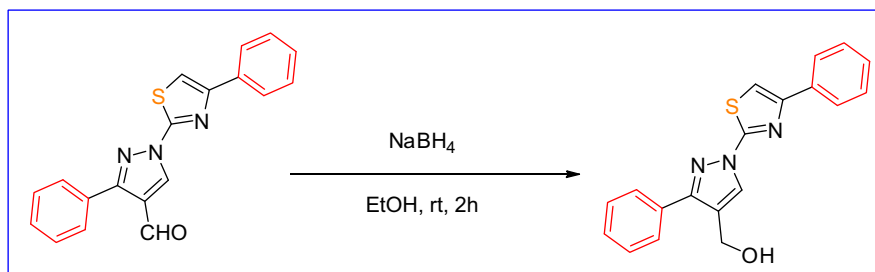
Figure 24: Structures of substrate scope for target compounds.

In addition to this work, another research paper was published in 2022 by Svetlana and co-workers in which novel peroxide-based hybrid compounds were synthesized and characterized, which proves their applications as inhibitory activity against SARS-CoV-2 and leukemia cell lines. Notably, the authors found that some of these hybrid

compounds, such as arsenic and peroxide-based hybrid compounds, are more potent against K562 leukemia and the reference anti-leukemia drug doxorubicin with high inhibition values (81–83%). A new class of peroxide-based hybrid compounds was demonstrated by performing a click reaction on the alkyne group of the linker and the



Scheme 2: Total synthesis scheme of the target compounds.



Scheme 3: NaBH₄ as a reducing agent.

aromatic azide group (Figure 22). The resulting compounds were tested against SARS-CoV-2 and cancer to prove their applications as an excellent candidate drug to treat cancer and SARS-CoV-2 infections.

Auhmani and co-workers published a new research paper in which a novel heterocyclic scaffold as an anticancer agent based on thymol [252]. The target compounds were synthesized via cyclization of the corresponding thymol compounds followed by characterization of the structure by IR, ¹H-NMR, ¹³C-NMR, HRMS, and single-crystal X-ray diffraction. Interestingly, some target compounds, such as limonene-based thiosemicarbazone derivatives, show significant inhibitory effects on the growth of cancer cell lines and prostate cells. In contrast, due to the high biological activity of some thiosemicarbazones such as thiadiazoles, thiazoline, and thiazolidin-4-ones as anti-inflammatory, antidiabetic, and anticancer, some compounds containing 1,3,4-thiadiazole scaffold in their structure exhibits significant antitumor activity against the tested cell lines. Figure 23 shows the synthetic procedures for the target thymol compounds.

In 2023, Xu and co-workers published a new research paper in which various Allosecurinine derivatives were synthesized along with the study mechanism of action of these compounds as anticancer agents [253]. The authors also tested the structure–activity of these anticancer families against nine human cancer cell lines and the possibility of working. A library of 23 novel Allosecurinine derivatives was designed and synthesized using the Baylis–Hillman reaction. The interaction between Allosecurinine and various types of aldehydes was facilitated by TiCl₄, as shown in Scheme 1 and Figure 24.

After the synthesis of Allosecurinine derivatives, anti-tumor activities *in vitro* and mechanism studies exhibited that these compounds could induce mitochondrial membrane potential within cancer cells as well as decrease the levels of antiapoptotic protein and induce apoptosis in leukemia cell lines. Interestingly, compound BA-3 proved to be the best among Allosecurinine derivatives to induce cell death through apoptosis by analysis using FCM technology as well as the high activity against tumor activities. To the

best of the author's knowledge, this is the first example of the synthesis and development of Allosecurinine derivatives in the discovery of anticancer drugs, especially for leukemia.

Recently, a new study has been published, which focused on design, synthesis, and antiproliferative activities for a series of thiazolyl pyrazole hybrid derivatives as novel heterocyclic compound-based antitumor agents [254]. The antiproliferative effects of the target compounds were biologically evaluated, and the structure–activity relationship (SAR) was tested against cancer and normal cells by using an MTT assay. Initially, the synthetic approach of the target compounds was conducted via conversion of substituted acetophenone under Vilsmeier Haack conditions (POCl₃, DMF at 80°C for 1 h) to generate the target aldehyde compounds in high yield by the neutralization reaction (Scheme 2).

On the other hand, the final product was studied further by converting the aldehyde functional group in the target compounds into primary alcohol to examine the antitumor reactivity of these compounds by using NaBH₄ as a reducing agent (Scheme 3).

The target compounds were investigated by ¹H-NMR and ¹³C-NMR spectroscopy. The functional group of aldehydes clearly disappeared and reduced to –OH proton. Furthermore, the compounds under study had a higher antiproliferative effect in the cancer cells. Remarkably, the targeted compounds appear to have a pharmacokinetic property, which can make them a potent drug candidate after successful molecular modifications.

3 Conclusion

The chemistry of nitrogen-, oxygen-, and sulfur-containing monocyclic, polynuclear, and heterocyclic compounds have a significant role in biological activities and prospects for medicinal chemistry. Cancer is considered the most common cause of death across the world. The time from the past up to

the present has witnessed a significant development in the field of cancer therapy by the development of innovative delivery technologies. Many cellular and molecular pathways growth in the sector of the treatment of cancer have been identified. Regrettably, all recently obtainable anticancer medications had flaws like undesirable effects and refusal to accept. In the current research, the most potent and privileged-based drugs are highlighted, which we believe are the most successful treatment tools in the fight of current years. These compounds have been divided into ten groups based on similarities in their chemical structures. The use of chemicals has been the most effective treatment approach in recent years. They show promise as candidates for the discovery and development of cancer drugs. This work hopefully presents assistance for chemists in medicinal areas to obtain a powerful design and development of new, strong anticancer drugs.

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