https://doi.org/10.48047/AFJBS.6.12.2024.2139-2158

African Journal of Biological Sciences

Journal homepage: http://www.afjbs.com

Research Paper Open Access

CANCER TARGETING THROUGH BIOMOLECULES: ROLE OF HETEROCYCLES CONTAINING NITROGEN, OXYGEN AND SULPHUR

Pol Sagar laxman[1], Nitin Kumar mittal[2*]

[1]Research Scholar, Lords University Bhiwadi Chickani Road Alwar Rajasthan India.

[2*]Professor, Lords University Bhiwadi Chickani Alwar, Rajasthan, India.

Corresponding Author*

Nitinkumar Mittal

Professor, Lords University, Alwar Rajasthan.

Email Id: mittalnitin1901@gmail.com

Article History
Volume 6, Issue 12, 2024
Received: 30 May 2024
Accepted : 30 June 2024
Doi:
10.48047/AFJBS.6.12.2024.2139-2158

Abstract

The heterocycle molecules and fragments are considered to be true the basis of medicinal chemistry due to the fact that they are naturally adaptable, possess particular physicochemical properties, and are widely used in pharmaceuticals. An extensive number of other drugs, in addition to those that have already been introduced to the market, are currently undergoing research to see whether or not they have the potential to be helpful against various types of cancer. In particular, the dynamic core scaffold and inherent adaptability of these molecules have been employed in research pertaining to the treatment of cancer. Although heterocyclic compounds are not yet ideal, there is reason to believe that they could be effective anticancer treatments. Within this article, we will provide a summary of the most significant medicinal applications of heterocyclic active chemical families and compounds. In every region of the world, cancer continues to be a substantial barrier to healthcare. Despite the fact that there are a lot of anticancer treatments available on the market, a significant proportion of them are ineffective, have severe adverse effects, are not safe, or are resistant to other types of the disease. In this article, we have discussed heterocycles that contain nitrogen, which include Indole, Pyrimidine, and quinoline derivatives; heterocycles that contain oxygen, such as Bis coumarin compounds and coumarin derivatives; heterocycles containing sulphur, such as Glitoxin and Benzothiazole and thiazole derivatives; and heterocycles that contain sulphur, which are utilised in the treatment of various cancers. Additional topics that have been discussed include the molecular mechanisms of action and cellular targets of these drugs.

Keywords: Anticancer, Nitrogen, Oxygen, Sulphur, Heterocyclic compounds

Introduction

Cancer, which is recognised as one of the main causes of death, is a significant contributor to the enormous financial and health care burden that society faces[1]. The improvements that have been made in cytogenetics and molecular biology have shed light on the intricate molecular pathways that are responsible for the growth and formation of tumours[2]. The chromosomal

aberrations, oncogene amplification, loss of tumour suppressor genes, up-regulation of growth factors and their receptors, activation of tumor-related signal transduction pathways, and other variables are all components of this mechanism[3]. Researchers are looking for novel anticancer medications that have a high selectivity, minimal side effects, and the ability to overcome drug resistance in order to successfully cure the tumours that patients are suffering from[4]. When it comes to the fight against cancer, scientists have made significant strides, shifting their attention from cytotoxic agents to the development of targeted therapies and nanomedicines[5]. The anticancer effects of targeted drugs and nanomedicines can be mediated by a wide variety of pathways, which can lead to remarkable outcomes[6][7].

The molecule that is produced as a result of the substitution of the carbon atom in the parent scaffold with one of the other three elements sulfur, nitrogen, or oxygen is referred to as a heterocyclic[8]. It is the presence of the altered atoms as well as the size of the scaffold that has an effect on the chemical and physical properties of the product. By altering the structure of a molecule's heterocyclic ring, it is possible to alter the anti-inflammatory, antibacterial, anti-tumor, antiviral, and antifungal properties of the molecule[9]. All kinds of molecules, including alkaloids, vitamins, hormones, colours, antibiotics, herbicides, and medications, are derived from heterocyclic compounds found in nature that contain nitrogen. These chemicals are derived from heterocyclic compounds. Alkaloids are a tiny class of naturally occurring compounds that contain nitrogen atoms[10]. There are several examples of alkaloids, including morphine, caffeine, nicotine, thiamine, and atropine. These molecules are classified according to the number of nitrogen atoms that are present within the ring, which can be three, four, five, or six. All of these numbers are possible. Imidazole and pyrazole both have two nitrogen atoms, whereas pyrrole and azoles have five-membered rings that contain only one nitrogen atom each. Pyridine and pyrimidine are two of the most well-known examples of heterocycles that contain nitrogen. Both of these compounds are composed of six-membered rings that contain one nitrogen atom[11].

This review focuses primarily on heterocycle scaffolds that are based on nitrogen, oxygen, and sulphur, with a particular emphasis on the functional roles that these scaffolds play in the treatment of cancer. The properties of these scaffolds as molecular medicines, general modes of action, primary biological targets, and structure-activity connections are also taken into consideration by the reviewers[12]. Through the evaluation of internal FDA databases and listed drugs from the Centre for Drug Evaluation and Research (CDER), previously approved treatments and the molecular medications that corresponded to them were taken into consideration for innovativeness and heterocycle classification. In addition to this, it addresses the inherent problems that are associated with the utilisation of heterocycles in chemotherapy and sets the groundwork for drug delivery systems that are foundational on nanoparticles and are therapeutically competitive with conventional drugs and strategies[13].

Researchers have been fascinated by nitrogen-containing heterocycles for a considerable amount of time due to the structural variety of these heterocycles as well as their biological significance[14]. The currently conducted research provides a concise summary of the most recent discoveries about the utilisation of heterocyclic compounds that include nitrogen as potential cancer chemotherapeutics. A brief examination of the data kept by the FDA demonstrates the structural significance of nitrogen-based heterocycles in the design of medications[15]. This is due to the fact that these heterocycles are present in about sixty percent of all unique small compounds. As a result of the formation of hydrogen bonds with the base, heteroatoms contribute to the increased stability of DNA-based molecules. It is strongly related

to the affinity of heterocyclic compounds for DNA that the efficiency of these chemicals against cancer is high[16]. Numerous natural and manmade substances, such as sensitizers, organic compounds, copolymers, dyestuff, dyes, and corrosion inhibitors, all contain nitrogen heterocycles in their structural framework. These heterocycles are present in a wide variety of substances.

There are heterocyclic derivatives that contain sulphur that have the ability to bind to a number of protein targets that are specific to cancer. It has been proven that many sulphur-containing heterocyclic derivatives, including phenothiazine, benzothiophene, thiazole, thiophene, thiazolidinedione, and benzothiophene, can disrupt various signalling pathways that are related with cancer. There have also been significant developments in molecular targeted therapy, which targets specific enzymes such as kinase receptors, as a result of potential binding interactions that take place within the ATP pocket. Phenothiazines, benzothiazole, thiazole, thiophene, and benzothiophene are some of the most potentially effective anticancer compounds that contain sulphur in their heterocyclic ring metal complexes[17]. Benzothiazole is another molecule that contains sulphur. In spite of this, sulphur heteroaromatic rings, particularly thiophene, are extremely susceptible to structural changes due of the fact that they are converted into reactive metabolites. In light of the fact that the mere existence of a structural warning is not sufficient to demonstrate toxicity, this review focuses on specific discoveries that shed light on the factors that influence toxicity[18].

Heterocycles clinical relevance in cancer treatment

It is important to note that the examples that are shown and discussed in this article are based on the ring scaffolds that are most commonly found in FDA-approved drugs. However, due to the structural diversity of heterocycles, it is not possible to explain all of the compounds that are currently being explored in detail[19].

Nitrogen based heterocycles

The structural significance of nitrogen-based heterocycles in pharmaceutical drug design and engineering is demonstrated by a short review of FDA databases. This is due to the fact that about sixty percent of all unique small-molecule drugs contain a nitrogen heterocycle[20]. Data on nitrogen heterocycle frequency, structural variety, and substitution patterns in drugs that have been granted a licence by the Food and Drug Administration of the United States was collected by Edon Vitaku and colleagues in a study that was conducted not too long ago. It is important to note that the typical number of nitrogen atoms found in a single medication is roughly 2.3, but the number of nitrogen atoms found in medications that contain a nitrogen heterocycle is 3.1. Due to the enormous diversity of chemical structures that are produced as a result of the dynamics of these compounds, as well as from more fundamental characteristics such as ring size and aromaticity, the molecular mechanisms of action of nitrogen-based heterocycles (and other heterocycle classes) can vary substantially[21]. This is because of the fact that these compounds are composed of nitrogen. As an illustration, indoles and indole derivatives constitute one of the most widespread and versatile nitrogen-based heterocyclic like fragments that are utilised in the production of fundamental drugs that have been approved by the FDA for the treatment of common pathological conditions[22]. Among these compounds, indoles possess the ninth position among the twenty-five most common nitrogen heterocycles among drugs that have been approved by the FDA in the United States. Because of the endless potential for constructing polycyclic structures with numerous fused heterocyclic scaffolds to produce new heterocycles with chemical and biological uses, indole derivative synthesis has gained a lot of interest in recent decades[23]. This is due to the fact that it has the prospective to design

polycyclic structures. There is a wide range of biological targets that have been found to be affected by the indole structural plasticity that is observed in pharmaceutical rational design. Some of these targets include topoisomerase inhibitors, G2/M abrogators, and others[24]. The field of oncology, in particular, has recently demonstrated a great deal of interest in the utilisation of the indole basic core structure for the synthesis of a number of potent tubulin polymerization inhibitors. These inhibitors are typically found among well-known medications that have been approved by the FDA, as well as others that have been reported in clinical trials[25].

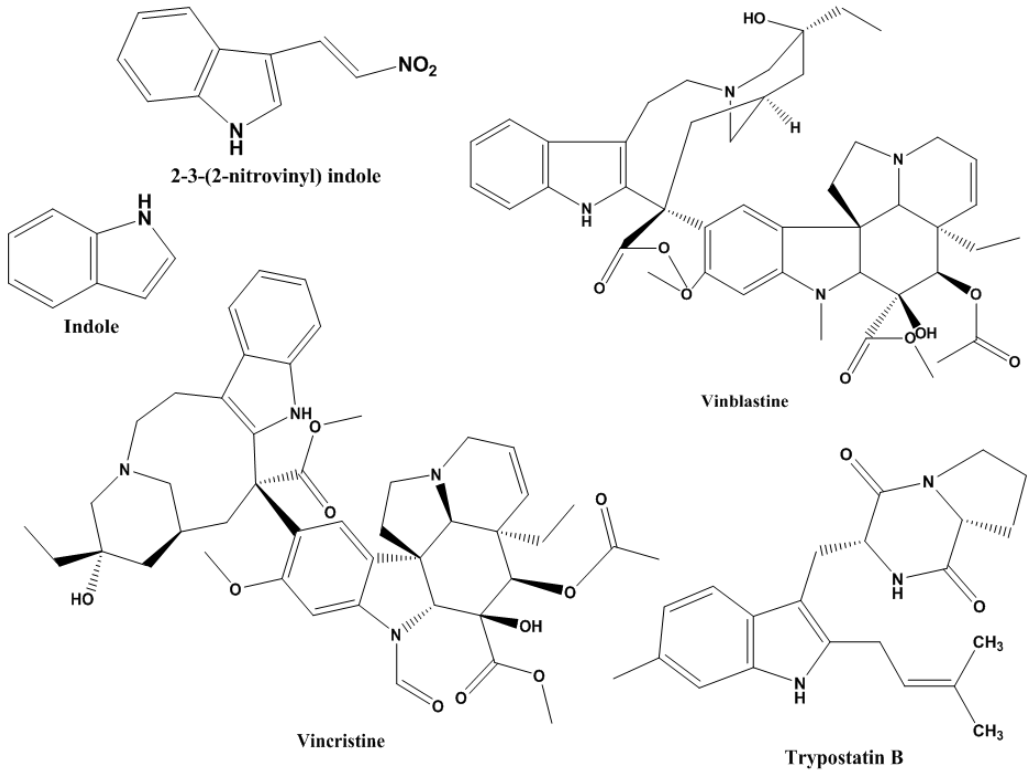


Fig 1: Indole basic core structure involved chemical structure reported FDA approved

Pyrimidine derivatives as anticancer agent

Pyrimidines, such as "m-Diazine," which is a result of the breakdown of uric acid, were the subject of widespread attention in the history of organic chemistry[26]. When Brugnatelli was oxidising uric acid with nitric acid in the year 1818, he discovered alloxan, which was the first pyrimidine derivative discovery[27]. Pyrimidine is a heterocyclic six-membered aromatic ring that contains nitrogen atoms in the first and third positions of the ring. In terms of temperature, pyrimidine has a melting point of 22.5 degrees Celsius and a boiling point of 124 degrees degree Celsius.

In their study, Fathalla et al. (2012) evaluated the antitumor activity of ten pyrimidine derivatives that were synthesised against a liver cancer (HepG2) cell line[28]. They did this by comparing the anticancer properties of these compounds to those of the well-known anticancer drugs 5-fluorouracil and doxorubicin. When the synthetic compounds were compared to the cancer cell line that was studied, the growth inhibition efficiency was exhibited at dosages ranging from 1 to

10 µg/mL[29]. Based on the results of this analysis, it was established that compound 1 possessed the highest level of potency, with an IC50 value of 3.56 µg/mL. The IC50 values for doxorubicin and 5-flurouracil were 3.56 µg/mL and 5 µg/mL, respectively, when compared to one another by comparison. In their study, Ahmed et al. (2020) synthesised and examined a total of sixteen nitrogen heterocyclic compounds that contained pyrimidine moieties. These compounds were evaluated for their potential anti-cancer activities. Based on the results of in vitro anti-proliferative experiments conducted with human liver (HepG2), breast (MCF7), and normal fibroblast (WI-38) cell lines, we compared the efficacy of the newly synthesised pyrimidine derivatives to that of doxorubicin. In compared to doxorubicin, which exhibited IC50 values of 4.5, 4.1, and 6.7 µM (WI-38), compound 2 demonstrated exceptional anticancer activity with IC50 values of 7.36, 10.76, and 6.7 µM, respectively. Gupta et al. (2022) focused their research on the application of spiroisoquinoline-pyrimidine compounds to the MCF-7 cancer cell line in order to investigate their potential anticancer effects. An ethoxy group derived from the acetylene molecule was shown to be the most effective cytotoxic agent, surpassing the reference medication Doxorubicin with an IC50 value of 98.8 µM[30]. This chemical was found to be the most effective cytotoxic agent. An MTT experiment was conducted at a dose of 50 µM, and the results showed that the cell vitality was 60%. On the other hand, the control group that was treated with doxorubicin had a cell viability of 100%. Over the course of 2013, Al-Issa developed fused pyrimidines and investigated the anti-cancer effects of these compounds in vitro by employing the HEPG2 human cancer cell line. Compound 4, which exhibited the most potent anticancer activity among these compounds, proved to be superior to even the traditional drug doxorubicin, which had an IC50 value of 1.2 µg/mL. Compound 4 had the highest anticancer activity among these compounds[31].

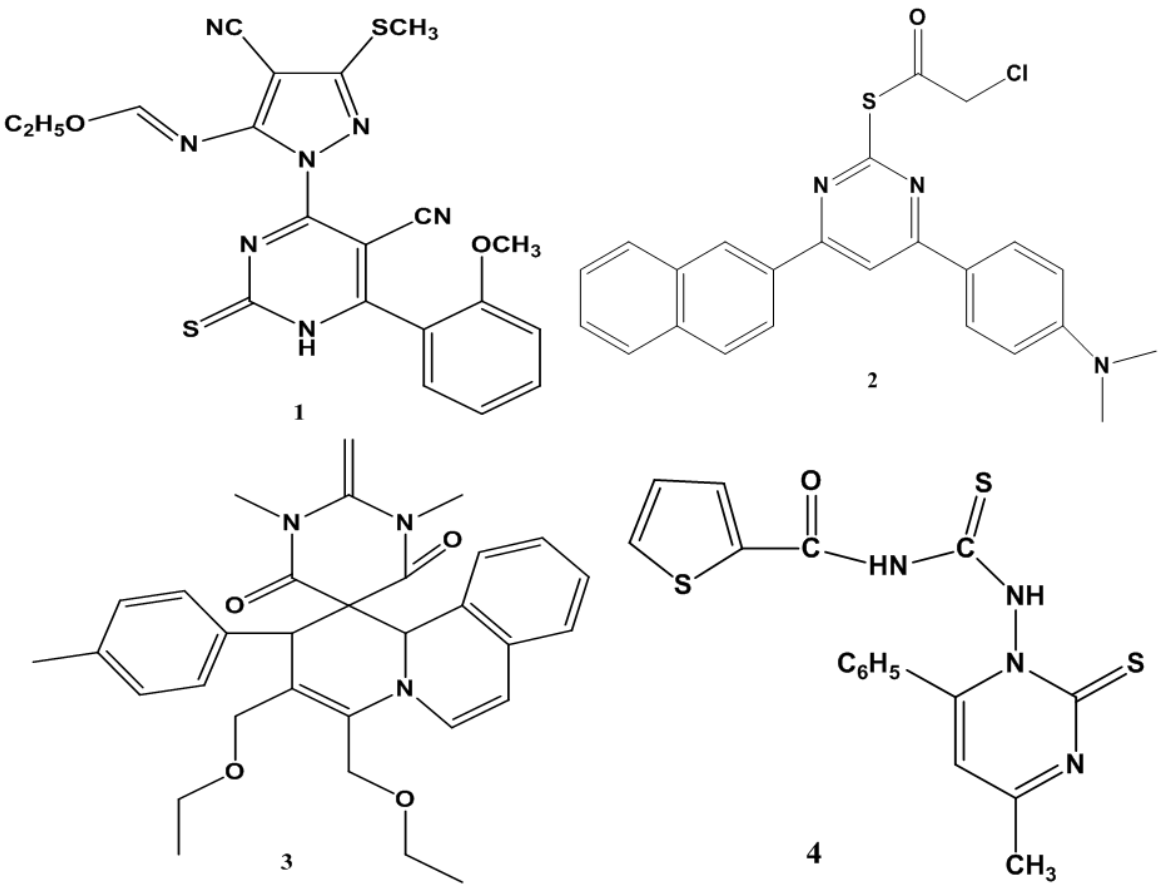


Fig 2: Pyrimidine derivatives (1-4) as anticanceragents

Quinoline derivatives as anticancer agents

Benzopyridine, 1-aza-napthalene, and quinoline are all names that refer to the same heterocyclic aromatic compound that contains nitrogen. Its molecular weight is 129.16, which is determined by its chemical formula, which is C9H7N. A log P value of 2.04 is associated with the values of pKb and pKa, which are 4.85 and 9.5, respectively[32]. Quinoline is a weak tertiary basic that, when mixed with acids, results in the formation of a salt and undergoes reactions that are comparable to those carried out by pyridine and benzene. In the architecture of a wide variety of naturally occurring chemicals (Cinchona alkaloids) and pharmaceuticals, quinoline nuclei can be found. These substances and medications have a wide range of biological effects. There have been numerous pharmacological benefits of quinoline that have been reported, such as its capacity to lessen the severity of seizures, alleviate pain, strengthen the heart, and combat infections, inflammation, and malaria.

Hamdy et al. (2019)[33] conducted an inquiry into anticancer agents that focused on quinoline-based heterocycles that were directed at Bcl-2. Among the compounds with IC50 values of 0.54, 1.42, 1.21, and >100 µM, Compound 5 shown remarkable activity in MDA-MB-231, HeLa, KG1a, and Jurkat. These compounds were evaluated for their ability to inhibit cell growth. This drug displayed an IC50 value of 0.15 µM, which is significantly lower than the IC50 value of 0.60 µM that Gossypol demonstrated when it was tested against Bcl-2. drug 5 demonstrated an anti-proliferative activity that was sub-micromolar in cancer cell lines that expressed Bcl-2. Additionally, the drug had an IC50 value that was sub-micromolar in an ELISA experiment that utilised the Bcl2-Bim peptide. Mathada et al. (2022) conducted research to determine whether or

not quinoline and its equivalents possessed any possible anticancer therapeutic properties. As a consequence of this, 62 distinct compounds were developed for the scientific investigation. The compound with the highest potency among these compounds was found to be compound 6, which exhibited IC50 values of 0.12 µM for MDA-MB-231, 0.08 µM for HeLa, and 0.34 µM for SMMC-7721 after being evaluated. The 50% inhibitory concentration (IC50) values for Etoposide, which is the usual medicine, were 5.26, 2.98, and 3.48 µM, respectively. Compound 6 exhibited a number of distinctive characteristics, including the induction of apoptosis in HeLa cells, the cessation of the cell cycle at the G0/G1 phase, the elevation of reactive oxygen species (ROS) levels within the cell, and a reduction in the potential of the mitochondrial membrane. In addition to this, the Ras/Raf/MEK/ERK signalling pathway was compromised, and the activity of MEK1 kinase was significantly diminished[34].

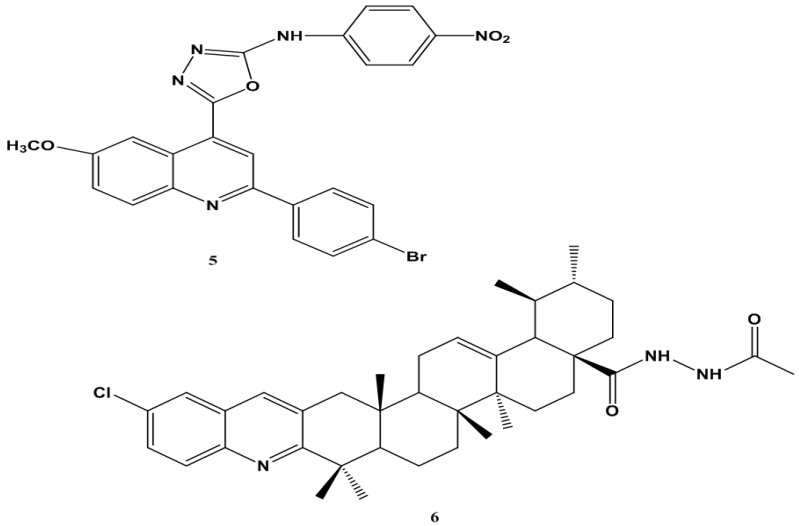


Fig 3: Quinoline derivatives (4-5) as a anticancer agents

Pyrazoline derivatives as anticancer agents

The production of pyrazoline calls for the Knoevenagel and Fisher reaction to be carried out. The procedure involves the utilisation of hydrazine or phenylhydrazine in an acidic environment, such as glacial acetic acid (GAA), in order to cyclize α, β-unsaturated ketones. Substituted chalcones can be cyclized with hydrazine by the Michael addition reaction, which is another method for producing pyrazoline. This method involves the use of basic media, such as triethylamine.

Some of the various biological activities that pyrazolines possess include anti-inflammatory, antibacterial, antifungal, analgesic, anti-diabetic, antioxidant, and anticancer effects. These are just some of the other features that pyrazolines has. The numerous drugs that include pyrazoline and have been approved for use in clinical settings are used to treat a wide range of psychological conditions. Examples of medications that contain the pyrazoline moiety include antipyrine, which is used to treat inflammation. Celecoxib, famprofazone, dipyrone, morazone, aminopyrine, ramifenazone, phenylbutazone, and celecoxib are some of the potent analgesics, antipyretics, and anti-inflammatory drugs that are available [35].

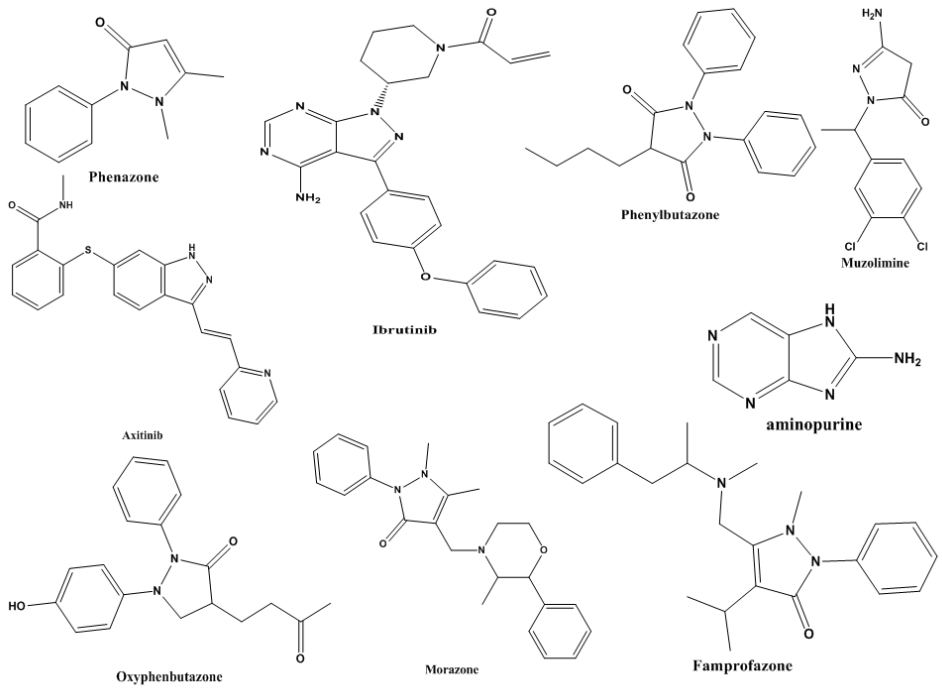


Fig 4: Clinically approved drugs containing pyrazoline scaffold

Oxygen based heterocycles

Paclitaxel (PTX, Taxol®), a heterocycle medication that is based on oxygen and has an integrated oxetane ring, is an essential component in the treatment of cancer. Paclitaxel is able to limit the progression of cancer cells through the mitotic phase by preventing the de-polymerization of microtubule polymers[36]. This process is comparable to that of microtubule associated proteins (MAPs), with the exception that it is irreversible. Since the discovery of PTX, there have been major advancements in the treatment of cancer; nevertheless, there are still a number of questions that have not been answered. As a result, there is a high strain on research and therapeutic approaches that are tied to cancer. In the literature, hypersensitivity, haematological problems, and neurotoxicity are some of the other systemic adverse effects of PTX that have been mentioned as being important. The profile of PTX is shared by a large number of other traditional chemotherapeutic drugs; however, the therapeutic benefits of these treatments are sometimes surpassed by the dreadful side effects they cause, which is why it is necessary to look for alternatives. Oxygen-based heterocycles have been found in around eight percent of the anticancer heterocycles that have been granted a licence by the FDA since the year 2010. Cabazitaxel and Eribulin were the most recent drugs to be granted permission for use[36].

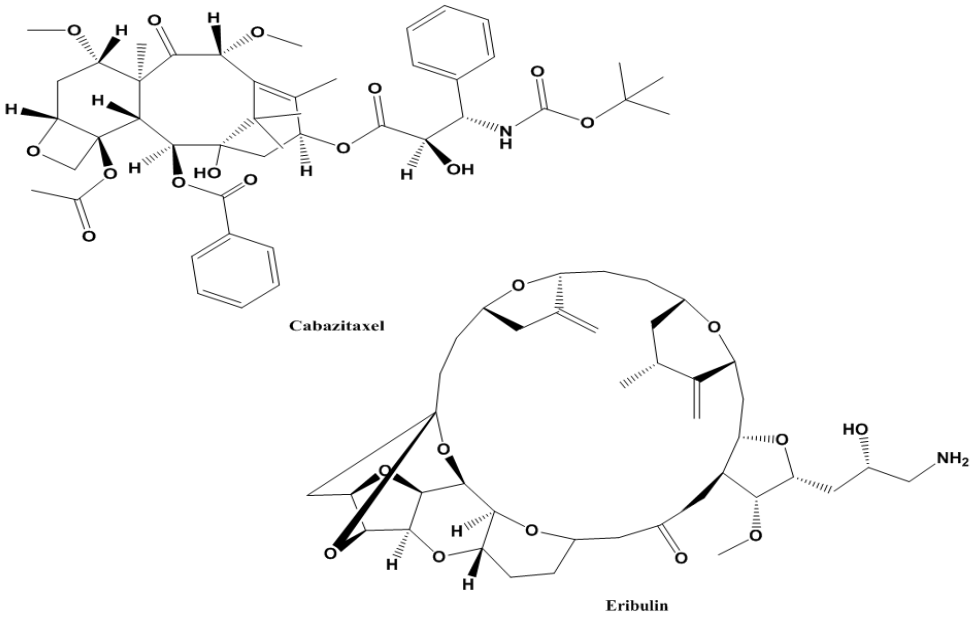


Fig 5: FDA approved oxygen based heterocycles Carbazitaxel and Eribulin

The discovery of tiny molecules that possess anticancer characteristics is one of the key objectives of the research group that we have under our medicinal chemistry umbrella. The influence of synthetic bis-coumarin compounds, specifically 7a and 7b, on cell models of myeloid leukaemia (CML) and lung cancer cells with KRAS mutations has been the subject of two significant studies that have been published by our research group. Both the production of aldehyde dehydrogenase and the development of spheroid are processes that contribute to the proliferation of non-small cell lung cancer cells associated with KRAS mutations. Research has demonstrated that 7a is capable of dramatically reducing both of these processes. In the subsequent mechanistic studies, it was demonstrated that 7a inhibits STAT3 transactivation and the expression of its target genes associated with cell proliferation. This is accomplished by inducing cellular stress, which includes metabolic catastrophe, mitochondrial stress, and ER/Golgi stress. These stressors are preceded by STAT3 inactivation[37]. At the same time, it was demonstrated that 40a activates sensitization against BH3 mimetics in non-small cell lung cancer, which in turn stimulates immunogenic cancer cell death pathways. Taking everything into consideration, the data that has been presented here clearly suggests that bis-coumarin templates could be valuable in the hunt for novel medications that treat lung cancer. As a result of the good results that 7a had in causing ER stress in lung cancer, more research was conducted on a variety of chronic myeloid leukaemia (CML) cell types to investigate the potential of 7b, which is a chlorinated counterpart of 7a. It was demonstrated once more that 7b is responsible for the stress that is induced in the endoplasmic reticulum, which in turn leads to caspase-dependent apoptosis and the production of molecular patterns that are linked with danger. The chemical 40b has the potential to inhibit the activation of nuclear factor-κB that is triggered by tumour necrosis factor α. This is in addition to its ability to reduce colony formation in vitro and the growth of Bcr-Abl+ patient blast xenografts in zebrafish. It produced synergistic effects when paired with imatinib, which was being used. Imatinib-resistant KBM-5 R cells exhibited an improved synergistic effect of 7b with omacetaxine, which resulted in the inhibition of Mcl-1 expression and the promotion of cell death. This mechanism of action was observed in the cells[38].

The bis-coumarin compounds 7a and 7b were the subject of discussion in both of these seminal studies beginning in the year 2014. The first study to make use of our synthesised bis-coumarins was one that investigated the effects of these compounds on the regulation of NF-kB and the proliferation of leukemic cell lines. The investigation started with the synthesis of the template bis-coumarin 7c, which was an endeavour that was carried out in collaboration with Professor Marc Diederich of the College of Pharmacy at Seoul National University. According to the findings, compound 7c was able to block the activation of NF-kB in the K-562 (chronic myeloid leukaemia) and JURKAT (acute T-cell leukaemia) cell lines. The IC50 value for compound 7c was 17.5 μM, while the value for JURKAT was 19.0 μM. Furthermore, it is worth noting that compound 7c did not have any impact on the vitality of peripheral blood mononuclear cells (PBMCs) from healthy participants, even when administered at levels above 100 μM. When the bis-coumarin molecule 7c was broken down into its component parts, which were 20-hydroxyphenylpropione and 4-hydroxycoumarin, inert compounds of the bis-coumarin type were produced[39].

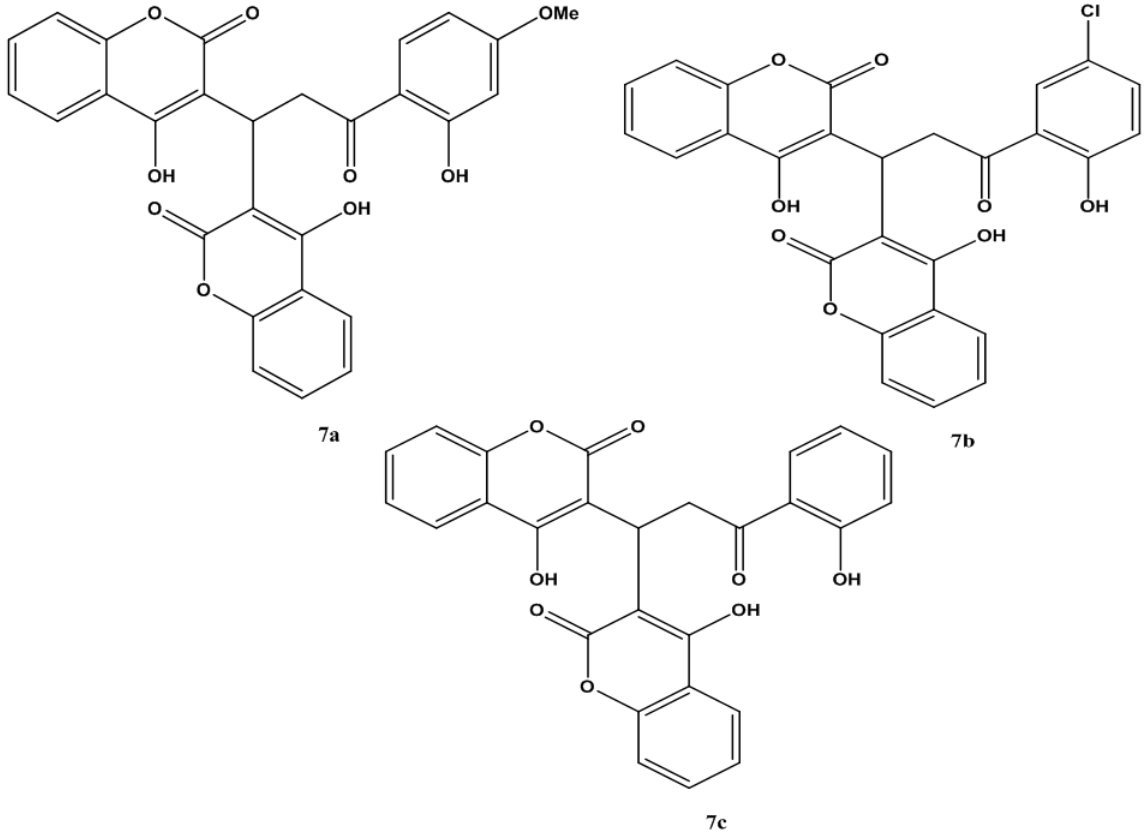
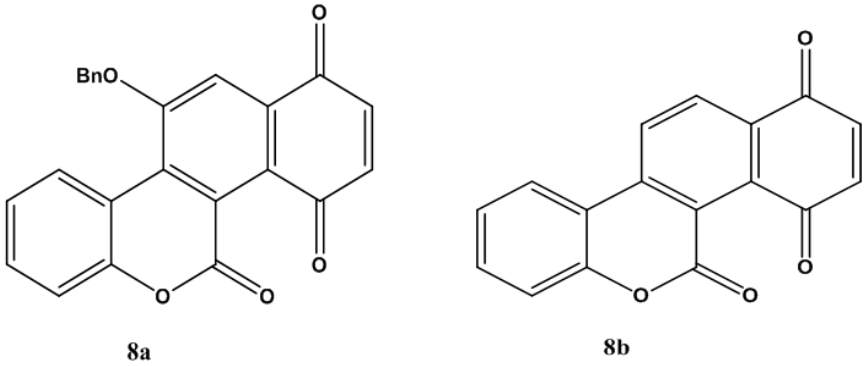


Fig 6: Bis coumarins 7a, 7b, 7c chemical structures and their anticancer activity

Enzymes that regulate the cell cycle, such as Cdc25 phosphatases, have the potential to treat cancer and are therefore prospective therapeutic targets. When it comes to determining the inhibitory potential of tiny substances with regard to Cdc25 phosphatases, human glutathione-S-transferase (GST)-Cdc25 recombinant enzymes are often the most effective choice. Studies conducted in the past have demonstrated that coumarin derivatives contain a great deal of potential for the development of innovative cancer treatments. As a result, the Cdc25 phosphatase-inhibition activity of a library of coumarin-based polycycles that were comparable to those in was examined. The screening revealed that the coumarins 8a and 8b had the lowest

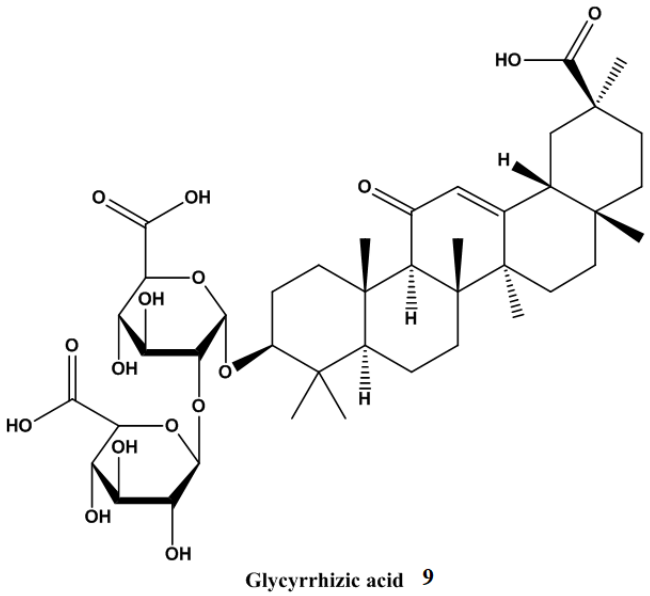
micromolar IC50 values, making them the most efficient phosphatase inhibitors. This was determined by the results of the screening. With regard to the benzylated compound 8a, the values of the IC50 were as follows: 13.2 μM for Cdc25A, 46.1 μM for Cdc25B, and 9.0 μM for Cdc25C each. On the other hand, the derivative 8b exhibited IC50 values of 5.8 μM for Cdc25A, 14.4 μM for Cdc25B, and 2.3 μM for Cdc25C against the target compound[40].



8a 8b

Fig 7: Coumarin derivatives as Cdc25 phosphatase inhibitors

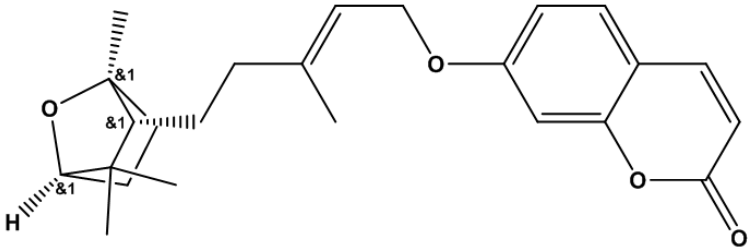
Glycyrrhiza species to be specific Fisch, which is scientifically known as Glycyrrhiza glabra Linn and is commonly known as licorice or Chinese liquorice, is considered to be one of the most significant and oldest phytomedicines in both China and the world[41]. There is a lengthy history of its application in the treatment of a wide range of ailments, particularly those that have an inflammatory element inside its foundation[42]. In addition, the sweetening qualities of this substance have been approved for usage in a variety of medical formulations as well as in food. In recent times, the crude medicine and its chemical ingredients have garnered attention due to the possibility that they possess anticancer properties[43][44]. Through the stimulation of the immune system and the modification of chemicals that induce inflammation, it is able to exert its effects[45]. The triterpenoid glycoside known as Glycyrrhizic acid (Glycyrrhizin), which is generated from the roots of the plant, was discovered to inhibit the pro-inflammatory proteins NF-κB and thromboxane synthase in vitro[46]. This resulted in the death of cells in lung adenocarcinoma, hepatoma, leukaemia, stomach, and prostate cancer cell lines[47]. The mechanism in which it influences the formation of tumours and the advancement of endometrial cancer is by lowering the activities of COX-2, TNF-α, IL-1, ornithine decarboxylase (ODC), DNA synthesis, and TxA2. In addition to this, the chemical mitigates the damage that is brought about by reactive oxygen species (ROS)[48][49].



Glycyrrhizic acid 9

Fig 8: Chemical structure of Glycyrrhizic acid

A sesquiterpene coumarin known as farnesiferol C (FC), 10 was isolated from the plant species Ferula, which belongs to the family Apiaceae. Cytotoxic, apoptotic, anticancer, and antimutagenic functions are just few of the various bioactivities that it possesses[50]. Compound 10, which is responsible for creating oxidative stress, is responsible for triggering apoptosis and cell cycle arrest in the MCF-7 cell line. It has been reported that it has the ability to prevent the processes that lead to the metastasis of cancer, such as the vascular endothelial growth factor (VEGF)-induced cell proliferation, migration, invasion, and tube formation[51].



Farnesiferol C 10

Fig 9: Chemical structure of Farnesiferol C

Radix O. japonicus, Ophiopogonis radix (auchiopogonis root), and O japonicus are the herbs that contain ophiopogonin B, 11. Radix O. japonicus is also a candidate. Traditional Chinese medicine makes extensive use of it in a variety of contexts. Some of the various types of cancer that it is able to treat include lung cancer, cervical cancer, and stomach cancer, to name just a few. Two proteins that are involved in intracellular signal transduction were found to be present in increased quantities in compound 11-treated cells, as determined by Western blotting analysis. These proteins are caspase 3 and B-cell lymphoma 2 (Bcl-2)-associated X protein. In addition, compound 11 inhibited the development of NPC cells by inducing apoptosis and causing mitochondrial integrity to be compromised. Additionally, compound 11 boosts the expression of phosphorylated-associated protein (YAP), mammalian STE20-like kinase 1, and big tumour

suppressor 1 in addition to increasing the transcription of the association domain in non-proliferative cells (NPCs).

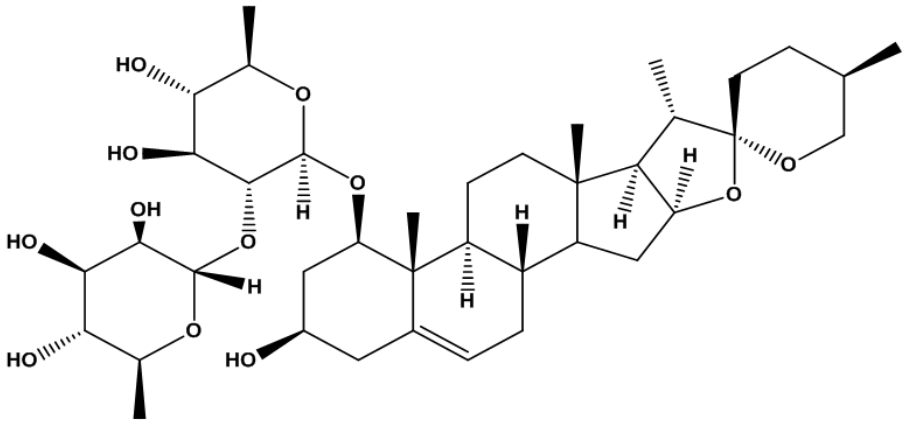


Fig 10: Chemical structure of Ophiopogonin B

Sulphur based heterocycles

In addition to N- and O-based heterocycles, medicinal chemists have begun to concentrate on S-based heterocycles as a result of the extraordinary biological capabilities that they possess as anticancer, antidiabetic, antifungal, and antihypertensive medicines[52]. The Food and Drug Administration (FDA) has given its approval to a variety of drugs that contain S-heterocycles as central components for the treatment of cancer and other various ailments. The following is a list of certain heterocycles that include S groups and exhibit anticancer activity against many targets. A wide range of moulds and fungi, such as Aspergillus fumigatus, Eurotium chevalieri, Gliocladium fimbriatum, and a number of species of Trichoderma, Penicillium, and Neosartorya pseudofischeri, are responsible for the production of mycotoxins[53]. One of these mycotoxins is called gliotoxin 12, which is produced by these moulds and fungi. This naturally occurring chemical belongs to the class of compounds known as 2,5-diketopiperazine. An illustration of the immunosuppressive properties it possesses is as follows: Compound 12 inhibits the activation of NF-κB, alters the immune response, has an effect on neutrophils that are circulating in the bloodstream, restricts the phagocytosis of conidia, and reduces the production of reactive oxygen species (ROS)[54]. Through the activation of caspases, followed by the up-regulation of Bax and the down-regulation of Bcl-2, it suppresses the growth of cells that are associated with colorectal and cervical malignancies, respectively, and promotes their death[55].

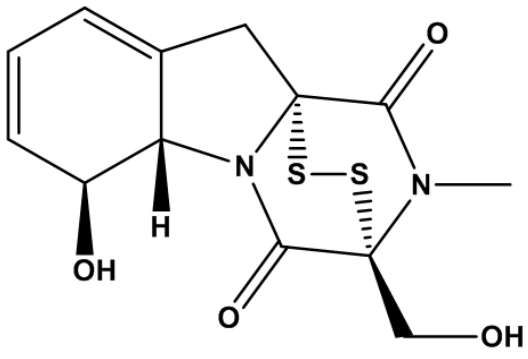
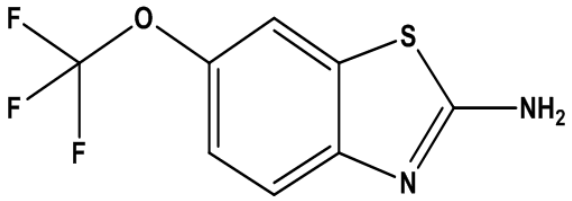


Fig 11: Chemical structure of Glitoxin 12 and its anticancer activity

Benzothiazole

Benzothaizole (BTA), which is a fused benzoheterocyle, is responsible for the medicinal, pharmacological, and pharmaceutical activities of a large number of naturally occurring chemicals[56]. The presence of BTA can be detected in compounds that exhibit a wide variety of biological activity, regardless of whether they are found on land or in water[57]. When a benzene ring and a thiazole ring get together, the result is the formation of the BTA nucleus[58]. As a result of the pharmacological profile of Riluzole 13, medicinal chemists have shown an interest in the use of physiologically active benzothiazole for the treatment of amyotrophic lateral sclerosis (ALS)[59].



Riluzole 13

Fig 12: Chemical structure of Riluzole 13

Thiazole

There is a strong correlation between the molecular structure of a molecule and the biological activity of that substance[60]. In contemporary medicinal chemistry, heterocycles such as azoles play a vital role, notably in the domains of drug discovery and design. This is mostly due to the extensive versatility that these compounds possess[61]. Research is being conducted to investigate their potential use in a variety of medical sectors, particularly in regard to potential anticancer medications. Due to the fact that it possesses beneficial biological properties, the heterocyclic ligand thiazole, which is composed of five members and contains both nitrogen and sulphur, has recently garnered a lot of attention[62]. Thiazole and its derivatives are among the most active classes of compounds because they have a wide variety of biological effects, including but not limited to the following: antimicrobial, antifungal, antimalarial, antitubercular, antiviral, anti-inflammatory, antidiabetic, anthelmintic, anticonvulsant, antioxidant, anticancer, cardiovascular, and so on[63]. Tiazofurin (14) inhibits IMP dehydrogenase, dasatinib (15) inhibits Bcr-Abl tyrosine kinase, dabrafenib (16) inhibits B-RAF, and ixabepilone (17) stabilises microtubules; these are only a few of the many anticancer medications that are currently available for clinical use due to the presence of thiazole-containing substances (Fig. 12)[64-66]. Anticancer activity can be demonstrated by compounds containing thiazole through a variety of different applications. As can be seen in Figure 12, thiazole scaffolds are present in a number of the anticancer medications that have been found to be among the most effective in a variety of scientific examinations[67]. A variety of topics concerning the anticancer potential of medications containing thiazole have been reviewed by us. We have made an effort to review these several topics[68][69].

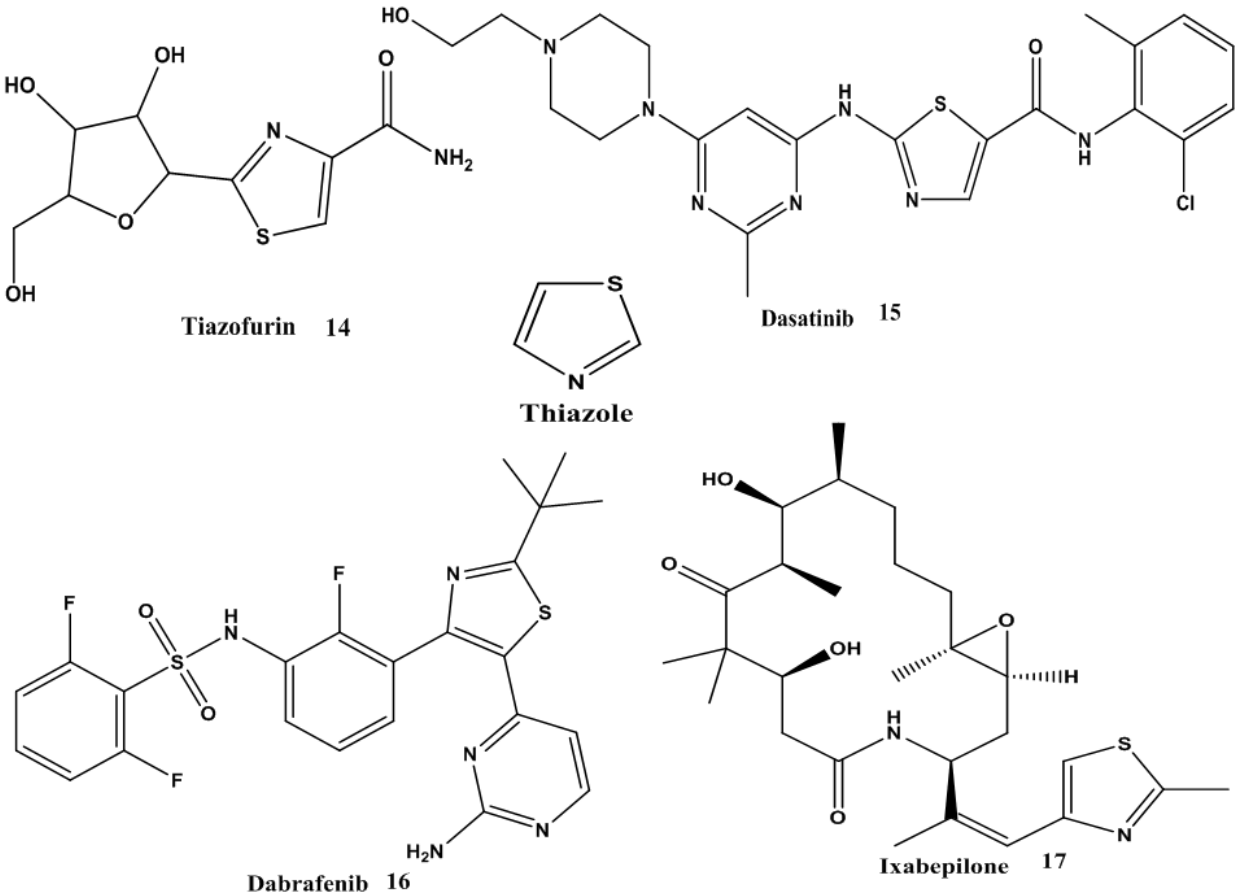


Fig 13: Some clinically used thiazole containing anticancer drugs

Conclusion

In the field of medicinal chemistry, heterocyclic systems have emerged as the true cornerstones due to the amazing physicochemical potencies, intrinsic flexibility, and inherent inventiveness that they possess. There is evidence of the primary heterocyclic systems in the majority of the natural items and pharmaceuticals that are currently prescribed. Nitrogen heterocycles are distinguished by the fact that sixty percent of the drugs that have been approved by the FDA are heterocycles based on nitrogen. The present study identified pyrimidine, quinolone, indole, pyrazole, quinazoline, and quinoxaline as nitrogen-containing heterocycles that can be efficiently targeted against a variety of cancers. These heterocycles were synthesised by chemical means. There is a wide range of biological applications for nitrogen-based compounds, and the spectrum of these compounds is continually expanding in the field of medicine. Analogues of nitrogen-based compounds offer a huge and encouraging avenue for the creation of new medications with their applications. In the context of cancer treatment, the role that heterocycles that include oxygen and sulphur play. Within the scope of this review, the unique anticancer potential of heterocyclic compounds based on nitrogen, oxygen, and sulphur is the primary focus.

Conflict of interest

The authors declare no competing interest.

References

1. Du, Z., & Lovly, C. M. (2018). Mechanisms of receptor tyrosine kinase activation in cancer. *Molecular cancer*, *17*, 1-13.

2. Flynn, A., & Fox, E. (2018). Evolving paradigms for new agent development in pediatric oncology. *Current Opinion in Pediatrics*, *30*(1), 10-16.
3. Dittmann, J., Haydn, T., Metzger, P., Ward, G. A., Boerries, M., Vogler, M., & Fulda, S. (2020). Next-generation hypomethylating agent SGI-110 primes acute myeloid leukemia cells to IAP antagonist by activating extrinsic and intrinsic apoptosis pathways. *Cell Death & Differentiation*, *27*(6), 1878-1895.
4. Huang, T. T., Lampert, E. J., Coots, C., & Lee, J. M. (2020). Targeting the PI3K pathway and DNA damage response as a therapeutic strategy in ovarian cancer. *Cancer treatment reviews*, *86*, 102021.
5. Garcia, J., Hurwitz, H. I., Sandler, A. B., Miles, D., Coleman, R. L., Deurloo, R., & Chinot, O. L. (2020). Bevacizumab (Avastin®) in cancer treatment: A review of 15 years of clinical experience and future outlook. *Cancer treatment reviews*, *86*, 102017.
6. Bagchi, S., Yuan, R., & Engleman, E. G. (2021). Immune checkpoint inhibitors for the treatment of cancer: clinical impact and mechanisms of response and resistance. *Annual Review of Pathology: Mechanisms of Disease*, *16*, 223-249.
7. Zhong, L., Li, Y., Xiong, L., Wang, W., Wu, M., Yuan, T., ... & Yang, S. (2021). Small molecules in targeted cancer therapy: advances, challenges, and future perspectives. *Signal transduction and targeted therapy*, *6*(1), 1-48.
8. Alvarez-Builla, J., & Barluenga, J. (2011). Heterocyclic compounds: an introduction. *Modern Heterocyclic Chemistry*, 1-9.
9. Ferreira, P. M., Maia, H. L., & Monteiro, L. S. (2002). Synthesis of 2, 3, 5-substituted pyrrole derivatives. *Tetrahedron letters*, *43*(25), 4491-4493.
10. Kijewska, M., Sharfalddin, A. A., Jaremko, Ł., Cal, M., Setner, B., Siczek, M., ... & Jaremko, M. (2021). Lossen rearrangement of p-toluenesulfonates of N-oxyimides in basic condition, theoretical study, and molecular docking. *Frontiers in Chemistry*, *9*, 662533.
11. Martins, P., Jesus, J., Santos, S., Raposo, L. R., Roma-Rodrigues, C., Baptista, P. V., & Fernandes, A. R. (2015). Heterocyclic anticancer compounds: recent advances and the paradigm shift towards the use of nanomedicine's tool box. *Molecules*, *20*(9), 16852-16891.
12. Ajani, O. O., Audu, O. Y., Aderohunmu, D. V., Owolabi, F. E., & Olomieja, A. O. (2017). Undeniable pharmacological potentials of quinazoline motifs in therapeutic medicine. *Am. J. Drug Discov. Dev*, *7*(1), 1-24.
13. Özkay, Y., Işıkdağ, İ., İncesu, Z., & Akalın, G. (2010). Synthesis of 2-substituted-N-[4-(1-methyl-4, 5-diphenyl-1H-imidazole-2-yl) phenyl] acetamide derivatives and evaluation of their anticancer activity. *European journal of medicinal chemistry*, *45*(8), 3320-3328.
14. Jangale, A. D., & Dalal, D. S. (2017). Green synthetic approaches for biologically relevant organic compounds. *Synthetic Communications*, *47*(23), 2139-2173.
15. Yang, D., An, B., Wei, W., Tian, L., Huang, B., & Wang, H. (2015). Copper-catalyzed domino synthesis of nitrogen heterocycle-fused benzoimidazole and 1, 2, 4-benzothiadiazine 1, 1-dioxide derivatives. *ACS Combinatorial Science*, *17*(2), 113-119.
16. Srivastava, M., Singh, J., Singh, S. B., Tiwari, K., Pathak, V. K., & Singh, J. (2012). Synthesis of novel fused heterocycle-oxa-aza-phenanthrene and anthracene derivatives via sequential one-pot synthesis in aqueous micellar system. *Green chemistry*, *14*(4), 901-905.
17. Czarnik, A. W. (1998). Peer Reviewed: Combinatorial Chemistry. *Analytical Chemistry*, *70*(11), 378A-386A.
18. García-Valverde, M., & Torroba, T. (2005). Sulfur-nitrogen heterocycles. *Molecules*, *10*(2), 318-320.

19. Maji, S., Debnath, B., Panda, S., Manna, T., Maity, A., Dayaramani, R., ... & Akhtar, M. J. (2024). Anticancer potential of the S-heterocyclic ring containing drugs and its bioactivation to reactive metabolites. *Chemistry & Biodiversity*, e202400473.
20. Vitaku, E., Smith, D. T., & Njardarson, J. T. (2014). Analysis of the structural diversity, substitution patterns, and frequency of nitrogen heterocycles among US FDA approved pharmaceuticals: miniperspective. *Journal of medicinal chemistry*, *57*(24), 10257-10274.
21. Shafakat Ali, N. A., Ahmad Dar, B., Pradhan, V., & Farooqui, M. (2013). Chemistry and biology of indoles and indazoles: a mini-review. *Mini reviews in medicinal chemistry*, *13*(12), 1792-1800.
22. Kaushik, N. K., Kaushik, N., Attri, P., Kumar, N., Kim, C. H., Verma, A. K., & Choi, E. H. (2013). Biomedical importance of indoles. *Molecules*, *18*(6), 6620-6662.
23. Sherer, C., & Snape, T. J. (2015). Heterocyclic scaffolds as promising anticancer agents against tumours of the central nervous system: Exploring the scope of indole and carbazole derivatives. *European journal of medicinal chemistry*, *97*, 552-560.
24. Brancale, A., & Silvestri, R. (2007). Indole, a core nucleus for potent inhibitors of tubulin polymerization. *Medicinal research reviews*, *27*(2), 209-238.
25. Kumar, S., Mehndiratta, S., Nepali, K., Gupta, M. K., Koul, S., Sharma, P. R., ... & Dhar, K. L. (2013). Novel indole-bearing combretastatin analogues as tubulin polymerization inhibitors. *Organic and Medicinal Chemistry Letters*, *3*, 1-13.
26. Lagoja, I. M. (2005). Pyrimidine as constituent of natural biologically active compounds. *Chemistry & Biodiversity*, *2*(1), 1-50.
27. Albratty, M., & Alhazmi, H. A. (2022). Novel pyridine and pyrimidine derivatives as promising anticancer agents: A review. *Arabian Journal of Chemistry*, *15*(6), 103846.
28. Fathalla, O. A., Mohamed, N. A., El-Serwy, W. S., AbdelHamid, H. F., Abd El-Moez, S. I., & Soliman, A. M. M. (2013). Synthesis of some new pyrimidine derivatives and evaluation of their anticancer and antibacterial activities. *Research on Chemical Intermediates*, *39*, 821-841.
29. Ahmed, M. H., El-Hashash, M. A., Marzouk, M. I., & El-Naggar, A. M. (2020). Synthesis and antitumor activity of some nitrogen heterocycles bearing pyrimidine moiety. *Journal of Heterocyclic Chemistry*, *57*(9), 3412-3427.
30. Gupta, S., Bartwal, G., Singh, A., Tanwar, J., & Khurana, J. M. (2022). Design, synthesis and biological evaluation of spiroisoquinoline-pyrimidine derivatives as anticancer agents against MCF-7 cancer cell lines. *Results in Chemistry*, *4*, 100386.
31. Al-Issa, S. A. (2013). Synthesis and anticancer activity of some fused pyrimidines and related heterocycles. *Saudi Pharmaceutical Journal*, *21*(3), 305-316.
32. Marella, A., Tanwar, O. P., Saha, R., Ali, M. R., Srivastava, S., Akhter, M., ... & Alam, M. M. (2013). Quinoline: A versatile heterocyclic. *Saudi Pharmaceutical Journal*, *21*(1), 1-12.
33. Hamdy, R., Elseginy, S. A., Ziedan, N. I., Jones, A. T., & Westwell, A. D. (2019). New quinoline-based heterocycles as anticancer agents targeting bcl-2. *Molecules*, *24*(7), 1274.
34. Jin, X. Y., Chen, H., Li, D. D., Li, A. L., Wang, W. Y., & Gu, W. (2019). Design, synthesis, and anticancer evaluation of novel quinoline derivatives of ursolic acid with hydrazide, oxadiazole, and thiadiazole moieties as potent MEK inhibitors. *Journal of enzyme inhibition and medicinal chemistry*, *34*(1), 955-972.
35. Haider, K., Shafeeque, M., Yahya, S., & Yar, M. S. (2022). A comprehensive review on pyrazoline based heterocyclic hybrids as potent anticancer agents. *European Journal of Medicinal Chemistry Reports*, *5*, 100042.

36. Markman, M., & Mekhail, T. M. (2002). Paclitaxel in cancer therapy. *Expert opinion on pharmacotherapy*, *3*(6), 755-766.
37. Lee, J. Y., Talhi, O., Jang, D., Cerella, C., Gaigneaux, A., Kim, K. W., ... & Diederich, M. (2018). Cytostatic hydroxycoumarin OT52 induces ER/Golgi stress and STAT3 inhibition triggering non-canonical cell death and synergy with BH3 mimetics in lung cancer. *Cancer Letters*, *416*, 94-108.
38. Mazumder, A., Lee, J. Y., Talhi, O., Cerella, C., Chateauvieux, S., Gaigneaux, A., ... & Diederich, M. (2018). Hydroxycoumarin OT-55 kills CML cells alone or in synergy with imatinib or Synribo: Involvement of ER stress and DAMP release. *Cancer letters*, *438*, 197-218.
39. Talhi, O., Schnekenburger, M., Panning, J., Pinto, D. G., Fernandes, J. A., Paz, F. A. A., ... & Silva, A. M. (2014). Bis (4-hydroxy-2H-chromen-2-one): Synthesis and effects on leukemic cell lines proliferation and NF-κB regulation. *Bioorganic & Medicinal Chemistry*, *22*(11), 3008-3015.
40. Valente, S., Xu, Z., Bana, E., Zwergel, C., Mai, A., Jacob, C., ... & Kirsch, G. (2013). Reactivity of 4-Vinyl-2H-1-benzopyran-2-ones in Diels–Alder Cycloaddition Reactions: Access to Coumarin-Based Polycycles with Cdc25 Phosphatase-Inhibiting Activity. *European Journal of Organic Chemistry*, *2013*(14), 2869-2877.
41. Chen, H., Zhang, X., Feng, Y., Rui, W., Shi, Z., & Wu, L. (2014). Bioactive components of Glycyrrhiza uralensis mediate drug functions and properties through regulation of CYP450 enzymes. *Molecular Medicine Reports*, *10*(3), 1355-1362.
42. Zhang, S. P., Zhou, Y. J., Liu, Y., & Cai, Y. Q. (2009). Effect of liquiritigenin, a flavanone existed from Radix glycyrrhizae on pro-apoptotic in SMMC-7721 cells. *Food and chemical toxicology*, *47*(4), 693-701.
43. Liu, Y., Xie, S., Wang, Y., Luo, K., Wang, Y., & Cai, Y. (2012). Liquiritigenin inhibits tumor growth and vascularization in a mouse model of HeLa cells. *Molecules*, *17*(6), 7206-7216.
44. Ayeka, P. A., Bian, Y., Mwitari, P. G., Chu, X., Zhang, Y., Uzayisenga, R., & Otachi, E. O. (2016). Immunomodulatory and anticancer potential of Gan cao (Glycyrrhiza uralensis Fisch.) polysaccharides by CT-26 colon carcinoma cell growth inhibition and cytokine IL-7 upregulation in vitro. *BMC complementary and alternative medicine*, *16*, 1-8.
45. Thirugnanam, S., Xu, L., Ramaswamy, K., & Gnanasekar, M. (2008). Glycyrrhizin induces apoptosis in prostate cancer cell lines DU-145 and LNCaP. *Oncology reports*, *20*(6), 1387-1392.
46. Chueh, F. S., Hsiao, Y. T., Chang, S. J., Wu, P. P., Yang, J. S., Lin, J. J., ... & Lai, T. Y. (2012). Glycyrrhizic acid induces apoptosis in WEHI-3 mouse leukemia cells through the caspase-and mitochondria-dependent pathways. *Oncology reports*, *28*(6), 2069-2076.
47. Huang, R. Y., Chu, Y. L., Jiang, Z. B., Chen, X. M., Zhang, X., & Zeng, X. (2014). Glycyrrhizin suppresses lung adenocarcinoma cell growth through inhibition of thromboxane synthase. *Cellular Physiology and Biochemistry*, *33*(2), 375-388.
48. Niwa, K., Lian, Z., Onogi, K., Yun, W. U., Tang, L., Mori, H., & Tamaya, T. (2007). Preventive effects of glycyrrhizin on estrogen-related endometrial carcinogenesis in mice. *Oncology reports*, *17*(3), 617-622.
49. Cathcart, M. C., Reynolds, J. V., O'Byrne, K. J., & Pidgeon, G. P. (2010). The role of prostacyclin synthase and thromboxane synthase signaling in the development and

progression of cancer. *Biochimica et Biophysica Acta (BBA)-Reviews on Cancer*, *1805*(2), 153-166.
50. Kasaian, J., & Mohammadi, A. (2018). Biological activities of farnesiferol C: a review. *Journal of Asian natural products research*, *20*(1), 27-35.
51. Hasanzadeh, D., Mahdavi, M., Dehghan, G., & Charoudeh, H. N. (2017). Farnesiferol C induces cell cycle arrest and apoptosis mediated by oxidative stress in MCF-7 cell line. *Toxicology reports*, *4*, 420-426.
52. Pathania, S., Narang, R. K., & Rawal, R. K. (2019). Role of sulphur-heterocycles in medicinal chemistry: An update. *European journal of medicinal chemistry*, *180*, 486-508.
53. Kupfahl, C., Michalka, A., Lass-Flörl, C., Fischer, G., Haase, G., Ruppert, T., ... & Hof, H. (2008). Gliotoxin production by clinical and environmental Aspergillus fumigatus strains. *International Journal of Medical Microbiology*, *298*(3-4), 319-327.
54. Nguyen, V. T., Lee, J. S., Qian, Z. J., Li, Y. X., Kim, K. N., Heo, S. J., ... & Jung, W. K. (2013). Gliotoxin isolated from marine fungus Aspergillus sp. induces apoptosis of human cervical cancer and chondrosarcoma cells. *Marine drugs*, *12*(1), 69-87.
55. Chen, J., Wang, C., Lan, W., Huang, C., Lin, M., Wang, Z., ... & Liu, H. (2015). Gliotoxin inhibits proliferation and induces apoptosis in colorectal cancer cells. *Marine drugs*, *13*(10), 6259-6273.
56. Keri, R. S., Patil, M. R., Patil, S. A., & Budagumpi, S. (2015). A comprehensive review in current developments of benzothiazole-based molecules in medicinal chemistry. *European Journal of Medicinal Chemistry*, *89*, 207-251.
57. Gunawardana, G. P., Koehn, F. E., Lee, A. Y., Clardy, J., He, H. Y., & Faulkner, D. J. (1992). Pyridoacridine alkaloids from deep-water marine sponges of the family Pachastrellidae: structure revision of dercitin and related compounds and correlation with the kuanoniamines. *The Journal of Organic Chemistry*, *57*(5), 1523-1526.
58. Jaiswal, S., Mishra, A. P., & Srivastava, A. (2012). The Different Kinds of Reaction involved in synthesis of 2-substituted Benzothiazole and its derivatives: A Review. *Res. J. Pharm. Biol. Chem. Sci*, *3*, 631-641.
59. Bryson, H. M., Fulton, B., & Benfield, P. (1996). Riluzole: a review of its pharmacodynamic and pharmacokinetic properties and therapeutic potential in amyotrophic lateral sclerosis. *Drugs*, *52*, 549-563.
60. Sharma, P. C., Bansal, K. K., Sharma, A., Sharma, D., & Deep, A. (2020). Thiazole-containing compounds as therapeutic targets for cancer therapy. *European journal of medicinal chemistry*, *188*, 112016.
61. Ewida, M. A., Abou El Ella, D. A., Lasheen, D. S., Ewida, H. A., El-Gazzar, Y. I., & El-Subbagh, H. I. (2017). Thiazolo [4, 5-d] pyridazine analogues as a new class of dihydrofolate reductase (DHFR) inhibitors: Synthesis, biological evaluation and molecular modeling study. *Bioorganic chemistry*, *74*, 228-237.
62. Rajak, H., Agarawal, A., Parmar, P., Thakur, B. S., Veerasamy, R., Sharma, P. C., & Kharya, M. D. (2011). 2, 5-Disubstituted-1, 3, 4-oxadiazoles/thiadiazole as surface recognition moiety: Design and synthesis of novel hydroxamic acid based histone deacetylase inhibitors. *Bioorganic & medicinal chemistry letters*, *21*(19), 5735-5738.
63. Wang, H. H., Qiu, K. M., Cui, H. E., Yang, Y. S., Xing, M., Qiu, X. Y., ... & Zhu, H. L. (2013). Synthesis, molecular docking and evaluation of thiazolyl-pyrazoline derivatives containing benzodioxole as potential anticancer agents. *Bioorganic & medicinal chemistry*, *21*(2), 448-455.

64. Lv, P. C., Zhou, C. F., Chen, J., Liu, P. G., Wang, K. R., Mao, W. J., ... & Zhu, H. L. (2010). Design, synthesis and biological evaluation of thiazolidinone derivatives as potential EGFR and HER-2 kinase inhibitors. *Bioorganic & medicinal chemistry*, *18*(1), 314-319.
65. Chang, S., Zhang, Z., Zhuang, X., Luo, J., Cao, X., Li, H., ... & Ding, K. (2012). New thiazole carboxamides as potent inhibitors of Akt kinases. *Bioorganic & medicinal chemistry letters*, *22*(2), 1208-1212.
66. Anandan, S. K., Ward, J. S., Brokx, R. D., Denny, T., Bray, M. R., Patel, D. V., & Xiao, X. Y. (2007). Design and synthesis of thiazole-5-hydroxamic acids as novel histone deacetylase inhibitors. *Bioorganic & medicinal chemistry letters*, *17*(21), 5995-5999.
67. Carradori, S., Rotili, D., De Monte, C., Lenoci, A., D'Ascenzio, M., Rodriguez, V., ... & Mai, A. (2014). Evaluation of a large library of (thiazol-2-yl) hydrazones and analogues as histone acetyltransferase inhibitors: enzyme and cellular studies. *European journal of medicinal chemistry*, *80*, 569-578.
68. Zhao, M. Y., Yin, Y., Yu, X. W., Sangani, C. B., Wang, S. F., Lu, A. M., ... & Zhu, H. L. (2015). Synthesis, biological evaluation and 3D-QSAR study of novel 4, 5-dihydro-1H-pyrazole thiazole derivatives as BRAFV600E inhibitors. *Bioorganic & medicinal chemistry*, *23*(1), 46-54.
69. Liu, Z. Y., Wang, Y. M., Li, Z. R., Jiang, J. D., & Boykin, D. W. (2009). Synthesis and anticancer activity of novel 3, 4-diarylthiazol-2 (3H)-ones (imines). *Bioorganic & medicinal chemistry letters*, *19*(19), 5661-5664.