**RECENT BREAKTHROUGH IN ANTICANCER ACTION OF HETEROCYCLES**

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**Abstract**

The recent ground-breaking discoveries in the field of anticancer research are examined in this chapter, with a special emphasis on the extraordinary potential of heterocycles. Heterocycles, a group of chemical molecules with ring structures including atoms other than carbon, have shown promise as a source of new and effective anticancer drugs. The important discoveries and developments in exploiting the anticancer properties of heterocycles are succinctly summarized in the abstract. Recent research has revealed the wide range of biological activities exhibited by heterocyclic substances, emphasizing their capacity to disrupt vital molecular pathways involved in cancer cell survival and proliferation. Scientists can create tailored medicines using their distinctive chemical structures, which have the potential to successfully treat cancer while minimizing collateral damage to healthy cells. Combination therapies that combine heterocyclic compounds with traditional anticancer medications have also shown promise in overcoming drug resistance and boosting therapeutic efficacy. This tactical strategy opens a promising new path for developing cancer therapy protocols and enhancing patient outcomes. A thorough understanding of the safety profiles, pharmacokinetics, and long-term consequences of heterocycles is still required despite the significant progress achieved in harnessing their anticancer properties. To turn these ground-breaking findings into useful therapeutic applications, the chapter emphasizes the necessity of ongoing collaborations between researchers, physicians, and pharmaceutical corporations.

**Introduction**

The second most common cause of mortality today, cancer affects millions of individuals globally [1]. It is brought on by the cell's unchecked expansion in any area of the body [2]. All ages of people have been discovered to be affected by this fatal lethal sickness. If we examine the global data on cancer, we can observe that women are more likely than men to develop the disease [3]. The most common cancers diagnosed in women of all ages are breast cancer, cervical cancer, prostate cancer, etc [4]. The main cancer treatments include chemotherapy, surgery, radiation therapy, and hormonal therapies [5]. Although cancer research has made significant progress, the medications used to treat the disease have some drawbacks, such as drug resistance, organ toxicity, a brief half-life, a lack of cell specificity, undesirable side effects, etc [6]. The death and morbidity rates from cancer are still very high due to the high cost and therapeutic resistance. To combat cancer nowadays, it is crucial to develop drugs having efficient and targeted action against cancer with the least or no toxic effects.

Medical chemists are constantly inspired by natural history and its sources to develop novel, cutting-edge pharmacological entities. Heterocyclic compounds have cyclic rings with five or six members and one or more heteroatoms, such as nitrogen (N), oxygen (O), or sulfur (S), other than carbon. These substances, which include pyridine, pyrrole, furan, indole, quinoline, oxadiazole, azole, benzimidazole, and thiophene as shown in Figure 1, can be aromatic or non-aromatic [7]. They are recognized as an essential component of nature. Heterocyclic compounds like purine and pyrimidine are components of DNA, vitamins, enzymes, information carriers, and neurotransmitters, hence are crucial for human survival [8].



Figure 1 Different Heterocyclic rings with reported Anticancer activity

Heterocyclic structures have long been important in the development of anti-cancer drugs, and they are widely present in the anti-cancer medication molecules currently on the market. The FDA approved 65% of anti-cancer medications between 2010 and 2017 that contained a heterocycle [9]. The reason why heterocycles have become so crucial for the development of anti-cancer drugs is because they are so common in nature. It is not unexpected that heterocycle-based compounds have frequently served as the foundation for therapeutic therapy given that they represent a very big cohort of molecules with an extraordinary amount of variety in terms of the interactions they can engage in [10]. Heterocycles are a suitable choice when creating compounds that will interact with targets and disrupt the biological pathways involved in the growth of cancer, as many enzyme-binding pockets are predisposed to interacting with heterocyclic moieties. These anti-cancer treatments frequently target pathways involved in cell growth and development. Furthermore, heterocyclic rings can cover a large region of chemical space due to the relative ease with which new substituents can be added, making them great starting places for the development of anti-cancer drugs [11].

Heterocycles can bind in a variety of ways due to their capacity for a wide range of intermolecular interactions, such as hydrogen bond donor/acceptor capabilities, pi-stacking interactions, metal coordination bonds, van der Waals and hydrophobic forces [12]. Heterocycles also occur in a variety of forms and sizes due to the huge range of ring diameters and structural permutations, which enables them to complement the equally diverse structural range of enzyme-binding pockets [13]. Numerous commercialized heterocyclic medications have shown anticancer efficacy, including doxorubicin, cisplatin, methotrexate, fluorouracil, quercetin, tryptanthrin, and napabucasin [14-17].

**Nitrogen-containing heterocyclic compounds**

Heterocycles that include nitrogen are quite an important class of heterocyclic compounds. The design of anticancer drugs has benefited greatly from the use of heterocyclic molecules. Particularly important chemicals are N-heterocyclic compounds, which are also included in numerous vitamins, nucleic acids, medicines, antibiotics, and natural alkaloids [18]. They are pharmacologically active compounds with properties that include those against diabetes, HIV, malaria, tuberculosis, and other diseases [19]. Vincristine, vinblastine, and indolocarbazole are examples of heterocyclic anticancer medications [20]. The structural importance of nitrogen-based heterocycles in medication design is demonstrated by a short scan of FDA archives, which reveals that almost 60% of unique small compounds have a nitrogen heterocyclic [21]. Complexes containing heteroatoms are more stable as a result of the hydrogen bonds that develop between these heteroatoms and DNA. The effectiveness of heterocyclic compounds as anti-cancer agents depends on how strongly they bind to DNA [22]. Nitrogen heterocycles can be found in the skeleton of natural goods, pharmaceuticals, organic compounds, sensitizers, copolymers, dyestuff, and corrosion inhibitors. Statistics show that more than 85% of physiologically active compounds are either heterocycles or have one nitrogen atom in their complex structures [23].

The benzo-pyridine family includes the substances quinoline and quinolone. One of the most common and privileged scaffolds, it can be found in many pharmaceutically active molecules with a variety of biological activities, including antibacterial, antimalarial, anticancer, anti-tubercular, anti-inflammatory, and many more [24]. According to reports, the analogs of quinoline and quinolone have several anticancer potencies including a variety of mechanisms, such as antiproliferation by cell cycle arrest, apoptosis, angiogenesis inhibition, etc [25]. Structures of some well-known anticancer medications with quinoline or quinolone as the core component like gasoline, mapping, flindersine, and haplamine are shown in Figure 2 [26-28]. Today, the majority of researchers place a strong emphasis on the hybridization technique to create multifunctional pharmacophores and escape the constraints related to single bioactive substances. A hybrid molecule, which has more potential biological capabilities than its parent homolog, is the result of the phenomenon when two bioactive pharmacophores are combined into a single molecule [29]. Anticancer medications include vomitoxin, quarfloxin, cefatrizine, and AT-3639, to name a few [30]. Scientists are using in silico drug design (based on SAR studies) to create novel anticancer drug molecules by combining quinoline or quinolone with other biologically active cores, which could eventually lead to next-generation anticancer drugs, to avoid drug resistance and toxicity while increasing drug specificity.



Figure 2 Quinoline/quinolone nuclei containing anticancer agents

Indole and its derivatives have been demonstrated to affect many cellular pathways connected to the development of cancer over the past few decades. As well as the capacity to cause cellular oxidative stress and cell death, these include the inhibition of cell signaling, regular cell cycle progression, tumor vascularization, and DNA repair. Vincristine and vinblastine are two of the most significant early indole-based anticancer drugs. Both have clinical relevance today and have been known to inhibit tubulin polymerization since the early to middle 1960s [31]. While vinblastine is commonly used to treat advanced Hodgkin's disease and testicular cancer, vincristine is used as a combination therapy for acute lymphoblastic leukemia, Hodgkin's disease, and both non-Hodgkin's and Hodgkin's lymphoma. Vinblastine's mode of action involves the suppression of tubulin polymerization, which results in cell cycle arrest and halts the division of cancer cells [32]. Similar to the broader scope of heterocycles itself, indolocarbazoles are a closely related derivative of indoles and have attracted a lot of attention in recent years for their potential to fight cancer. The ability of several indolocarbazoles to inhibit protein kinases is particularly significant since constitutively active protein kinases are frequently important players in the malignant transformation of cells during cancer initiation [33]. Some Indole derived anticancer medications available in the market are shown in Figure 3. The different nitrogen-containing heterocycles, whose derivatives have shown anticancer effects include pyrimidine, quinoline, carbazole, pyridine, imidazole, benzimidazole, triazole, β-lactam, indole, pyrazole, Quinazoline, Quinoxaline, Isatin, lo-benzodiazepines, and Pyrido[2,3-d] Pyrimidine. Various indole derivatives have shown their anticancer potential and have got FDA approval. Indole-derived FDA-approved drugs, along with their targets and mode of action have been listed in Table 1.



Figure 3 Indole-based anticancer drugs available in market

**Table 1: List of Nitrogen-containing drugs having FDA approval [34-43].**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **S.no.** | **Drug** | **Target** | **Mode of action** | **Cancer** |
|  | Brigatinib | Anaplastic lymphoma kinase (ALK) inhibitor | It inhibits the ability of the phosphate group to bind ALK and inhibits the activity of proteins STAT3, A.K.T., ERK1/2, and S6 both in vitro and in vivo. | lung cancer [non-small cell lung cancer (NSCLC)] |
|  | Alectinib Hydrochloride | Anaplastic lymphoma kinase (ALK) inhibitor | It prevents the multiplication of cancer cells by blocking the action of abnormal proteins. | lung cancer [non-small cell lung cancer (NSCLC)] |
|  | Entrectinib | Anaplastic lymphoma kinase (ALK) inhibitor | It interferes with the growth of cancer cells, which are eventually destroyed. | lung cancer [non-small cell lung cancer (NSCLC)] |
|  | Midostaurin | Fms-like tyrosine kinase (FLT3) inhibitor | It Prevents the multiplication of cancer cells by blocking the action of abnormal proteins. | acute myeloid leukemia |
|  | Gilteritinib fumarate | Fms-like tyrosine kinase (FLT3) inhibitor | Blocks the action of naturally occurring substances that promote cancer cell growth. | acute myeloid leukemia |
|  | Osimertinib mesylate | Epidermal growth factor (EGF) receptor inhibitor | The abnormal protein’s ability to cause cancer cells to grow is blocked, which may also help tumors get smaller and slow down the spread of cancer cells. | Non-small-cell lung cancer (NSCLC) |
|  | Neratinib maleate | Epidermal growth factor (EGF) receptor inhibitor | The autophosphorylation is prevented on tyrosine residues receptor, and the oncogenic signaling is reduced | HER2-positive Breast cancer |
|  | Levatinib mesylate | Vascular endothelial growth factor (VEGF) inhibitors | The kinase activities of vascular endothelial growth factor (VEGF) receptors VEGFR1 (FLT1), VEGFR2 (K.D.R.), and VEGFR3 (FLT4) are inhibited | Endometrial, renal and hepatocellular carcinoma |
|  | Acalabrutinib | Tyrosine kinase inhibitor (TKI) | Bruton Tyrosine Kinase inhibitor that stops B cells from chemotactic, proliferating, moving, and adhesion of B cells | Lymphocytic leukemia |
|  | Cytarabine | Antineoplastic anti-metabolite | It prevents cancer cells from generating and repairing the D.N.A., which they require to thrive and proliferate. | Leukemia |

**Oxygen-containing heterocyclic compounds**

The development of numerous N-heterocyclic compounds has caused researchers' attention to turn to O-based heterocyclic compounds. Oxygen-based heterocycles with anticancer action make up about 8% of the heterocycles that the FDA has approved since 2010 [44]. Two powerful O-heterocyclic medications, cabazitaxel, and eribulin, have recently received FDA approval for their ability to block microtubules, which has an anti-cancer effect. Paclitaxel, one of the earliest drugs developed, is essential in the treatment of cancer [45]. The function of this compound, which has an oxetane ring, is based on the depolymerization of microtubule polymers, which prevents cancer cells from progressing through mitosis. This causes a delay in the division of cancer cells, which ultimately stops cancer in its tracks. This is similar to the mode of action used by vinblastine. Despite its advantages, the medication has been linked to many systemic side effects, such as hypersensitivity, hematological problems, and neurotoxicity [46]. As a result, substantial work has gone into developing substitute treatments that are less likely to cause side effects while retaining paclitaxel's potent therapeutic effects. The microtubule inhibitors cabazitaxel and eribulin, which are used to treat prostate and metastatic breast cancer, respectively, are more recently created oxygen-containing heterocyclic anti-cancer medications. Cabazitaxel is a tubulin stabilizer, but because it resists cellular efflux by the p-glycoprotein efflux pump, which is expressed by many resistant cancer cells, it may be especially useful for treating tumors that are resistant to many drugs. Additionally, capable of crossing the blood-brain barrier is Cabazitaxel. While other medications connect to both the growing and shortening ends of microtubules during cell division, eribulin exclusively binds to the growing ends, causing protracted mitotic obstruction and ultimately cell death by apoptosis [47]. In addition, recent studies have led to the repurposing of oxygen-based heterocyclic medications that were initially created for use in other disease areas, for use as anti-cancer treatments. Numerous research projects are being carried out to evaluate auranofin as a therapeutic agent for the treatment of various cancer types, such as leukemia, lymphoma, and ovarian cancer [48].



Figure 4 Pyran derivative bioactive metabolites have a variety of biological properties

Pyran is a heterocyclic moiety that contains oxygen and possesses a variety of pharmacological characteristics. One of the crucial structural building blocks included in a variety of natural compounds, including coumarins, benzopyrans, sugars, flavonoids, xanthones, etc., is pyran. The fact that pyrans have recently attracted the attention of researchers from all over the world is further evidence of their various anticancer properties [49]. A common example of a pyran derivative is the bioactive metabolite -apache, which often exhibits a variety of biological properties (such as anticancer, antibacterial, and anti-inflammatory actions), making it significant for drug development [50]. For example, zanamivir has been authorized for the treatment of influenza A and B. In addition, zanamivir was the first neuraminidase inhibitor to be produced for commercial use. The trade name "Relenza" is presently used by GlaxoSmithKline to promote this medication [51]. Due to their extensive spectrum of biological activities, which include anticancer characteristics, benzopyrans, and fused pyran-based compounds are an essential class of structural motifs for many natural and synthetic drugs.

In the search for novel lead molecules in the realm of cancer chemotherapy, flavanones have been considered to be quite promising. According to Hsiao et al., while other flavanones (4′-OH flavanone, 6-OH flavanone) showed little to no inhibition, flavanone and 2′-OH flavanone significantly suppressed the growth of A549, LLC, AGS, SK-Hepl, and HA22T malignant cells [52]. Due to the structural variety and medicinal qualities of coumarins and pyrans, an unusual class of oxygen-containing heterocyclic compounds, they play a significant role in medicinal chemistry. The presence of coumarin scaffolds in natural phytoconstituents allows them to exhibit a variety of biological activities, including anticancer effects through several different routes, making them a prized structure. Pyranocoumarin derivatives, which have different structural arrangements between the coumarin and pyran rings, are among the coumarin hybrids derived from natural sources [53].

**Sulfur containing heterocyclic compounds**

In addition to being an essential component of many vitamin cofactors, sugars, and nucleic acids, sulfur also plays a significant role in controlling translation by sulfurating transfer RNA. Similar to their oxygen- and nitrogen-based counterparts, sulfur-containing heterocycles have attracted a lot of attention in the development of anti-cancer medications [54]. For instance, several compounds were discovered to exhibit promising inhibitory effects when the antiproliferative activity of thiophene derivatives against human breast cancer cells was evaluated in a recent screening research. According to the researchers, their findings may serve as a foundation for the development of future tyrosine kinase inhibitors that have fewer negative effects. Several thiazole-based nitrogen mustard heterocycles have recently been found to exhibit substantial inhibitory effects towards a panel of human cancer cell lines, further demonstrating the importance of thiadiazole and thiazole structures for cancer research in recent years [55]. The FDA authorized the use of dabrafenib, a thiazole-containing anti-cancer therapeutic molecule, in 2013 for people with malignancies linked to mutant BRAF genes. Patients with metastatic melanoma, of which nearly half were found to have the mutant form of BRAF, were one such group of patients [56].

According to the findings of numerous research, the sulfur heterocyclic framework is a crucial structure in a variety of synthetic analogs that represent a wide range of medicinal activities. Many heterocyclic scaffolds with five, six, and seven sulfur atoms, including thiazoles, thiadiazoles, thiazolidinediones, thiophenes, thiopyrans, benzothiazoles, thiophenes, thienopyridines, simple and modified phenothiazines, and thiazepines, have been reported to have anticancer potential. The derivatives' cytotoxic effects were revealed in subsequent investigations through a variety of methods, including the inhibition of tyrosine kinases, topoisomerase I and II, tubulin, COX, DNA synthesis, and the PI3K/Akt and Raf/MEK/ERK signaling pathways, among others (including inhibition of tyrosine kinases, COX, and DNA synthesis) [57].

For many years, the molecules that are therapeutically effective and have been approved by the Food and Drug Administration (FDA) have included sulfur-containing heterocyclic compounds. Some of the several S-containing heterocyclic derivatives that have been approved by the US FDA are included in Table 2 to highlight their versatility.

**Table 2: List of FDA-approved Sulphur containing drugs with anticancer properties.**

|  |  |  |  |
| --- | --- | --- | --- |
| **S.no.** | **Drugs** | **Market name and company** | **Treated cancer** |
|  | Bleomycin | Blenoxane® (Bristol Myers Squibb company) | Hodgkin's and non-Hodgkin’s lymphoma, ovarian, cervical, and testicular cancers |
|  | Raloxifene | Evista® (Eli Lilly and Company) | Breast cancer in postmenopausal women |
|  | Ixabepilone | Ixempra™ (Bristol‐Myers Squibb Company) | Treatment of metastatic or locally advanced breast cancer |
|  | Romidepsin | Istodax® CELGENE | Treatment of cutaneous T‐cell lymphoma (CTCL)  Peripheral T‐cell lymphomas (PTCLs) |
|  | Dasatinib | Sprycel® Bristol Myers Squibb Company | Acute lymphoblastic leukemia and chronic myelogenous leukemia |
|  | Dabrafenib | Tafinlar® GlaxoSmithKline | In the therapy of melanoma that expresses BRAF V600E gene mutation |

**Conclusion:**

Heterocycles play a crucial role in the development of anti-cancer drugs due to their frequency in nature and the diversity of their chemical and structural makeup. Their involvement in around two-thirds of the cancer medications FDA-approved in the first part of this decade underscores their continued significance in cancer research, with studies repeatedly highlighting the crucial role they must play in the battle against cancer.

In conclusion, recent advances in heterocycles' anticancer effects have shown tremendous promise in the fight against cancer. Due to their amazing biological activity and capacity for precise targeting, these special compounds, which are distinguished by their various ring configurations including atoms other than carbon, have emerged as possible game-changers in cancer therapy. Scientists have effectively identified and created heterocyclic compounds with strong anticancer capabilities through novel research and cutting-edge technology, providing fresh hope for more effective and tailored treatments.

One of the main benefits of anticancer drugs based on heterocyclic compounds is their capacity to disrupt particular biochemical pathways involved in the development of cancer, allowing for customized treatments that minimize harm to healthy cells. Additionally, their adaptability enables the creation of a variety of structures and derivatives, expanding the possibility for personalized treatment techniques based on the distinctive qualities of individual tumors.

The discovery and creation of heterocyclic compounds have also created new opportunities for combination therapy, in which these drugs can be utilized with already-effective treatments to boost effectiveness and get around drug resistance. This collaborative strategy has a lot of potential for improving patient outcomes and overcoming some of the difficulties associated with traditional cancer treatment.

Although there has been significant development in this area, it is vital to recognize that more investigation, in-depth testing, and clinical trials are required to fully realize the potential of heterocyclic compounds as anticancer drugs. To make sure they are suitable for widespread clinical usage, safety, pharmacokinetics, and long-term effects must be thoroughly evaluated.

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