

# RECENT BREAKTHROUGH IN ANTICANCER ACTION OF HETEROCYCLES

## 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.

**Keywords:** Anticancer, Heterocycles, Chemotherapy, Nitrogen.

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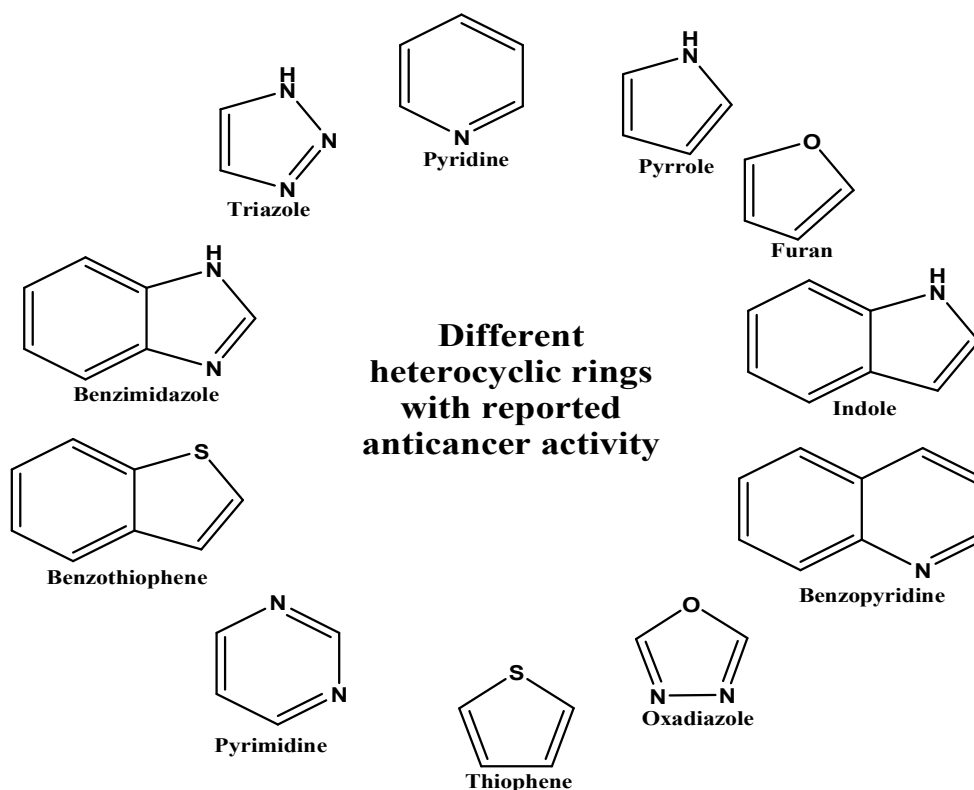
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## I. INTRODUCTION

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 males are less likely than females to suffer from this 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 preparation of drugs fighting against cancer, 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 were having a heterocyclic ring [9]. Due to their prevalence in nature, heterocycles have grown to be extremely important for the development of anti-cancer medications. It is not unexpected that heterocycle-based compounds have frequently served as the foundation for therapeutic therapy given that they represent a very big molecular group with an extraordinary amount of variety regarding the interactions they can have [10]. When formulating substances which communicate with targets and obstruct the biological mechanisms that contribute to the development of cancer, heterocycles are an excellent choice, 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].

Due to their ability to engage in a number of intermolecular interactions, including hydrogen bond donor/acceptor properties, pi-stacking interactions, metal coordination bonds, van der Waals forces, and hydrophobic forces, heterocycles can bind in a variety of ways [12]. Due to the wide range of ring sizes and structural permutations, heterocycles also come in a variety of shapes and sizes, which allows them to go along with the equally varied structure ranges of enzyme-binding pockets. [13]. Numerous commercialized heterocyclic medications have shown anticancer efficacy, including doxorubicin, cisplatin, methotrexate, fluorouracil, quercetin, tryptanthrin, and napabucasin [14-17].

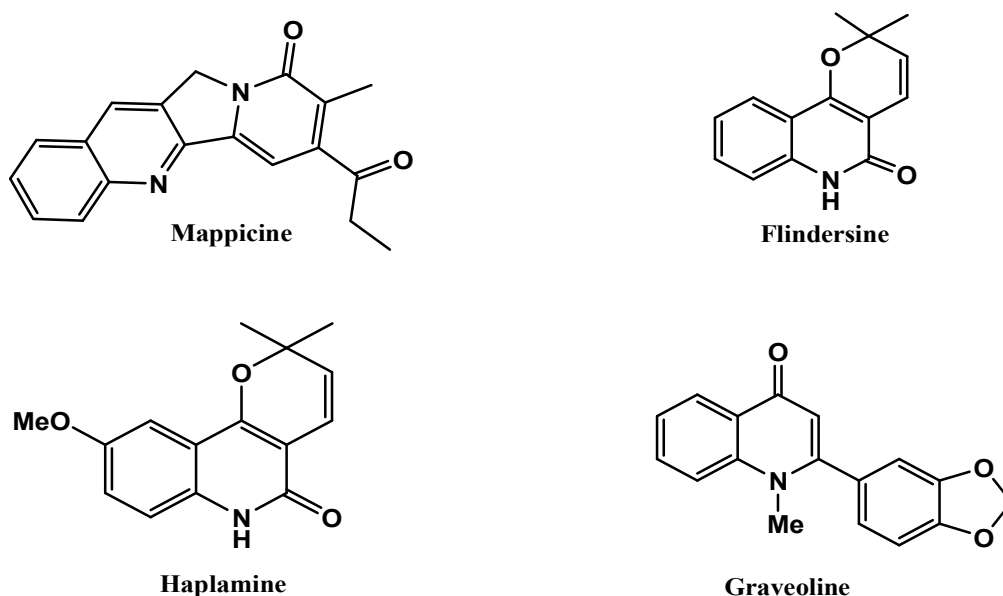
## II. NITROGEN-CONTAINING HETEROCYCLIC COMPOUNDS

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].

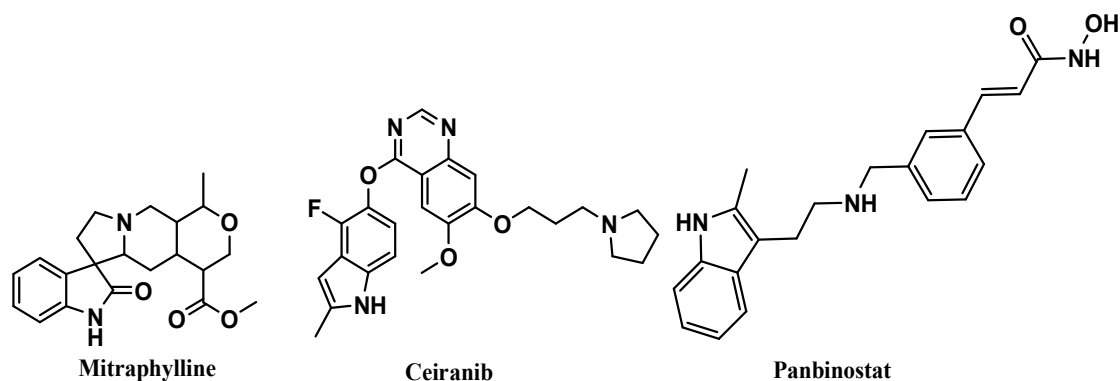
Today, the majority of researchers place a strong emphasis on the hybridization technique to create multifunctional pharmacophores and escape the constraints related to single bioactive substances. A hybrid molecule, which has more potential biological capabilities than its parent homolog, is the result 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 derivatives and indole have been demonstrated to affect many cellular pathways connected to the development of cancer over the past few decades. As well as the capability to cause cellular oxidative stress and cell death, these include the inhibition of cell signaling, regular cell cycle progression, tumor vascularization, and DNA repair. Two of the most important early indole-based anticancer medicines are vincristine and vinblastine. Since the early to middle 1960s, both have been known to prevent tubulin polymerization and are relevant to modern medicine [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 very similar 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 activated protein kinases are typically crucial participants in the malignant cell transformation 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,  $\beta$ -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].

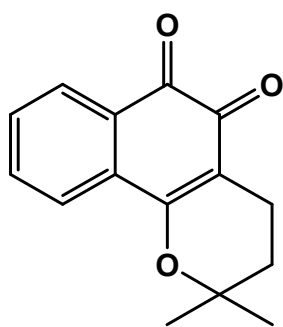
S. no.	Drug	Target	Mode of action	Cancer
1.	Brigatinib	Anaplastic lymphoma kinase (ALK) inhibitor	Both in vitro and in vivo, it prevents the phosphate group from binding to ALK and inhibits the activity of the proteins STAT3, A.K.T., ERK1/2, and S6.	Non-small cell lung cancer (NSCLC)
2.	Alectinib Hydrochloride	Anaplastic lymphoma kinase (ALK) inhibitor	By hindering the activity of abnormal proteins, it stops the growth of cancer cells.	Non-small cell lung cancer (NSCLC)]
3.	Entrectinib	Anaplastic lymphoma kinase (ALK) inhibitor	Cancer cells are eventually eliminated because it prevents their proliferation.	Non-small cell lung cancer (NSCLC)
4.	Midostaurin	Fms-like tyrosine kinase (FLT3) inhibitor	By hindering the activity of abnormal proteins, it stops the growth of cancer cells.	Acute myeloid leukemia

5.	Gilteritinib fumarate	Fms-like tyrosine kinase (FLT3) inhibitor	Stops the effect of naturally occurring chemicals that encourage the development of cancer cells.	Acute myeloid leukemia
6.	Osimertinib mesylate	Epidermal growth factor (EGF) receptor inhibitor	By preventing the growth of cancer cells caused by the aberrant protein, tumours may shrink and the spread of cancer cells may be slowed.	Non-small-cell lung cancer (NSCLC)
7.	Neratinib maleate	Epidermal growth factor (EGF) receptor inhibitor	Tyrosine residues receptor autophosphorylation is avoided, and oncogenic signalling is diminished.	HER2-positive Breast cancer
8.	Levatinibmesylate	Vascular endothelial growth factor (VEGF) inhibitors	Inhibit the kinase activities of vascular endothelial growth factor (VEGF) receptors VEGFR1 (FLT1), VEGFR2 (K.D.R.), and VEGFR3 (FLT4)	Endometrial, renal and hepatocellular carcinoma
9.	Acalabrutinib	Tyrosine kinase inhibitor (TKI)	B cell chemotaxis, proliferation, motility, and adhesion are all inhibited by the Bruton Tyrosine Kinase inhibitor.	Lymphocytic leukemia
10	Cytarabine	Antineoplastic anti-metabolite	Cancer cells are unable to produce or repair the DNA that they need to survive and spread.	Leukemia

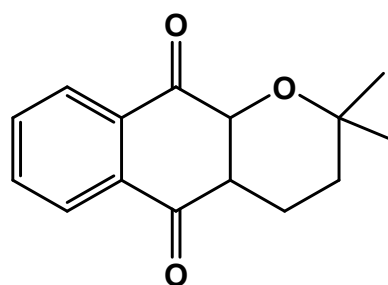
### III. OXYGEN-CONTAINING HETEROCYCLIC COMPOUNDS

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 oxygen-containing heterocyclic anti-cancer drugs cabazitaxel and eribulin, which are used to treat prostate and metastatic breast cancer, respectively, respectively, microtubule inhibitors. 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 prompted the use of oxygen-based heterocyclic medications that were initially created for use in other category diseases, 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].



**Beta-lapachone**



**Alpha-lapachone**

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, xanthenes, 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-Hep1, 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].

#### IV. SULFUR CONTAINING HETEROCYCLIC COMPOUNDS

Sulphur is a key component of several vitamin cofactors, carbohydrates, and nucleic acids and is also important for sulfurating transfer, which regulates translation RNA. The creation of anti-cancer drugs has focused a lot of interest on heterocycles that include sulphur, much like their counterparts with bases in oxygen and nitrogen have[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. The researchers believe that their findings could be used as a basis for the creation of tyrosine kinase inhibitors in the future that have fewer side 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.	Cancer	Treated by drugs	Name in market	Company
1.	Hodgkin's and non-Hodgkin's lymphoma, ovarian, cervical, and testicular cancers	Bleomycin	Blenoxane®	Bristol Myers Squibb company



2.	Breast cancer in postmenopausal women	Raloxifene	Evista®	Eli Lilly and Company
3.	Treatment of metastatic or locally advanced breast cancer	Ixabepilone	Ixempra™	Bristol-Myers Squibb Company
4.	Treatment of cutaneous T-cell lymphoma (CTCL) Peripheral T-cell lymphomas (PTCLs)	Romidepsin	Istodax®	CELGENE
5.	Acute lymphoblastic leukemia and chronic myelogenousleukemia	Dasatinib	Sprycel®	Bristol Myers Squibb Company
6.	In the therapy of melanoma that expresses BRAF V600E gene mutation	Dabrafenib	Tafinlar®	GlaxoSmithKline

## V. CONCLUSION

Heterocycles play a crucial contribution in developing anti-cancer medications due to their frequency in nature and the diversity of their chemical and structural makeup. Their participation in more than 60% 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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