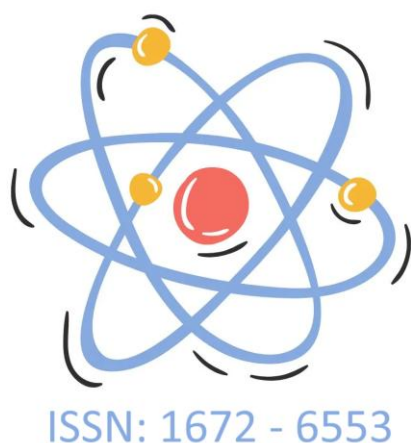




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PROMISING SCAFFOLDS FOR
ANTICANCER DRUG DEVELOPMENT**

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BIOACTIVE CHEMICAL NUCLEI AS PROMISING SCAFFOLDS FOR ANTICANCER DRUG DEVELOPMENT

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Abstract: Given the prevalence of unchecked cellular growth, genetic instability, metastasis, therapeutic resistance, and treatment-associated toxicity, cancer continues to be one of the biggest threats to world health. While targeted therapy, immunotherapy, conventional chemotherapy, and other multimodal techniques have significantly improved cancer management, therapeutic outcomes are still limited by tumor heterogeneity, drug resistance, side effects, and poor selectivity. In this regard, privileged heterocyclic scaffolds and bioactive chemical nuclei have become significant structural frameworks for the identification and improvement of new anticancer drugs. They can interact with a variety of cancer-associated targets and enable systematic structure–activity relationship (SAR) optimization thanks to their advantageous electronic, steric, hydrogen-bonding, and molecular-recognition features. The structural traits, primary anticancer processes, molecular targets, and significant SAR aspects of a few heterocyclic bioactive scaffolds—benzimidazole, quinazoline, pyrimidine, indole, and triazole/pyrazole are highlighted in this review. The successful conversion of these scaffolds into FDA approved, clinically effective anticancer medications is highlighted, highlighting their importance in contemporary medicinal chemistry. Recent developments in scaffold-based anticancer drug discovery, such as molecular hybridization, multitarget drug design, structure-based drug design. These new methods offer chances to enhance pharmacokinetic and pharmacodynamic characteristics, overcome medication resistance, and increase target selectivity. There are still issues with toxicity, resistance, tumor heterogeneity, drug-like characteristics, and clinical translation despite significant advancements. Therefore, the integration of bioactive scaffold optimization with precision oncology, computational technologies, biomarker-guided design, and novel target-modulation techniques will be necessary for future anticancer drug discovery. All things considered, bioactive heterocyclic nuclei remain flexible and clinically proven platforms for the creation of novel anticancer treatments.

Keywords: Heterocyclic nuclei; bioactive scaffolds; Benzimidazole, Quinazoline, Pyrimidine, Indole, Triazole, Pyrazole, anticancer agents, targeted drug discovery.

Introduction:

Uncontrolled cellular proliferation, resistance to cell death, genomic instability, altered cellular metabolism, angiogenesis, invasion, and metastatic dissemination are all characteristics of cancer, one of the most important global health challenges.¹ Millions of people worldwide die from cancer, which nevertheless places a heavy strain on healthcare systems and society despite significant advancements in cancer biology, diagnostic tools, and treatment approaches.² The International Agency for Research on Cancer (IARC) estimates that there were about 20 million new cancer cases and 9.7 million cancer-related deaths worldwide in 2022. By 2050, demographic shifts and population growth are expected to raise the annual number of new cases to about 35 million, a nearly 77% increase from 2022.³

Among the most common cancers diagnosed globally are breast, lung, liver, gastric, cervical, colorectal, prostate, and stomach cancers; lung, colorectal, liver, breast, and stomach cancers also significantly increase cancer-related mortality. Genetic variables, internal physiological stress, environmental exposures, lifestyle, and dietary habits all play a complex role in the development of cancer.^{4,5} These contributing factors may differ depending on the patient's location and kind of cancer, highlighting the necessity for customized evaluation and treatment plans. Moreover, it is that the rising incidence of cancer worldwide is a result of industrialization-related changes to the environment and climate as well as dietary and lifestyle choices.⁶⁻⁸

Current Treatment Modalities

Nonspecific cytotoxic methods of treating cancer have given way to multimodal, molecularly based treatments.⁹ Treatment options may include surgery, radiation, chemotherapy, endocrine therapy, immunotherapy, targeted therapy, stem-cell transplantation, or combinations of these, depending on the kind, stage, molecular profile, and patient characteristics of the tumor.¹⁰ For localized solid tumors, surgery is essential, and radiotherapy, either by itself or in conjunction with systemic medicines, offers local control.¹¹ Chemotherapy is still essential in cases of advanced and metastatic disease because it kills cancer cells that divide quickly. Targeted therapies produce kinase inhibitors, hormone-directed medicines, and monoclonal antibodies by interfering with certain proteins or pathways that drive tumor growth. Although immunotherapy increases anticancer immunity, it has drawbacks like as immune-related toxicities, resistance, and inconsistent efficacy.¹²

Limitations of Chemotherapy

Although it is still essential, conventional chemotherapy has poor selectivity between cancerous and healthy cells that divide quickly. Cytotoxic medications unintentionally damage bone marrow, gastrointestinal mucosa, and hair follicles by interfering with DNA replication, mitosis, or integrity. This reduces the therapeutic window and restricts safe dosage.¹³ Depending on the protocol, chemotherapy can have a variety of side effects, including myelosuppression, gastrointestinal issues, mucositis, alopecia, exhaustion, neurotoxicity, nephrotoxicity, cardiotoxicity, and hepatotoxicity. Dosage maintenance, quality of life, and treatment adherence are all hampered by these toxicities.¹⁴ Certain substances cause delayed or cumulative toxicities that continue after therapy. Therefore, one of the main objectives of contemporary medicinal chemistry is to increase tumor selectivity while maintaining or increasing anticancer activity.¹⁵

Drug Resistance

A significant obstacle to effective cancer treatment is drug resistance, which can develop as intrinsic or acquired resistance via cellular, epigenetic, genetic, and microenvironmental processes.¹⁶ Drug-target mutations, overexpression of efflux transporters, increased metabolism, changes in apoptotic signaling, changes in DNA repair, metabolic shifts, and activation of compensatory pathways are important factors. Because different subpopulations coexist, tumor heterogeneity makes sustained responses more difficult.¹⁷ Treatment removes sensitive clones while choosing resistant ones that promote progression. Additionally, cancer cells use different paths to avoid blocked targets, which decreases the effectiveness of focused therapy. Through secondary mutations, route reactivation, phenotypic plasticity, and microenvironmental alterations, resistance impacts both chemotherapy and targeted medicines. One of the main challenges in the search for anticancer drugs is creating compounds with high affinity, selectivity, and efficacy against resistant states.¹⁸

Toxicity and Selectivity

The goal of targeted therapies is to improve the therapeutic index by utilizing cancer-preferential molecular abnormalities, such as oncogenic kinase inhibition, angiogenesis blockade, DNA-repair modulation, hormone-receptor targeting, and tumor-specific dependency interference. However, targeted agents are not toxicity-free; their targets may function physiologically in normal tissues, and off-target interactions cause additional adverse effects.¹⁹

Need for Targeted Anticancer drugs

Targeted anticancer drugs have been developed as a result of conventional chemotherapy's poor selectivity, toxicity, and growing resistance. The goal of modern oncology is to identify molecular flaws that set cancerous cells apart from healthy ones. Proteins and processes governing cancer development, survival, and metastasis are disrupted by targeted therapy.^{20,21} This area is dominated by therapeutic antibodies and small-molecule inhibitors, which are particularly good at accessing intracellular targets. Finding druggable targets and creating selective, high-affinity ligands are essential for success. Thru pharmacokinetic refinement, modeling, and SAR investigations, medicinal chemistry optimizes bioactive heterocyclic scaffolds to provide safer, more potent anticancer medications.^{22,23}

Bioactive/Privileged Scaffolds and Heterocyclic Nuclei in Targeted Anticancer Drug Design

Often referred to as privileged scaffolds, bioactive chemical nuclei are recurrent molecular frameworks with structural and physicochemical characteristics that allow interaction with a variety of biological targets when substituted appropriately. These scaffolds are prevalidated starting points for hit identification and lead generation in medicinal chemistry, having been introduced to define cores that can provide ligands for many receptors by minor alterations. For effective chemical-space exploration during drug discovery, scaffold hopping, analog generation, and structure activity relationship (SAR) studies are made possible by a scaffold, which serves as the fundamental architecture around which functional groups are methodically added or altered to maximize activity.²⁴

Rational

The need for safer, more effective, and selective anticancer drugs is highlighted by the rising incidence of cancer worldwide and the shortcomings of current treatments. In pharmaceutical chemistry, heterocyclic chemical nuclei offer flexible platforms for lead optimization and molecular identification. This review focuses on specific bioactive heterocyclic scaffolds that have been shown to be relevant to the development of anticancer drugs, specifically benzimidazole, quinazoline, pyrimidine, indole, and triazole/pyrazole systems. We talk about their molecular targets, methods of action, structural properties, and key SAR traits. The effective conversion of bioactive scaffolds into FDA-approved anticancer medications is given special attention. Additionally featured are recent developments in scaffold-based drug design, computational methods, hybrid pharmacophores, AI-assisted discovery, and targeted protein degradation. The

article attempts to give a succinct overview of the development of bioactive chemical nuclei from ideas in medicinal chemistry to therapeutic applications for cancer.²⁵

Bioactive Nuclei as Scaffold for Anticancer Drug Design

Benzimidazole

A five-membered imidazole ring is fused with a benzene ring to form benzimidazole, a fused bicyclic heterocycle that contains nitrogen. Because of its structural and electrical properties that enable interaction with a wide variety of biological targets, the scaffold is regarded as a favored pharmacophore. Its similarity to the purine nucleus is crucial for biological identification and aids in electrostatic and hydrogen-bonding interactions with target proteins and nucleic acids. Because of these qualities, benzimidazole is a valuable scaffold in medicinal chemistry and a desirable place to start when creating anticancer drugs.^{26,27}

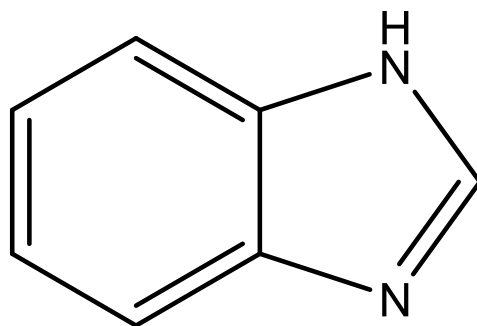


Figure 1: Benzimidazole

Benzimidazole derivatives exhibit multifaceted anticancer action. Inhibition of tubulin polymerization, topoisomerases, tyrosine kinases, PARP, androgen-receptor-associated pathways, and other cancer-related targets are among the mechanisms that have been reported. Additionally, derivatives of benzimidazoles may interact with DNA, cause cell-cycle arrest, induce DNA fragmentation, interfere with DNA replication or repair, and promote death. This scaffold's broad anticancer potential is explained mechanistically by its capacity to interact with both proteins and nucleic acids.^{28,29}

Quinazoline

Quinazoline is a fused bicyclic heterocycle that contains nitrogen and is made up of a pyrimidine ring and a benzene ring. Favorable electrical and hydrogen-bonding properties are provided by the presence of two ring nitrogen atoms, which make interactions with protein kinases' ATP-binding domains easier. These characteristics have made quinazoline a valuable favored scaffold in medicinal chemistry, especially for the creation of receptor tyrosine kinase inhibitors. It is a

desirable framework for targeted anticancer drug design because it allows for a variety of substitutions around the quinazoline nucleus, allowing for the modification of potency, selectivity, lipophilicity, and pharmacokinetic features.³⁰

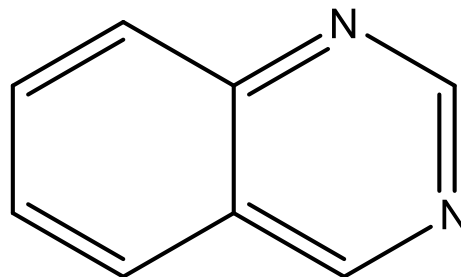


Figure 2: Quinazoline

By blocking human epidermal growth factor receptor 2 (HER2), vascular endothelial growth factor receptor (VEGFR), epidermal growth factor receptor (EGFR), and other tyrosine kinases, quinazoline derivatives demonstrate strong anticancer action. Cancer-cell proliferation, survival, migration, and angiogenesis can all be inhibited by blocking EGFR/HER2 signaling. The anticancer medications gefitinib, erlotinib, lapatinib, afatinib, and dacomitinib are examples of quinazoline-based medications. Additional derivatives with enhanced kinase selectivity and activity against clinically significant resistant cancer phenotypes have been created by structurally altering the quinazoline nucleus and adding substituted anilines or other pharmacophores.³¹

Pyrimidine

Pyrimidine is an aromatic heterocycle with six members that has two nitrogen atoms at the 1,3-positions. Its structural similarity to pyrimidine bases found in nucleic acids and its capacity to take part in hydrogen-bonding and other molecular recognition interactions make it a significant biological heterocycle. Medicinal chemists can add a variety of functional groups and enhance target affinity and drug-like properties because to the pyrimidine ring's electrical properties and numerous substitution opportunities. As a result, pyrimidine has emerged as a crucial scaffold in the rational design of anticancer drugs, especially for the creation of kinase inhibitors and medicines targeting cell-cycle regulatory pathways.³²

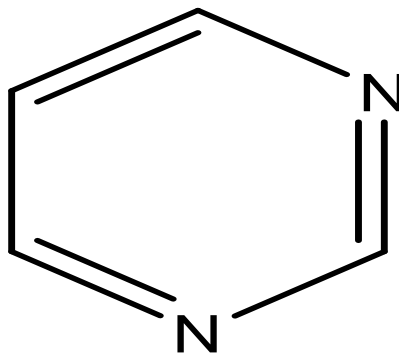


Figure 3: Pyrimidine

Pyrimidine derivatives exhibit anticancer action via modulating a number of significant molecular targets, including as cyclin-dependent kinases (CDKs), BCR-ABL, EGFR, vascular endothelial growth factor receptors, and phosphoinositide 3-kinase (PI3K). Oncogenic signaling, cell proliferation, survival, and cell-cycle progression can all be hampered by inhibition of these targets. Imatinib and a number of CDK-directed drugs are examples of pyrimidine-containing molecules that highlight the clinical significance of nitrogen-containing heterocyclic frameworks in cancer treatment. Derivatives with enhanced potency, selectivity, and potential activity against resistant cancer cells have been produced thru structural alteration at various pyrimidine nucleus locations and hybridization with additional pharmacophores.³³

Indole

A five-membered pyrrole ring and a benzene ring fuse to generate indole, a bicyclic heterocycle that contains nitrogen. It is often found in physiologically active compounds and natural products, and in medicinal chemistry, it is regarded as a significant favored scaffold. Indole's nitrogen atom can engage in hydrogen bonding with biological targets, and its planar aromatic structure offers chances for hydrophobic and π - π interactions. It is possible to systematically optimize the electrical, steric, and physicochemical properties of indole derivatives because there are multiple structurally modifiable locations. These qualities have made indole a flexible scaffold for the creation of anticancer drugs.³⁴

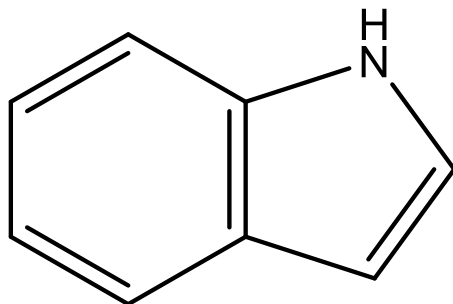


Figure 4: Indole

Through a variety of mechanisms, such as tubulin inhibition, kinase modulation, apoptosis induction, cell-cycle arrest, suppression of angiogenesis, and disruption of signaling pathways linked to cancer, indole derivatives demonstrate anticancer properties. Numerous indole-based substances have the ability to interfere with tubulin's colchicine-binding region and alter microtubule dynamics, which can cause apoptosis and mitotic arrest. Other derivatives have been studied against kinase-related targets and enzymes implicated in the growth and survival of tumors. While many indole, oxindole, and bis-indole derivatives have been explored as potential multitarget anticancer medicines, sunitinib is a significant clinically used indole-containing anticancer medication.³⁵

Triazole and Pyrazole

The five-membered nitrogen-containing heterocyclic nucleus triazole and pyrazole have garnered significant attention in medicinal chemistry due to their structural diversity, adjustable electrical characteristics, and capacity to form advantageous interactions with biological targets. The two nitrogen atoms in pyrazole and the three nitrogen atoms in triazole have distinct electrical and hydrogen-bonding properties. These heterocycles are often used as pharmacophores or linkers in bigger molecular frameworks because they are easily functionalized. Triazole and pyrazole are useful scaffolds for the design and optimization of new anticancer drugs because of their structural adaptability and compatibility with molecular hybridization.^{36,37}

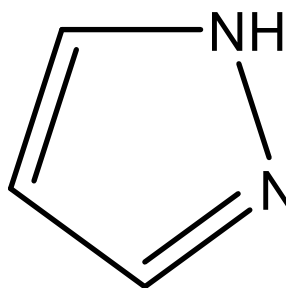
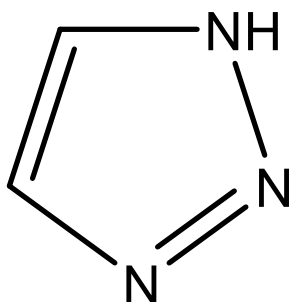


Figure 5: Triazole**Figure 6: Pyrazole**

Through a variety of methods, such as inhibition of protein kinases, tubulin polymerization, angiogenic signaling, cell-cycle regulatory proteins, and other cancer-associated targets, triazole and its derivatives exhibit anticancer action. While triazole-containing drugs have been created as kinase inhibitors and multitarget anticancer medicines, pyrazole derivatives have been studied against targets like EGFR, VEGFR-2, CDKs, BRAF, and tubulin. A successful method for producing compounds with complimentary mechanisms and increased biological activity is the hybridization of triazole or pyrazole with pharmacophores such benzimidazole, quinazoline, indole, pyrimidine, quinoline, coumarin, and chalcone. Triazole and pyrazole are appealing nuclei for modern anticancer drug research because of these characteristics.³⁸

Bioactive scaffold-based anticancer medications approved by the FDA

Since heterocyclic scaffolds' structural and electrical characteristics allow for specific interactions with enzymes, receptors, kinases, and other cancer-associated targets, they have made a significant contribution to the development of clinically effective anticancer medications. The chosen nuclei covered in this article are found in a number of authorized anticancer medications, including the benzimidazole, quinazoline, pyrimidine, indole, triazole, and pyrazole systems. These medications show how the optimization of a bioactive chemical nucleus can result in effective targeted treatments that are clinically helpful.³⁹ Bioactive scaffold-based anticancer medications approved by the FDA show in table 1.

Table: 1 Bioactive scaffold-based anticancer medications approved by the FDA.

S. No.	Bioactive Scaffold	Representative FDA-Approved Drugs	Molecular Target	Cancer Indication
1.	Benzimidazole	Abemaciclib	CDK4/6Inhibition	HR-positive/HER2-negative breast cancer
2.	Benzimidazole	Selumetinib	MEK1/2Inhibition	Neurofibromatosis type 1-associated tumors
3.	Quinazoline	Gefitinib	EGFR Inhibition	EGFR- mutated NSCLC
4.	Quinazoline	Erlotinib	EGFR Inhibition	non-small cell lung cancer, pancreatic cancer

5.	Quinazoline	Afatinib	Irreversible EGFR/HER2/HER4 Inhibition	non-small cell lung cancer
6.	Quinazoline	Lapatinib	EGFR/HER2 Inhibition	HER2- positive breast cancer
7.	Pyrimidine	Imatinib	BCR-ABL, KIT, PDGFR Inhibition	Chronic Myeloid Leukemia, Gastrointestinal Stromal Tumor
8.	Pyrimidine	Palbociclib	CDK4/6Inhibition	HR-positive/HER2- negative breast cancer
9.	Pyrimidine	Ribociclib	CDK4/6 Inhibition	HR-positive/HER2- negative breast cancer
10.	Indole	Sunitinib	VEGFR.PDGFR and other kinase Inhibition	Chronic Myeloid Leukemia, Gastrointestinal Stromal Tumor and other tumors
11.	Triazole	Anastrozole	Aromatase Inhibition	Hormone-receptor-positive breast cancer
12.	Triazole	Letrozole	Aromatase Inhibition	Hormone-receptor-positive breast cancer
13.	Pyrazole	Ruxolitinib	JAK1/JAK2 Inhibition	Myelofibrosis polycythemia vera

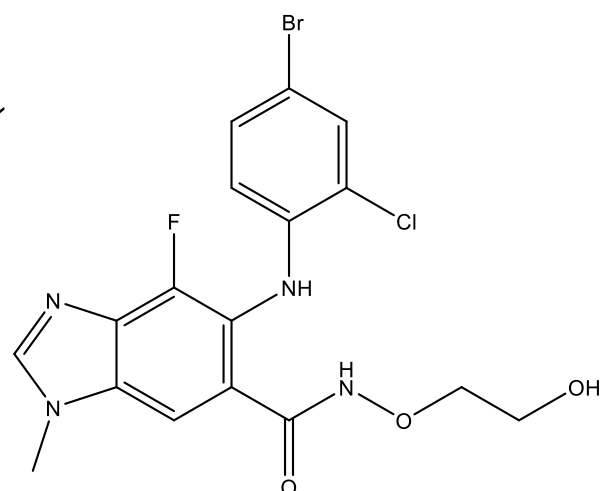
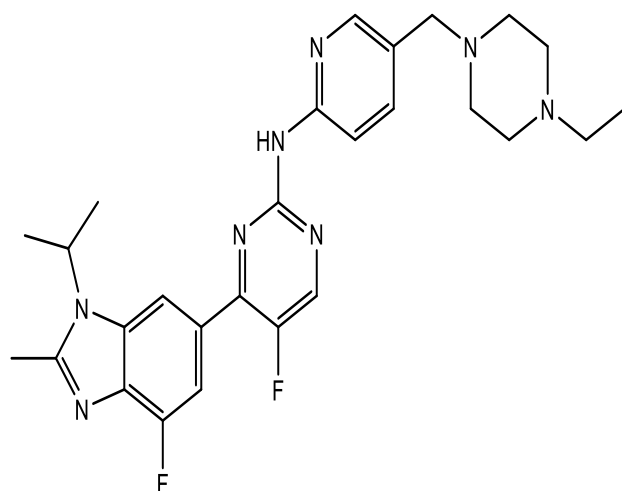
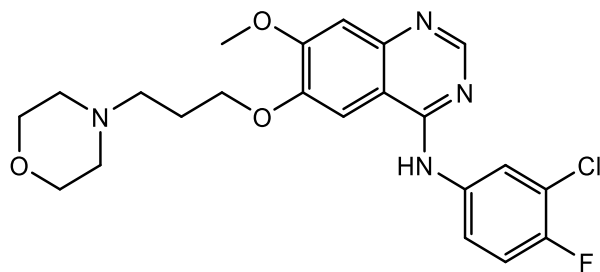
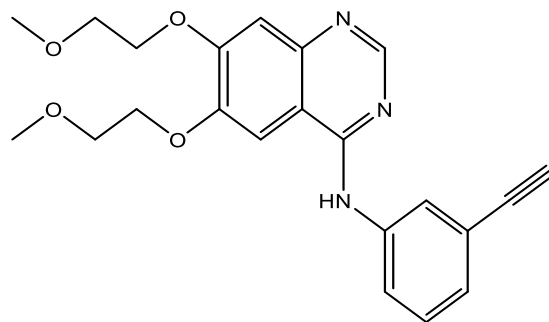
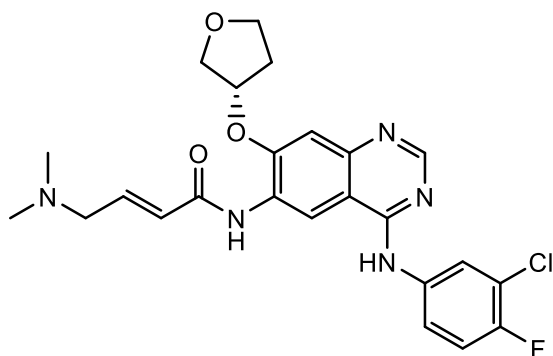
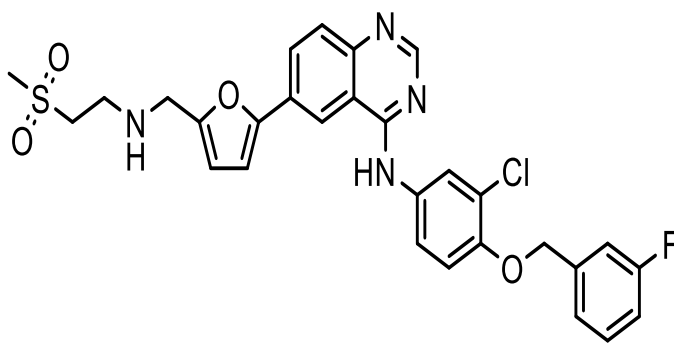
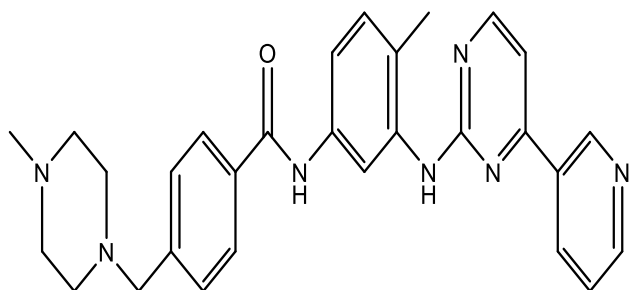
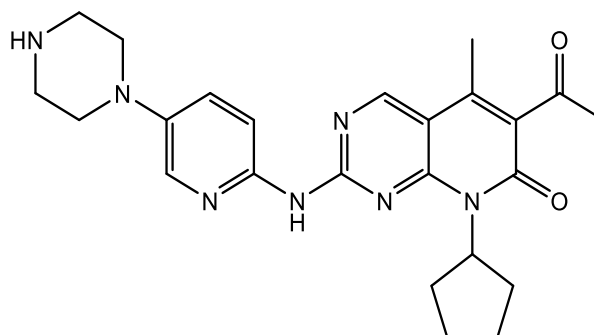
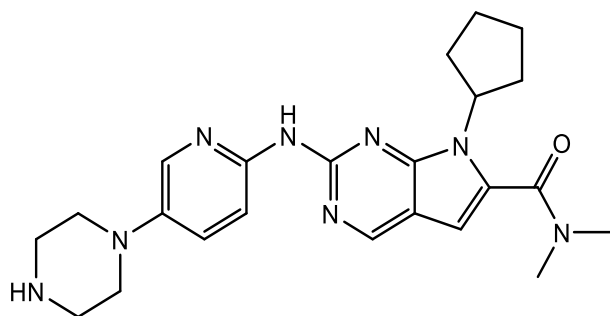
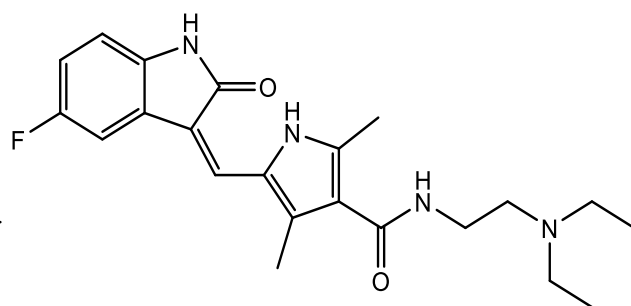


Figure 7: Abemaciclib**Figure 8: Selumetinib****Figure 9: Gefitinib****Figure 10: Erlotinib****Figure 11: Afatinib****Figure 12: Lapatinib****Figure 13: Imatinib****Figure 14: Palbociclib****Figure 15: Ribociclib****Figure 16: Sunitinib**

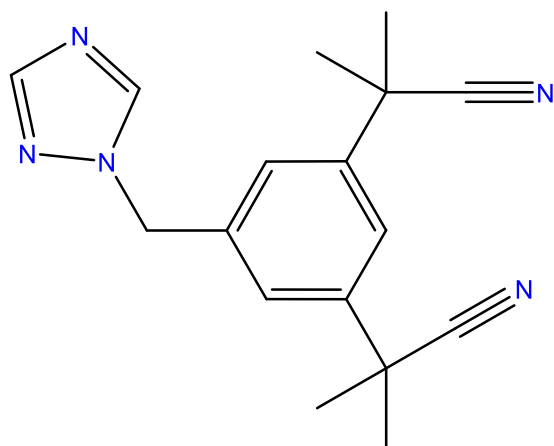


Figure 17: Anastrozole

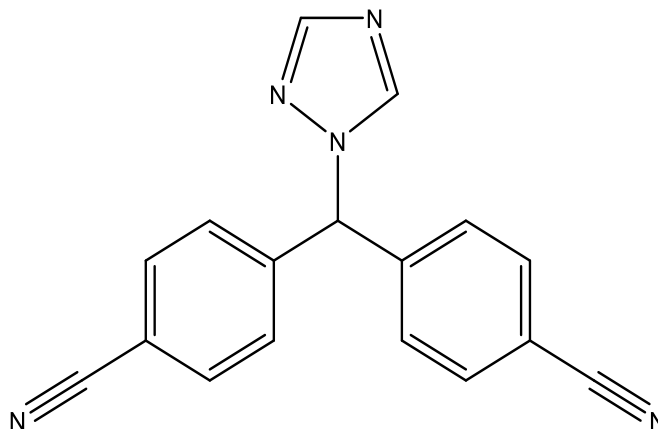


Figure 18: Letrozole

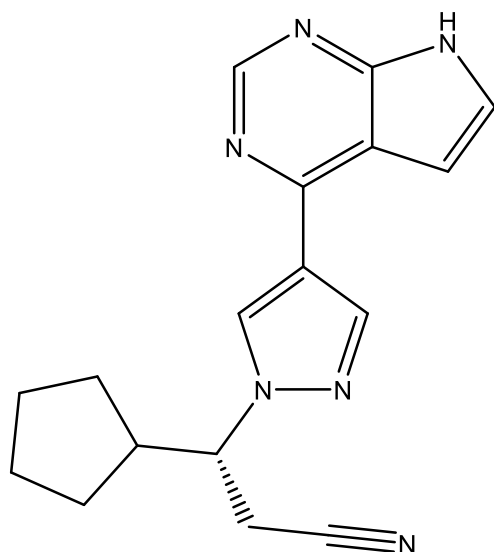


Figure 19: Ruxolitinib

Recent Advances in Bioactive Scaffold-Based Anticancer Drug Discovery

Bioactive chemical scaffolds function as flexible molecular frameworks that can be altered to improve target affinity, selectivity, potency, pharmacokinetic properties, and activity against resistant cancer phenotypes. The range of targets that can be addressed using scaffold-based medicinal chemistry has expanded due to the ongoing identification of kinase, DNA-repair, epigenetic, metabolic, and cell-cycle vulnerabilities. Heterocyclic nuclei continue to be particularly important because their electronic and hydrogen-bonding properties can be systematically adjusted thru substitution and scaffold modification.⁴⁰

Scaffold Hybridization and Multitarget Drug Design

Molecular hybridization, which combines two or more pharmacologically significant structural patterns into a single molecule, is one of the most important modern approaches. This method can produce chemicals that interact with several cancer-associated sites by combining complimentary processes inside a single chemical entity. Kinase inhibition, tubulin disruption, apoptosis induction, and suppression of angiogenic signaling have all been studied in heterocyclic hybrids such as benzimidazole–triazole, quinazoline–triazole, indole–chalcone, pyrimidine–pyrazole, and others. By concurrently influencing linked signaling pathways, hybridization also offers a chance to get beyond the drawbacks of single-target therapy.⁴¹

Although cancer cells often activate compensatory mechanisms after inhibition of a single target, the development of dual- and multitarget inhibitors has become especially important. For instance, pyrimidine- and pyrazole-containing drugs have been created against several kinase families, whereas quinazoline-based compounds have been thoroughly optimized for EGFR/HER2 and other receptor tyrosine kinases. While preserving a rather compact molecular architecture, such scaffold modification can enhance biological coverage. However, multitarget action needs to be carefully weighed against toxicity and any off-target consequences.⁴²

Computational techniques and structure-guided design

Molecular docking, pharmacophore modeling, molecular dynamics simulations, QSAR, virtual screening, and ADMET prediction are increasingly being used with experimental medicinal chemistry in contemporary scaffold-based drug development. These computational methods enable researchers to prioritize derivatives before synthesis and assist in identifying significant interactions between heterocyclic scaffolds and target proteins. Specifically, hydrogen-bonding interactions, hydrophobic pockets, steric needs, and suitable substitution sites that affect biological activity can be found using structure-based optimization.⁴³

Designing drugs against clinically relevant resistance targets has made the integration of computational methods with SAR investigations very beneficial. For instance, efforts to create EGFR inhibitors that can treat resistance-associated mutations are part of the current study on nitrogen-containing heterocycles. This approach demonstrates the progression from merely finding strong compounds to creating molecules with enhanced target interaction, mutation selectivity, and possible effectiveness against resistant cancers.⁴⁴

Conclusion

In light of their adjustable electronic, steric, and hydrogen-bonding characteristics, which enable selective interactions with a variety of cancer-associated biological targets, bioactive heterocyclic nuclei have become essential structural components in contemporary anticancer drug research. Benzimidazole, quinazoline, pyrimidine, indole, triazole, and pyrazole are examples of scaffolds that offer flexible molecular frameworks that can be methodically altered to maximize potency, selectivity, physicochemical characteristics, and pharmacokinetic behavior. They are consequently useful starting points for rational design and structure–activity relationship (SAR)-driven optimization of anticancer drugs due to their unique structural features.

These scaffolds' therapeutic importance is further demonstrated by the fact that they have been successfully translated into clinically relevant medications. These heterocyclic nuclei are incorporated into a number of FDA-approved anticancer medications that target key molecular targets including as EGFR, HER2, BCR-ABL, CDK4/6, JAK1/2, VEGFR, PDGFR, and aromatase. The clinical success of drugs like gefitinib, erlotinib, afatinib, imatinib, palbociclib, ribociclib, sunitinib, anastrozole, and letrozole demonstrates how suitable scaffold selection combined with methodical structural optimization can result in effective and useful anticancer treatments.

The fact that these scaffolds have been effectively converted into clinically useful drugs serves as additional evidence of their therapeutic significance. Many FDA-approved anticancer drugs that target important molecular targets like EGFR, HER2, BCR-ABL, CDK4/6, JAK1/2, VEGFR, PDGFR, and aromatase contain these heterocyclic nuclei. The clinical success of medications such as gefitinib, erlotinib, afatinib, imatinib, palbociclib, ribociclib, sunitinib, anastrozole, and letrozole shows how careful structural optimization in conjunction with appropriate scaffold selection can produce valuable and effective anticancer medicines.

The development of effective anticancer drugs is still hampered by issues such drug resistance, off-target toxicity, poor pharmacokinetic qualities, tumor heterogeneity, insufficient tumor penetration, and limited clinical translation. Therefore, the integration of scaffold-based medicinal chemistry with precision oncology, AI-driven design, biomarker-guided therapy, resistance-oriented optimization, and targeted protein degradation should be the main emphasis of future research. In the end, the logical development of bioactive chemical nuclei from proven

pharmacophores into extremely patient-specific and selective therapeutic agents may offer fresh chances to get over the present constraints in cancer treatment.

Conflict of Interest: None

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