Review Article

Heterocyclic Tyrosine Kinase Inhibitors: Structural Insights and Medicinal Chemistry Strategies in Cancer, Immune-Mediated Disorders and Myeloproliferative Neoplasms

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Abstract

Tyrosine kinases (TRs) regulate cellular signaling pathways involved in cell growth changes in cell type, survival, formation of new blood vessels, and responses from the immune system. When tyrosine kinases on the surface or inside the cells work, they play a significant role in making cancer problems with the immune system and inflammation and also in making too many blood cells. The creation of medicines that block tyrosine kinases has shown how important special ring-shaped molecules are for making these medicines work well, be specific, and have good effects in the body. This review provides a look at the chemistry side of medicines that block tyrosine kinases and focuses on how their chemical shapes, ring structures, the kinases they target, and the ways they are used in treatment are connected. The review talks about gefitinib, which is based on a quinazoline ring and targets EGFR, Lapatinib, which is made from a quinoline ring and targets EGFR and HER2, Imatinib, which has a part and targets BCR–ABL, KIT, and PDGFR, Ponatinib, which has an imidazopyridazine part and was made to work against BCR–ABL, especially the T315I mutation, and Dasatinib, which has a thiazole part and works against BCR–ABL and SRC-family kinases. In diseases where the immune system is not working correctly or there is much inflammation, the review talks about Tofacitinib, which is a heterocyclic JAK inhibitor, and Ibrutinib and Zanubrutinib, which are covalent BTK inhibitors based on a pyrazolopyrimidine ring. The way these medicines work with the kinases and the shapes they have are explained. The way blocking kinases helps in neoplasms is shown by Pacritinib, which blocks many kinases and targets JAK2 and related paths and Ruxolitinib, which blocks JAK1 and JAK2. Special attention is given to the variety of ring structures how they work with the ATP molecule how they find the hinge area how they block the kinase in an temporary way how specific they are and how the shapes of the medicines relate to their effects. Overall, the medicines described show how changing the ring parts and other parts of the molecules has led to medicines that target specific problems, in cancer, immune diseases, and myeloproliferative neoplasms.

Keywords: Tyrosine kinase inhibitors; heterocyclic scaffolds; quinazoline; quinoline; piperazine; thiazole; indazole; pyrimidine; pyrazolopyrimidine; JAK inhibitors; BTK inhibitors; myeloproliferative neoplasms.

Introduction

Protein phosphorylation is a mechanism by which cells regulate numerous critical processes, including growth, differentiation, motility, energy utilization, survival, and immune system function. Protein tyrosine kinases are enzymes that take phosphate from ATP and place it on the tyrosine parts of proteins. This helps set up signals that link events outside the cell to changes inside the cell. The human kinome includes hundreds of kinases. These include kinases that sit on the cell surface and those that work inside the cell. When these kinases do not work correctly, it can lead to problems, such as cancer and diseases in which the immune system acts incorrectly [1].

Receptor tyrosine kinases are proteins that cross the cell membrane once. They usually have a part outside the cell that binds signals and a part that goes through the membrane and a part, inside the cell that works as a kinase. When a signal binds, the shape of the receptor changes or two receptors pair up [2]. Helper proteins join. These actions activate the kinase part. The receptor adds phosphate groups to itself. The phosphotyrosine spots then bring in signaling proteins [3]. Start the RAS–RAF–MEK–ERK, PI3K–AKT–mTOR and JAK–STAT pathways. If a gene mutates copies itself many times rearranges or is made in excess the normal signaling can become a constant cancer promoting signal.

From a medicinal chemistry perspective, the kinase ATP-binding cleft is very appealing. The cleft is a pocket. It can spot hydrogen bond acceptors, hydrophobic groups and basic or polar groups that sit in the right places. The success of kinase inhibitors has led to extensive research on quinazoline, quinoline, pyrimidine, pyrazolopyrimidine, indazole, imidazopyridazine, thiazole, and other fused heterocycles [4].

2. TYROSINE KINASE CLASSIFICATION AND SIGNALING

Tyrosine kinases can be classified into two groups: receptor tyrosine kinases and non-receptor tyrosine kinases. Examples of receptor tyrosine kinase families include EGFR/ErbB, ALK, DDR, Eph, FGFR, the insulin/IG-1 receptor, MET, MuSK, PDGFR, RET, ROR, ROS1, RYK, TAM, TIE, TRK, and VEGFR families. Key non-receptor tyrosine kinase groups include ABL, ACK, CSK, FAK, FES, FRK, JAK, SRC, SYK, and TEC families [5].

Class/family	Representative targets	Major signaling or disease relevance
RTKs-EGFR/ErbB	EGFR, HER2,HER3,HER4	Solid tumors; RAS-MAPK and PI3K-AKT signaling
RTKs-VEGFR	VEGFR-3	Angiogenesis and tumor vascularization
RTKs-PDGFR/FGFR	PDGF α/β, FGFR1-4	Proliferation, stromal signaling and selected malignancies
RTKs-KIT/MET/RET	KIT,MET,RET	Hematologic and solid tumors
RTKs-TRK/ALK/ROS1	NTRK1-3,ALK,ROS1	Oncogenic fusion/rearrangement driven cancers
NRTKs-JAK	ABL1/BCR-ABL,SRC family	CML,ALL and signaling in solid tumors
NRTKs-JAK	JAK1-3,TYK2	Cytokine signaling; autoimmune/inflammatory disease and MPNs
NRTKs-BTK/TEC	BTK,TEC,ITK	B-cell receptor and immune signaling-cell malignancies
NRTKs-SYK	SYK,ZAP70	Immune-receptor signalling and inflammatory disease

Figure 1. Schematic classification of receptor and non-receptor tyrosine kinases. A ready-to-publish figure should be redrawn in a vector format and cited to a reliable kinase-classification source.[6]

3. PHYSIOLOGICAL ACTIVATION OF RECEPTOR TYROSINE KINASES

Receptor tyrosine kinases are activated through interactions with ligands and the arrangement of receptors on the cell surface. The exact mechanism of activation depends on the receptor type. In some cases, a ligand causes two receptors to pair up, forming a dimer. In other cases, the receptor itself changes shape when a ligand binds. Sometimes several receptors gather together in a cluster because of the ligand. Accessory molecules, such as sulfate, can also help control the process. For instance neurotrophins bind to Trk receptors. Turn them on [7]. EGFR activation requires a change in the receptor's structure triggered by its ligand. FGFR signaling is especially influenced by sulfate proteoglycans.

After activation, the receptors add groups to each other. This process is called trans-autophosphorylation. These phosphate groups become docking sites for proteins that have SH2 or PTB domains. Once these proteins attach, they kick off pathways inside the cell. Common pathways include RAS/MAPK/ERK, PI3K/AKT, PLCγ, and STAT signaling. Because these signals need to be turned on and off at the right time and place, tight control over phosphorylation is crucial for maintaining healthy tissues. When kinase activity remains active for a long time —due to mutations, extra copies of the gene, fusion proteins, or failure of natural brakes—what should be a normal physiological signal can instead drive disease [8].

4. TYROSINE KINASES AS ANTICANCER TARGETS

Cancer cells often become dependent on kinase signaling due to activating mutations, gene amplification, chromosomal rearrangements, or autocrine growth-factor loops. Examples include EGFR alterations in non-small-cell lung cancer, BCR–ABL1 in CML, VEGFR-driven angiogenesis, and abnormal JAK/STAT signaling in neoplasms [9]. Small-molecule tyrosine kinase inhibitors can block these pathways by competing with ATP stabilizing forms of the kinase binding to allosteric sites or forming covalent bonds with cysteine residues in the correct position.

The challenge in chemistry is not just about making the drug more potent against the enzyme. Clinically effective inhibitors must also have solubility, proper permeability, metabolic stability, selectivity, sufficient tissue exposure, and acceptable tolerability. Resistance can develop through mutations at the target site signaling pathways, gene amplification, changes in cell behavior, or altered drug distribution. Because of this, changing the core scaffold and carefully optimizing substituents are key steps in designing next-generation tyrosine kinase inhibitors [10].

5. HETEROCYCLIC SCAFFOLDS IN CLINICALLY TYROSINE KINASE INHIBITORS

The following sections organize the provided information based on chemical scaffold and disease area. This method works better for a chemistry-focused review than listing drugs by disease.

5.1 Quinazoline and Quinoline Scaffolds: EGFR/HER2-Directed Therapy

Gefitinib – quinazoline scaffold

Gefitinib is a 4-anilinoquinazoline EGFR tyrosine kinase inhibitor. The quinazoline ring has heteroatoms and fits well into the hinge region of the kinase. The anilino group and side chain that helps with solubility reach into parts of the ATP-binding pocket. Gefitinib blocks ATP from binding to EGFR. This prevents the receptor from phosphorylating itself. It halts signaling through pathways such as RAS/RAF/MEK/ERK and PI3K/AKT [11].

In patients, certain EGFR mutations, such as exon 19 deletions and the L858R mutation, make tumors respond strongly to first-generation EGFR TKIs. The reason for this response shows how important the shape of the kinase and the way the drug recognizes the heterocyclic core are in targeted cancer treatment [12]. Over time, resistance developed through EGFR changes or alternate signaling routes. This led scientists to design second- and third-generation EGFR inhibitors to overcome resistance.

Lapatinib – quinoline-derived scaffold

Lapatinib is a drug based on a quinoline structure. It is a 4-anilinoquinoline-derived compound that acts as an inhibitor of EGFR and HER2. The drug works by binding to the inside of the kinase at the ATP -binding site. This prevents the activation of signaling pathways that depend on phosphorylation. By blocking these signals, lapatinib interrupts the growth and survival of cancer cells.

The dual action of lapatinib on both EGFR and HER2 gives it a unique profile. This feature was key in designing treatments for breast cancer with copies of the HER2 gene. Changing the core ring structure and adding substituents can influence the targeted kinases. This demonstrates how minor chemical changes can alter the selectivity of a drug toward receptors [13].

Clinical trials showed that lapatinib had activity in HER2- cancers. Its effects were stronger when used with drugs. Still not all patients respond well. Some tumors develop resistance over time. In groups, the benefits are limited. These results highlight the need to select patients based on markers. Combining Lapatinib with agents could improve outcomes and overcome resistance.

5.2 Piperazine-Containing Scaffolds: ABL/PDGFR/KIT Inhibition

Imatinib – piperazine-containing 2-phenylaminopyrimidine

Imatinib contains a 2-phenylaminopyrimidine kinase-binding motif. Imatinib also has an N-methylpiperazine group that helps with polarity and water handling. Imatinib was developed to inhibit BCR–ABL1. Later, Imatinib showed activity against KIT and PDGFR kinases. By stabilizing the conformation of ABL1, Imatinib suppresses constant kinase signaling in Philadelphia chromosome-positive CML and related disorders.

From a chemistry perspective, imatinib is an example of a modular heterocycle-based kinase design [14]. The pyrimidine nitrogen atoms provide hinge recognition. Aromatic regions occupy hydrophobic pockets. The piperazine-containing portion improves the properties while extending toward the solvent-exposed space. This architecture has become a template for kinase inhibitor optimization.

5.3 Imidazopyridazine Scaffold: Broad-Spectrum BCR–ABL Inhibition

Ponatinib

Ponatinib is an active third-generation BCR–ABL inhibitor. It contains an imidazopyridazine system and an ethynyl linker. A linear carbon–carbon triple bond was specifically added to fit the gatekeeper T315I mutation in BCR–ABL1. Ponatinib blocks the form of BCR–ABL1 and also works against the T315I mutant. It shows activity against other

kinases, including members of the VEGFR, FGFR, PDGFR, SRC, KIT, and RET families [15].
The example of Ponatinib highlights an idea in medicinal chemistry: making the linker more rigid and maintaining the correct direction from the hinge-binding heterocycle can help maintain target binding even when resistance mutations cause steric changes. Its broad effect on kinases also shows the balance between strong activity against resistant targets and the risk of off-target side effects.

5.4 Thiazole-Containing Multikinase Scaffolds

Dasatinib

Dasatinib has a thiazole-containing structure. It also includes hydroxyethyl-piperazine and other polar groups. This compound is a second-generation inhibitor of BCR–ABL1 and SRC-family kinases. It also inhibits KIT and PDGFR along with other kinases. Unlike Imatinib Dasatinib can bind to both inactive forms of the kinase. This ability helps to explain its potency and wide range of targets.

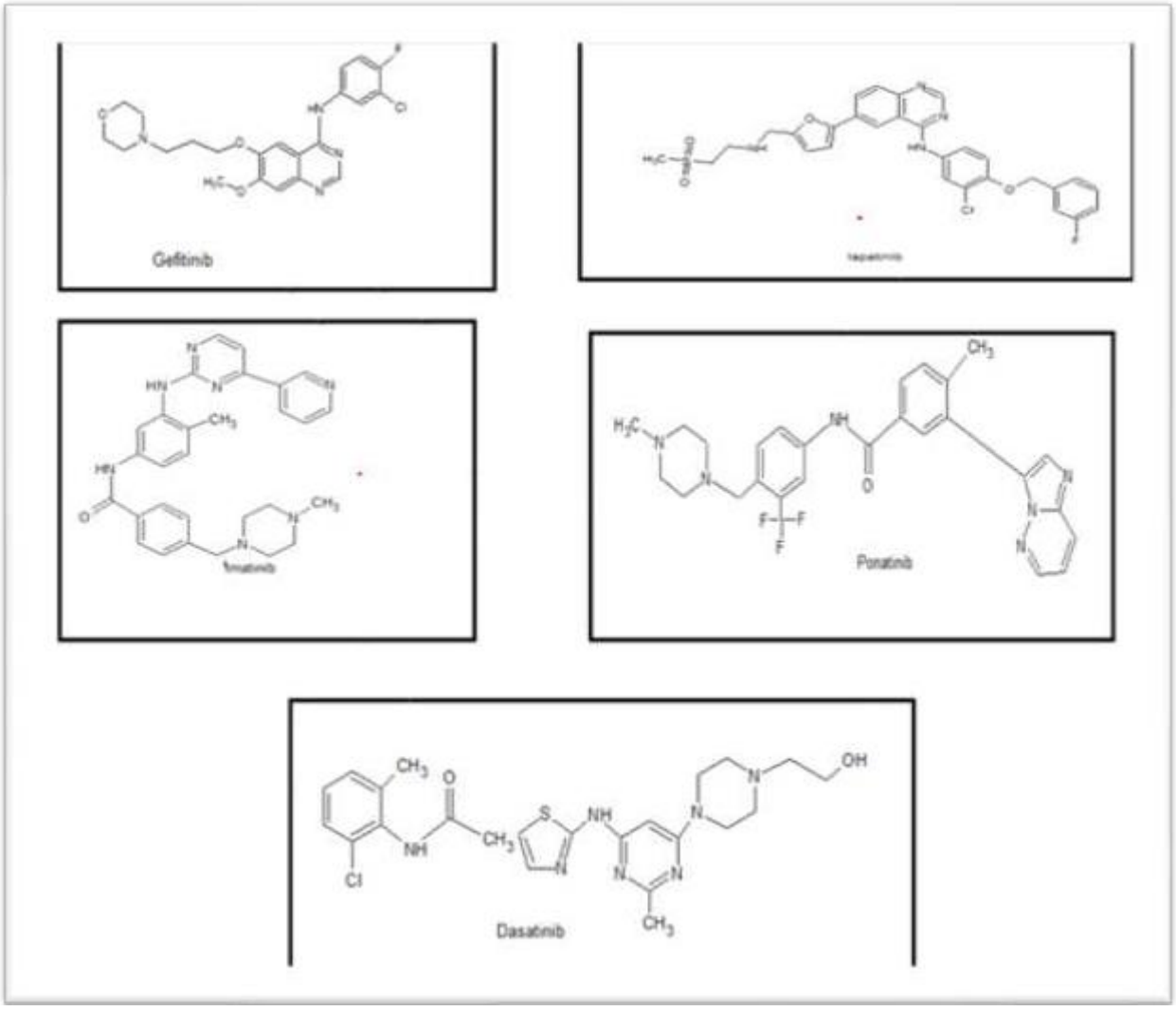


Figure 2. Chemical structures of representative tyrosine kinase inhibitors, including Gefitinib, Lapatinib, Imatinib, Ponatinib, and Dasatinib, illustrating the structural diversity of small-molecule kinase inhibitors used in cancer therapy [16].

The chemical design of dasatinib shows how effective it can be to combine a hinge-binding heterocycle with a solubilizing basic group [17].While inhibiting SRC kinase has raised interest in treating tumors such as breast cancer, the results in clinical settings have not been as consistent as those in leukemia. The role of Dasatinib in leukemia

remains clearly established. Its use in solid tumors has not fully delivered on early expectations.

6. TYROSINE KINASE INHIBITION IN AUTOIMMUNE/INFLAMMATORY DISORDERS

Unlike receptor tyrosine kinases many immune mediated disorders are driven by too much cytokine signalling through intracellular JAKs. Cytokine receptor engagement activates receptor-associated JAKs, which add groups to STAT proteins. Phosphorylated STAT proteins pair together. Move into the nucleus, where STAT proteins control genes that cause inflammation and immune responses [18]. Pharmaceutical interruption of this pathway has made JAK inhibitors an important class of medicines for rheumatoid arthritis, psoriatic arthritis, inflammatory bowel disease, and inflammatory skin diseases [19].

From a chemistry point of view selective JAK inhibition is difficult because the ATP-binding sites of JAK family members are very similar. Modern development therefore mixes hinge binding heterocycles with contacts, in neighboring pockets to give JAK1, JAK2, JAK3 or TYK2 preference. Upadacitinib shows how JAK1 preference can be achieved while Tofacitinib demonstrates how broader JAK pathway modulation can succeed clinically [20].

6.1 Fused Heteroaromatic JAK Inhibitors in Autoimmune and Inflammatory Disease

Tofacitinib

Tofacitinib is a type of JAK inhibitor that works by competing with ATP. It has a core made up of a structure that contains a pyrrolopyridine. It mainly stops JAK1 and JAK3 from working in cells. This action affects the signals from cytokines that are needed for the activation of lymphocytes and the body's inflammatory responses [21]. It is used for treating rheumatoid arthritis, psoriatic arthritis, ulcerative colitis, and some inflammatory conditions in children. The structure of Tofacitinib provides chemical information because a fused nitrogen heterocycle can help in recognizing the hinge and also offer a stable base for placing other groups. The development of Tofacitinib also shows that small changes in which kinases are targeted can lead to differences in how well the medicine works and how safe it is.

6.2 Pyrazolopyrimidine-Based Covalent BTK Inhibitors

Ibrutinib

Ibrutinib contains a pyrazolo [3,4-d] pyrimidine core that has been modified and it also has an acrylamide group that acts as an electrophile. The heteroaromatic part of Ibrutinib fits into the ATP-binding site of Bruton tyrosine kinase (BTK). The acrylamide part then forms a covalent bond with the cysteine residue Cys481. This way of working makes Ibrutinib different from inhibitors that only bind reversibly to the ATP site [22].

BTK acts as a messenger in the signaling pathway of B-cell receptors. Because Ibrutinib blocks BTK, Ibrutinib stops downstream pathways, such as NF-κB, PI3K/AKT, and ERK signaling. Ibrutinib can also lower the growth, survival, movement, and interactions with the surrounding environment of B cells. Ibrutinib has proven useful in treating lymphocytic leukemia (CLL) and other B-cell cancers.

Zanubrutinib

Zanubrutinib is a next-generation covalent BTK inhibitor that uses a substituted pharmacophore. Like Ibrutinib it works on Cys481 but the way the molecules are structured was made better to get a higher level of BTK coverage and better choice over some TEC and EGFR family kinases [23]. This example shows how small changes, around a heteroaromatic part can make the target more specific and the drug work better while still using a covalent method.

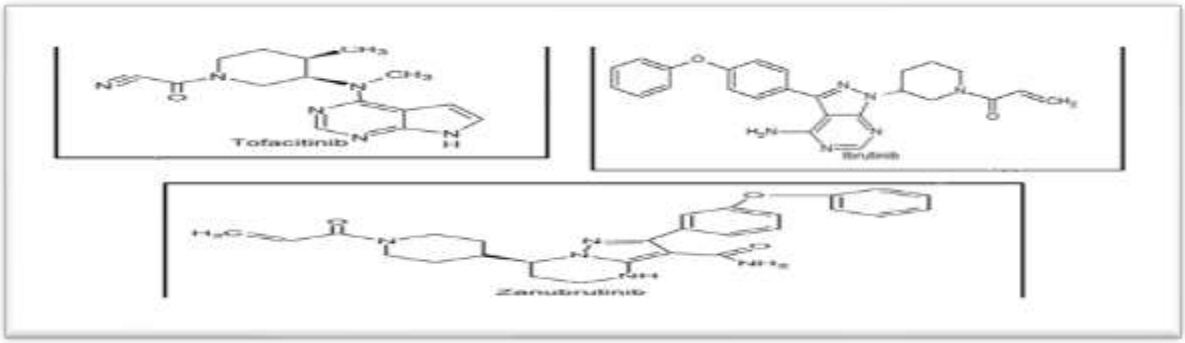


Figure 3. Chemical structures of selected clinically relevant kinase inhibitors: Tofacitinib (JAK inhibitor), Ibrutinib

(first-generation covalent BTK inhibitor), and Zanubrutinib (next-generation covalent BTK inhibitor) [24].

7. TYROSINE KINASES IN MYELOPROLIFERATIVE NEOPLASMS

MPNs illustrate the importance of intracellular tyrosine kinase signaling in hematologic diseases. The Philadelphia chromosome-positive category is driven by constitutively active BCR–ABL1 fusion kinase, whereas Philadelphia chromosome-negative MPNs commonly involve activating mutations in JAK2, CALR, or MPL and persistent JAK–STAT signaling. Therefore, therapeutic kinase inhibition is strongly linked to the molecular pathology of these disorders [25, 26].

Bleeding complications may also occur in MPNs. Acquired von Willebrand syndrome has been described, particularly in settings of marked thrombocytosis, with the loss of high-molecular-weight von Willebrand factor multimers and a disproportionate reduction in ristocetin cofactor activity. This clinical phenotype illustrates that kinase-driven myeloproliferation can influence platelet and coagulation biology beyond the primary signaling pathways [27].

7.1 JAK2-Directed Heterocyclic Inhibitors in Myeloproliferative Neoplasms

MPNs are myeloid neoplasms that include polycythemia vera, essential thrombocythemia, and myelofibrosis. Abnormal JAK-STAT signaling, often linked to JAK2, CALR, or MPL changes, is a feature of the disease. TKIs that target JAK signaling can ease symptoms reduce an enlarged spleen, and lower inflammation. They vary in terms of their selectivity and their effect on low blood cell counts [28, 29].

Pacritinib

Pacritinib is a multikinase inhibitor that works against JAK2, FLT3, IRAK1, and ACVR1. Its unique chemical structure includes a macrocyclic-like tetracyclic core and a side chain with N-pyrrolidine. Unlike JAK1 and JAK2 inhibitors, which worsen blood cell counts, Pacritinib was developed for patients with myelofibrosis with low platelet counts. Its action against ACVR1 and IRAK1 may explain its effects in patients [30].

The Pacritinib example shows the importance of considering targets in drug design. By focusing only on JAK2, the drug was made to block the JAK2 pathway and also hit other targets that matter for the disease and anemia that comes with treatment.

Ruxolitinib

Ruxolitinib is a drug that blocks JAK1 and JAK2 enzymes. It contains a chemical structure with a cyclopentyl group, on a pyrazolopyrimidine ring. Ruxolitinib stops cytokine signals by blocking JAK1 and JAK2 activity, which reduces STAT activation [31]. Ruxolitinib is used to treat myelofibrosis and polycythemia vera and doctors have studied it for inflammatory diseases.

Ruxolitinib shows the importance of balancing JAK1 and JAK2 activity. The drug works well against inflammation and general sickness signs. It also changes blood cell numbers, showing how JAK signals help normal blood cell production [32].

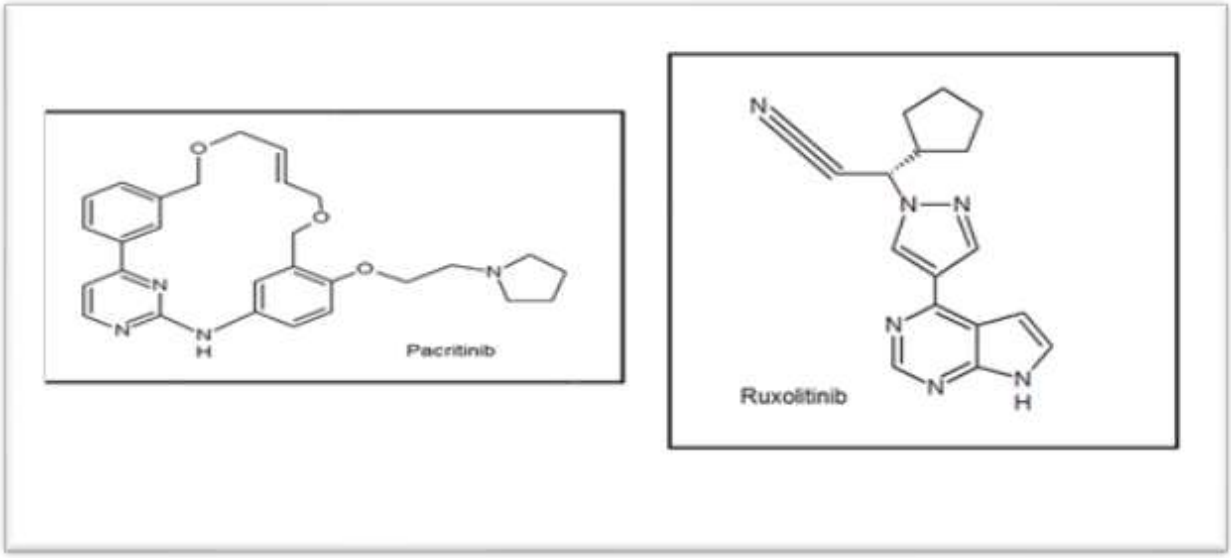


Figure 4. Chemical structures of selected clinically relevant kinase inhibitors: Tofacitinib (JAK inhibitor), Ibrutinib (first-generation covalent BTK inhibitor), and Zanubrutinib (next-generation covalent BTK inhibitor). [33]

8. STRUCTURE–ACTIVITY RELATIONSHIP PRINCIPLES ACROSS HETEROCYCLIC TKIs

Chemical feature	Medicinal-chemistry function	Examples
Nitrogen-rich hinge-binding heterocycle	Mimics ATP hinge interactions through hydrogen bonding	Gefitinib, Imatinib, Ibrutinib, Ruxolitinib
Fused bicyclic heteroaromatic core	Rigidifies ligand and controls vectors	Axitinib,Ponatinib, Tofacitinib
Piperazine/basic solubilizing group	Improves polarity and can project toward solvent	Imatinib, Dasatinib
Electrophilic acrylamide	Covalent reaction with target cysteine	Ibrutinib, Zanubrutinib
Rigid ethynyl linker	Maintains geometry and accommodates resistant kinase pocket	Ponatinib
Heterocycle plus hydrophobic aryl group	Balances hinge binding with hydrophobic-pocket occupancy	Gefitinib, Lapatinib, Imatinib

Across these examples, heterocyclic nitrogen atoms are frequently positioned to reproduce key ATP–hinge hydrogen bonds, while aromatic substituents occupy hydrophobic subpockets. Solvent-exposed amines, such as piperazine, can improve polarity, whereas electrophilic substituents enable target engagement. However, lipophilicity nonspecific kinase binding and metabolic instability can reduce the clinical utility of otherwise potent scaffolds [34, 35].

9. COMPARATIVE OVERVIEW OF REPRESENTATIVE DRUGS

Drug	Dominant heterocycle/scaffold	Principal kinase target(s)	Major disorder/application
Gefitinib	4-Anilinoquinazoline	EGFR	EGFR-mutated NSCLC
Lapatinib	4-Anilinoquinoline	EGFR/HER2	HER2-positive breast cancer
Imatinib	2-Phenylaminopyrimidine + piperazine	EGFR/HER2	CML, GIST and other selected malignancies
Ponatinib	Imidazopyridazine + ethynyl linker	BCR–ABL, T315I; multikinase	CML/Ph+ ALL
Dasatinib	Thiazole-containing multikinase scaffold	BCR–ABL, SRC, KIT, PDGFR	CML/Ph+ ALL
Tofacitinib	Pyrrolopyridine-based scaffold	JAK1/JAK3 preferential	RA, PsA, UC and selected inflammatory disease
Ibrutinib	Pyrazolopyrimidine + acrylamide	BTK (covalent)	CLL and B-cell malignancies
Zanubrutinib	Pyrazolopyrimidine + electrophilic warhead	BTK (covalent)	B-cell malignancies
Pacritinib	Polycyclic heteroaromatic/pyrrolidine-containing scaffold	JAK2, FLT3, IRAK1, ACVR1	Myelofibrosis with severe thrombocytopenia
Ruxolitinib	Pyrazolopyrimidine-type scaffold	JAK1/JAK2	Myelofibrosis, polycythemia vera

10. DRUG RESISTANCE AND FUTURE CHEMICAL STRATEGIES

Resistance to kinase inhibitors can arise from changes that modify the ATP pocket, activation loop, or allosteric sites.

It can also occur when the target is made in amounts, when other pathways take over when cells switch type or lineage, or when drug levels change. T315I BCR–ABL mutation is an example. In this mutation, steric hindrance blocks earlier inhibitors, leading scientists to design Ponatinib [36, 37].

Future discovery of heterocyclic TKIs will probably aim at inhibitors, substrate site inhibitors, covalent inhibitors that react in a controlled way, macrocyclic cores, PROTAC-based kinase degraders, or molecules guided by structure that hit several targets. Tools such as intelligence, molecular docking, free energy calculations, high throughput screening, and kinas panel profiling can speed up the search for promising hits, but lab tests are still essential. Selectivity should be checked across the human kinome, not just from one enzyme test [38].

A helpful workflow for chemistry focused pharmacy research could be: (i) finding the kinase that drives the disease; (ii) selecting a proven hinge binding or allosteric pharmacophore; (iii) using structural biology to map substituent directions; (iv) improving potency and kinase selectivity; (v) checking physical chemical traits and metabolic risks; (vi) examining how well the compound blocks cellular pathways; and (vii) examining resistance mutations and off target effects. This combined approach would connect the chemical structure with the drug's activity.

11. CONCLUSION

Heterocyclic chemistry has played a crucial role in the development of tyrosine kinase inhibitors used in clinical settings. Quinazoline and quinoline structures have helped create drugs that target EGFR and HER2. A piperazine-containing pyrimidine structure was used to develop Imatinib. The imidazopyridazine and ethynyl building blocks made Ponatinib effective against forms of BCR–ABL1. Thiazole-based compounds contributed to the design of Dasatinib. Indazole scaffolds allowed for VEGFR inhibition, as seen with Axitinib. Fused heteroaromatic rings have also supported the development of JAK and BTK inhibitors. In neoplasms, JAK2-targeted drugs show how heterocyclic kinase inhibitors can be designed to block signaling pathways while still offering clinically meaningful selectivity and different effects on anemia or thrombocytopenia.

The main idea from chemistry is that the heterocyclic core is not just a structural label. Its nitrogen arrangement, nature, rigidity, positions for attaching substituents, and ability to form hydrogen bonds all determine how well it fits into a kinase binding pocket. Future studies should combine heterocycle design with biology, kinome-wide selectivity screening, resistance profiling, and computational modeling.

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