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AML and FLT3: An Update on FDA-approved or Under Review Kinase Inhibitors Targeting FLT3 Kinase

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Abstract

Acute myeloid leukemia (AML) is an aggressive form of cancer characterized by the abnormal proliferation of hematopoietic progenitor cells that disrupts normal cell differentiation, leading to serious health complications. Although AML is a rare malignancy, its poor prognosis and low overall survival rates represents a serious health challenge. Among the drivers implicated in the development and progression of AML, is the FMS-like tyrosine kinase 3 (FLT3) enzyme, which is frequently mutated in AML and is associated with poor outcomes. FLT3 mutations result in constitutive activation of the FLT3 receptor, leading to dysregulated cellular proliferation and survival. To combat this, several kinase inhibitors targeting FLT3 have been developed, with the aim of inhibiting the aberrant signalling pathway and improving patient outcomes. Among these kinase inhibitors, three agents have gained approval from the US FDA for the treatment of AML. Additionally, there are candidate inhibitors currently approved or under review by the FDA for indications other than AML but have potent activity against FLT3 and are being evaluated in clinical trials for various AML indications at present. This review focuses on the significance of FLT3 mutations in AML and the FDA-approved or under review kinase inhibitors targeting FLT3 with emphasis on their profile, limitations, and current clinical status regarding AML therapy.

Keywords: Acute myeloid leukemia; FLT3 kinase; FDA-approved, kinase inhibitors, FLT3 mutations; anticancer

1. Introduction

1.1. Acute myeloid leukemia

Cancer or malignancy are broad terms used to describe an assembly of diseases characterized by the presence of a group of cells that divide and proliferate abnormally and uncontrollably.[1] The ability of malignant cells to invade and spread to other organs, known as metastasis,[2] the development of resistance against clinically approved anticancer drugs, and the high mortality rates make cancer one of the leading causes of death worldwide, with a 10 million cancer-related deaths in 2020[3] and a projected 16.4 million deaths expected by 2040.[4]

Acute myeloid leukemia (AML) also known as acute myelogenous leukemia is defined by the loss of normal differentiation and uncontrolled proliferation of hematopoietic progenitor cells in the bone marrow.[5] The buildup of immature and abnormal blood cells, including platelets, non-lymphocyte white blood cells, and red blood cells, causes serious health problems such as fatal bleeding, dangerous infections, and severe anaemia, respectively.[6] AML is a heterogenous blood cancer with no exact cause identified, but it is characterized by the accumulation of hematopoietic cell genetic alteration with age and it can arise from other disorders such as myeloproliferative disorders or myelodysplastic syndrome.[7]

AML represents one-third of all leukemia cases even though it is a rare malignancy that only accounts for 1.2% of new cancer diagnoses in the United States each year.[5] It is most common in adults aged 68 and above and it has a very poor prognosis with 15% cure rates in patient over 60 and an average of 24% 5-year survival rate.[7,8]

Over time, the pathogenesis of cancer became clear, and various enzymes, receptors, and cellular channels were discovered to be triggers in the development of malignancies. Among all these biological molecules, the kinase enzymes were deemed

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one of the most important targets for developing anti-cancer agents with promising therapeutic activity and minimal side effects.[9,10]

1.2. Kinase inhibitors

Kinase enzymes are a series of enzymes that play a critical role in cell division, proliferation, migration, and apoptosis by transferring gamma phosphate from phosphate-donating groups like ATP onto the hydroxy groups of various substrates like lipids, sugars, and amino acids.[10] Most human tumors are characterized by over-expression, constitutive activation, or mutation of these kinases, resulting not just in abnormal cell differentiation but also in angiogenesis, which is needed for tumor growth and metastasis.[9]

Due to the fundamental role of protein kinases in regulating cell growth, proliferation, and migration, and the logical link between the development of various and fatal types of cancers, and the dysregulation and mutations of protein kinases, understanding the structure of these enzymes have already become essential to design powerful and selective anti-cancer agents that can block and regulate their activities to target malignancies.[11]

All kinases share a common structure known as a catalytic domain, which comprises the enzyme's active site where natural ligands (such as ATP) or synthetic ligands (such as drugs) bind. The catalytic domain is made up of two other domains (also known as lobes) that are connected by a flexible hinge region.[12] The small *N*-terminal lobe is made up of a 5-stranded β-sheets (β_1-β_5) and at least one helix known as the αC-helix. The large C-terminal lobe, on the other hand, is mostly made up of α- helices (αD-αI) and minor β-sheets (β_6-β_7).[11] The adenine ring of ATP forms strong hydrogen bonds with the hinge region amino acids located between both lobes.[13] The activity of protein kinase is regulated by the formation of a salt bridge between β3-lysine and a glutamate residue in the αC-helix (αC-in, active; αC-out, inactive). The second regulatory element is the DFG motif (Asp-Phe-Gly) (**Figure 1**) where the aspartate extends into the ATP-binding site and binds to two Mg^{2+} ions (DFG-Asp in, active; DFG-Asp out, inactive).[14]

The small molecule protein kinase inhibitors can be classified into seven main groups (**Figure 2**) including reversible (Groups **I**, **I½**, **II**, **III**, **IV**, and **V**) and targeted covalent irreversible inhibitors (**VI**).[15] Type I inhibitors can bind to the ATP binding sites in the active configuration of the enzyme (DFG-in; αC-in). To improve the efficacy and selectivity of type I kinase inhibitors, their structures are not only designed to occupy the adenine binding site as ATP but also to extend to other regions such as the front pocket region, the hydrophobic pocket region, the DFG motif, and the P-loop region while keeping the DFG motif in its active state.[16]

Some type I inhibitors (recently known as type I ½ inhibitors) were found to have special structure features that contributed to their different binding mode. The extra hydrophobic group extends into the hydrophobic pocket region and this extension leads to the αc-Helix-out displacement while keeping the DFG-in configuration.[17]

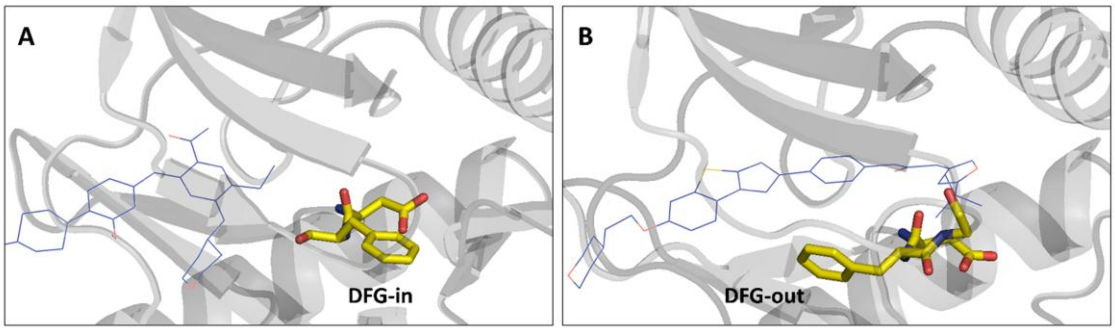

Figure 1. X-ray crystal structures of the ATP-binding site of FLT3 enzyme showing both active and inactive conformations. (A) DFG-in conformation of FLT3 kinase bound to gilteritinib (PDB ID: 6JQR). (B) DFG-out conformation of FLT3 kinase bound to quizartinib (PDB ID: 4XUF). DFG motif is shown as sticks with yellow backbone. Gilteritinib and quizartinib are represented as lines with blue backbone. This figure was generated using PyMOL software (v 0.99rc6).

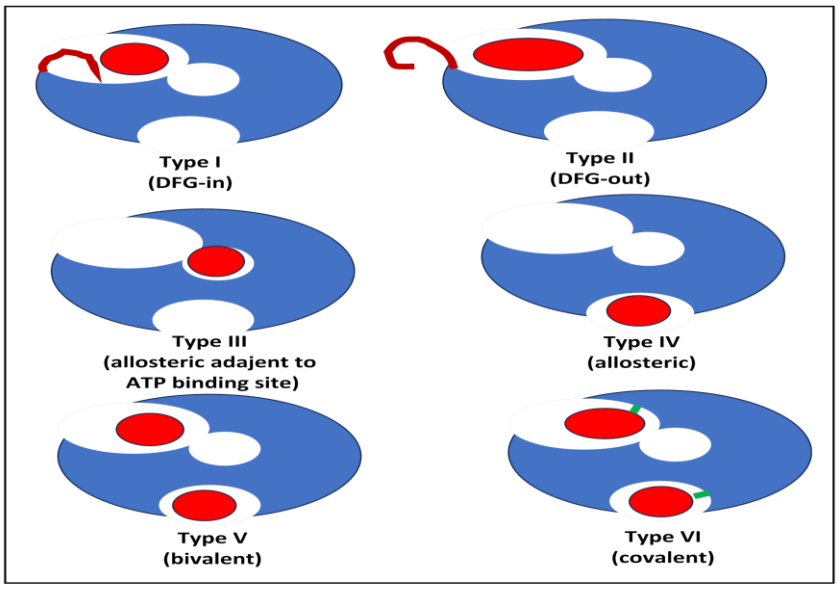

Figure 2. Diagrammatic representation of different types of kinase inhibitors based on their biochemical mode of action.

The binding mode of type II inhibitors is similar to that of type I inhibitors regarding the hydrogen bond formation with the adenine binding site, and the difference comes from the ability of type II inhibitors to extend and interact with a special allosteric site adjacent to the ATP binding site. Because of this unique interaction with the allosteric site, the DFG motif is forced to become inactive (DFG-out).[18]

1.3. FMS-like tyrosine kinase 3 (FLT3)

FLT3 is a class III receptor tyrosine kinase that has sequence resemblances to other kinases like KIT, and PDGFR kinases.[19] Birnbaum and colleagues[20] first detected it in hematopoietic progenitor cells in 1993 and its biological function became clear in promoting myeloid cell growth, proliferation, survival, and differentiation.[21] Nearly all patients with acute myeloid leukemia have FLT3-WT receptors that are overexpressed.[22] In addition to that, mutations in the FLT3 gene, which were found in one-third of AML patients and is associated with inferior overall survival, are among the most frequently found genetic changes that disrupt intracellular signalling networks and contribute to leukemia pathogenesis.[21]

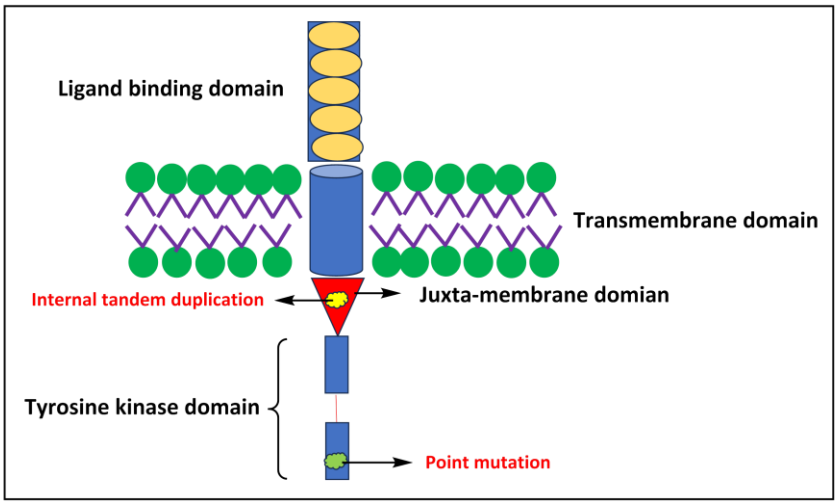

Figure 3. Diagrammatic representation of FLT3 receptor tyrosine kinase illustrating ITD and TKD mutations.

The first type of FLT3 mutations is the internal tandem duplications (ITD), which are found in the

receptor's autoinhibitory juxta-membrane region, causing constitutive activation and ligand-independent autophosphorylation. FLT3-ITD mutations, which can affect around 25% of AML patients, range in length from 3 to 1236 nucleotides and can vary in both location and size.[23] The overall survival rate of AML patients with FLT3-ITD mutations declines as the size of the mutation increases.[24] The other type of FLT3 mutations, which impacts around 5% of patients, is a missense point mutation that replaces an amino acid residue in the receptor's activation loop of the tyrosine kinase domain (TKD).[25] The most common TKD mutation is D835Y, which occurs when aspartic acid at position 835 is replaced with a tyrosine amino acid, which keeps the DFG motif active (DFG-in), and in consequence, sterically impairs type II inhibitor binding.[19] Furthermore, the TKD mutation can increase FLT3's kinase activity by maintaining the active kinase conformation and causing constitutive kinase activation as observed with FLT3-ITD mutations (**Figure 3**).[21]

A gatekeeper mutation is the substitution of an amino acid residue at the beginning of the hinge region near the ATP binding site with either smaller or larger side chain and it is considered a common mechanism of resistance to pharmacological ATP-competitive kinase inhibitors.[26] The gatekeeper residue typically enhances binding specificity by limiting the inhibitor's access to a hydrophobic pocket located deep within the active site that is unoccupied by ATP, where the nature of the gatekeeper residue plays an important role in determining the size and shape of the hydrophobic pocket.[27] The back cavity is small when the gatekeeper residue has a bulky side chain and vice versa.[17] The steric hindrance caused by replacing the small amino acid residue (usually threonine) with a bulkier one is an example of the resistance caused by gatekeeper mutations.[27] Alternatively, in the case of FLT3, the kinase already harbours a bulky phenylalanine as a gatekeeper residue (F691), which forms an important edge-face hydrophobic interaction with the middle phenyl ring in the case of quizartinib. A lack of this interaction results from the FLT3-F691L mutation, which replaces phenylalanine with leucine hence conferring resistance to quizartinib and most FLT3 inhibitors.[28]

2. FDA-approved or under review selective and non-selective FLT3 kinase inhibitors

Based on the previous findings, targeting FLT3 signalling through either small-molecule inhibitors or antibodies[19] is a promising therapeutic strategy for the treatment of AML patients.[21] While antibodies bind to the extracellular domain of the receptor, thus blocking ligand-receptor interaction followed by inhibiting ligand-stimulated receptor activation and cell proliferation,[29] small-molecule FLT3 inhibitors can bind to the ATP binding site of the intracellular TKD, hence preventing receptor autophosphorylation and the subsequent activation of downstream signalling.[23] FLT3 kinase inhibitors are classified into two generations based on their selectivity and specificity. First-generation FLT3 inhibitors, which include midostaurin, lestaurtinib, sunitinib, sorafenib, and tandutinib, lack selectivity against FlT3 since they target various kinases in addition to FLT3, which might result in different degrees of off-target toxicity.[23,30] In contrast, second-generation FLT3 inhibitors, including gilteritinib, crenolanib, and quizartinib are more effective due to their selectivity against FLT3, and as a result, have less off-target effects at therapeutic doses.[31] Furthermore, FLT3 inhibitors are classified into two types depending on how they interact with the intracellular tyrosine kinase domain of FLT3 receptors and, in sequence, their impact on FLT3-ITD and TKD mutations. Type I FLT3 inhibitors (**Figure 4**) have been reported to be active against both FLT3-ITD and TKD mutations, and that is due to their ability to occupy the ATP-binding site in both active (DFG-in) and inactive (DFG-out) conformations. On the other hand, type II FLT3 inhibitors (**Figure 5**) show their activity only against FLT3-ITD mutations as their structure is found to occupy an extra hydrophobic pocket adjacent to the ATP-binding site, and this hydrophobic pocket cannot be reached unless the receptor is in its inactive conformation (DFG-out).[30] This makes them less effective against FLT3-TKD mutations, as these mutations bias the active kinase conformation of FLT3 enzyme and sterically hinder their binding.[19]

2.1. Type I FLT3 inhibitors

2.1.1. Midostaurin

Midostaurin is the first FLT3 inhibitor approved by the FDA in 2017 for the treatment of adult patients with newly diagnosed FLT3-mutated acute myeloid leukemia (AML).[35] Midostaurin, the *N*-benzoyl

derivative of staurosporine (**Figure 6**) is a non-selective FLT3 kinase inhibitor with potent activity against several other kinases as PKC, PDGFRs, SYK, KIT, and VEGFR2.[35] It is a type I protein kinase inhibitor as it binds to the ATP binding site of the kinase enzyme in its active state (DFG-in) where the 2-pyrrolidone group interacts with the hinge region, and the benzamide group extend into the P-loop cleft (**Figure 4-A**).[36]

Cell-based assays indicated that midostaurin showed potent activity against FLT3 wild type and mutant forms with IC_{50} values of 15 nM (FLT3-WT),[37] 4.5 nM (FLT3-ITD), 1.5 nM (FLT3-TKD-D835Y), and 19 nM (FLT3-ITD-F691L).[38] In addition, when tested against two FLT3-ITD^{+} AML cell lines, MOLM-13 and MV4-11, midostaurin exhibited IC_{50} values of 4.7 nM[39] and 12 nM[37] respectively.

2.1.2. Gilteritinib

Gilteritinib is the first small, highly selective FIT3 inhibitor approved by the FDA in 2018 as a monotherapy for patients with relapsed or refractory FLT3-mutated AML.[41] Gilteritinib is a pyrazine carboxamide derivative (a general scheme for synthesis

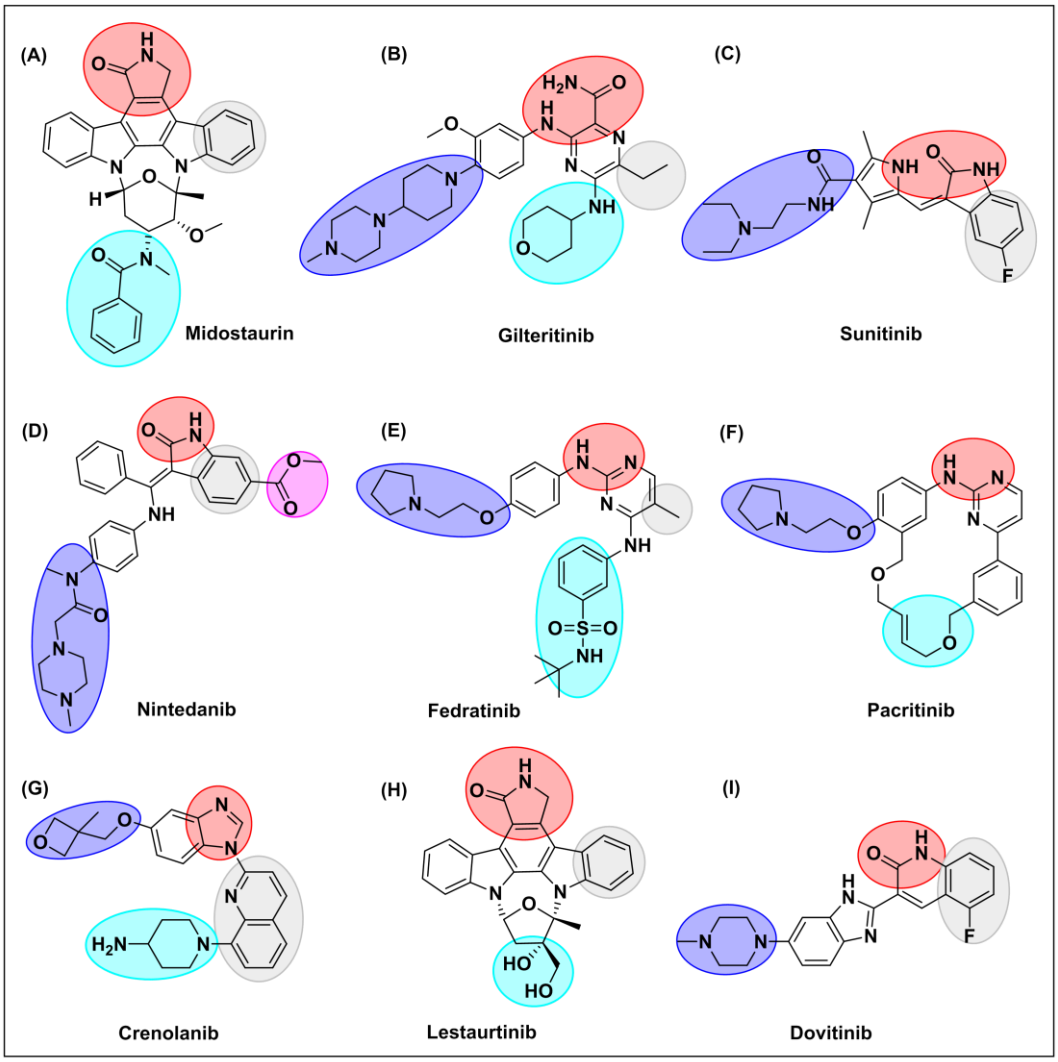

Figure 4. Chemical structures and representation of the predicted binding modes of type I FLT3 inhibitors. Binding modes were predicted in reference to the inhibitors' x-ray crystal structures with different kinase enzymes or based on their reported molecular docking poses as follows: midostaurin (PDB code: 4NCT, DYRK1A kinase), gilteritinib (PDB code: 6JQR, FLT3 kinase), sunitinib (PDB code: 6JOK, PDGFRα kinase), nintedanib (PDB code: 6NEC, RET kinase), fedratinib (PDB code: 6VNE, JAK2), pacritinib (docked with JAK2)[32], crenolanib (PDB code: 6JOJ, PDGFRα kinase), lestaurtinib (PDB code: 4OTG, PRK1 kinase), and dovitinib (PDB code: 5AM6, FGFR1 kinase). Binding regions are presented as follows: adenine binding region or hinge region (red), P-loop cleft (cyan), front pocket or solvent accessible region (blue), hydrophobic pocket (grey), and DFG-motif region (pink).

is outlined in **Figure 7**) reported as a second-generation FLT3 inhibitor, where it binds to the FLT3 enzyme more effectively compared to other kinases which probably accounts for it is safer profile and lower myelosuppressive effect than other FLT3 inhibitors.[42] Gilteritinib is a type I FLT3 inhibitor that binds to the ATP binding site of FLT3 enzyme in its active conformation (**Figure 1-A**) by forming strong hydrogen bonds with the amino acids in the hinge region in a manner similar to that of other type I kinase inhibitors and ATP.[43] It has also been demonstrated that gilteritinib interacts hydrophobically with F691 (**Figure 4-B**).[42] In cell-based assays, gilteritinib showed excellent inhibitory activity against FLT3 wild type and mutant forms with IC_{50} values of 5 nM (FLT3-WT), 1.6 nM (FLT3-ITD), 1.4 nM (FLT3-TKD-D835Y), and 12.2 nM (FLT3-ITD-F691L).[44] Moreover, gilteritinib exhibited potent antiproliferative activity against MV4–11 and MOLM-13 cells with IC_{50} values of 0.92 and 2.9 nM respectively.[42] Additionally, unlike most FLT3 inhibitors that show potent activity against KIT which results in marrow suppression, gilteritinib demonstrated weak KIT inhibitory activity with an IC_{50} of 102 nM (around 100 times less activity compared to FLT3) thus exhibiting negligible effects on hematopoiesis.[44]

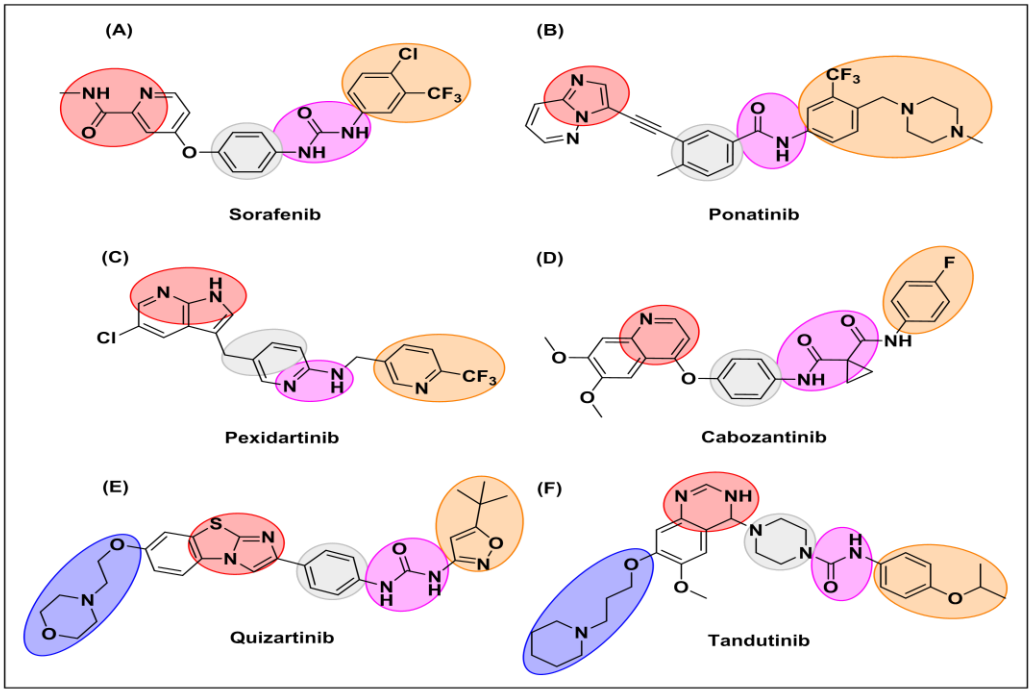

Figure 5. Chemical structures and representation of the predicted binding modes of type II FLT3 inhibitors. Binding modes were predicted in reference to the inhibitors' x-ray crystal structures with different kinase enzymes or based on their reported molecular docking poses as follows: sorafenib (PDB code: 3WZE, KDR kinase), ponatinib (PDB code: 4U0I, KIT kinase), pexidartinib (PDB code: 4R7H, CSF1R kinase), cabozantinib (docked with ROS1 kinase)[33], quizartinib (PDB code: 4XUF, FLT3), tandutinib (docked with FLT3 kinase)[34]. Binding regions are presented as follows: adenine binding region or hinge region (red), front pocket or solvent accessible region (blue), hydrophobic pocket (grey), DFG-motif region (pink), allosteric pocket (buff).

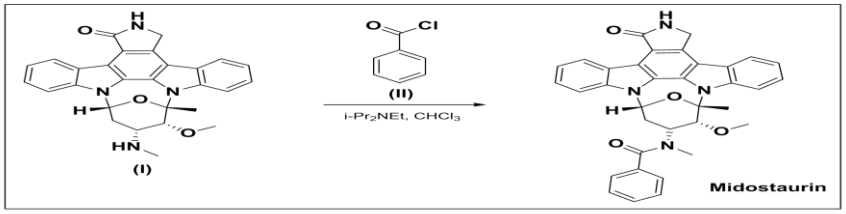

Figure 6. The preparation of midostaurin by acylation of the alkaloid staurosporine **(I)** with benzoy
l chloride **(II)** in the presence of diisopropylethylamine in chloroform.[40]

As concluded, gilteritinib, unlike type II inhibitors, is not affected by mutations in the activation loop (for example, at D835) because it does not extend to the hydrophobic pocket that is regulated by the DFG motif.[44] Due to its interaction with the gatekeeper residue F691, it shows slightly weaker activity against F691 mutation (IC_{50} = 12.2 nM) as compared to other FLT3 mutations.[45] This finding suggests that AML blasts that harbour F691L mutation would exhibit a poor response to gilteritinib, and this is considered a second mode of resistance to gilteritinib in addition to the activation of downstream or parallel pathways, like RAS mutation.[45]

2.1.3. Sunitinib

Sunitinib received FDA approval in 2006 for the treatment of advanced renal cell carcinoma and gastrointestinal stromal tumours in patients whose disease has progressed or who are unable to tolerate imatinib treatment.[47] It is an oxindole-containing compound (a general scheme for synthesis is outlined in **Figure 8**) and a non-selective kinase inhibitor with potent activity against several kinases, including VEGFR, PDGFR, FLT3, KIT, and RET.[48]

Sunitinib is a type I kinase inhibitor, where it binds to the adenine binding area, forming two hydrogen bonds with the hinge region, and it also binds to the front pocket region via the hydrophilic tail and does not extend to the hydrophobic pocket adjacent to the ATP binding site like type II inhibitors (**Figure 4-C**).[49] It has been reported that sunitinib inhibits FLT3-WT (IC_{50} = 250 nM), FLT3-ITD (IC_{50} = 50 nM) and FLT3-TKD-D835Y (IC_{50} = 30 nM) in cell-based assays.[40] Sunitinib demonstrated potent antiproliferative activity against the MV4-11 cell line with an IC_{50} value of 8 nM.[50]

As one of the first steps in the exploratory clinical development of sunitinib in AML, several clinical studies were conducted to evaluate sunitinib activity alone or in combination for different AML indications. Two clinical trials were completed and one was discontinued.[51]

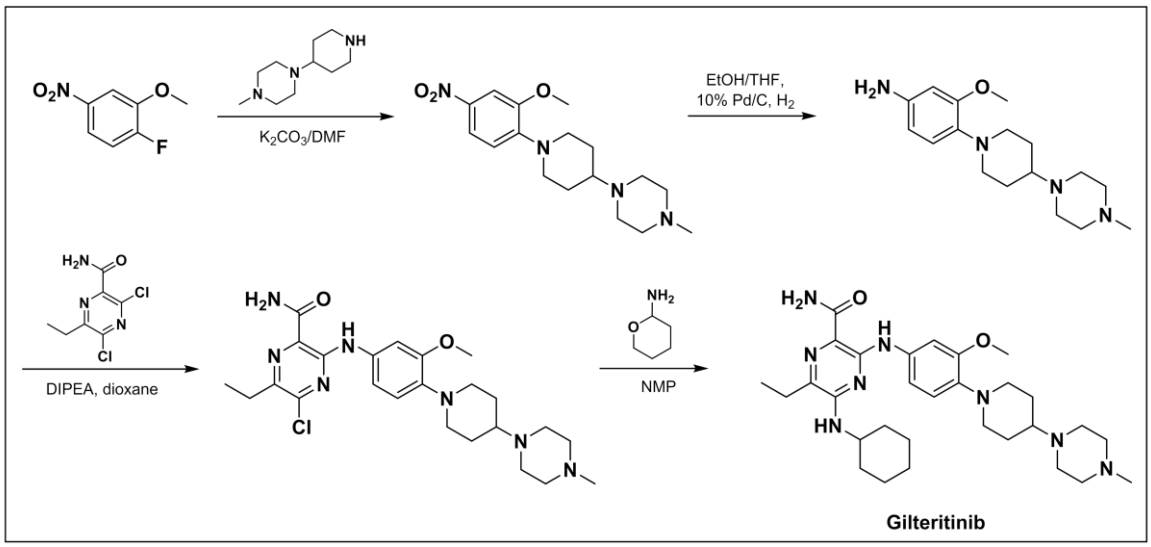

Figure 7. General scheme for the synthesis of gilteritinib.[46]

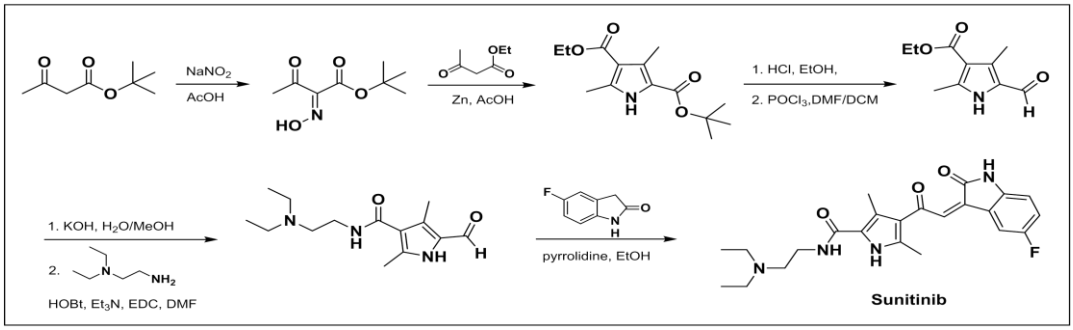

Figure 8. General scheme for the synthesis of sunitinib.[52]

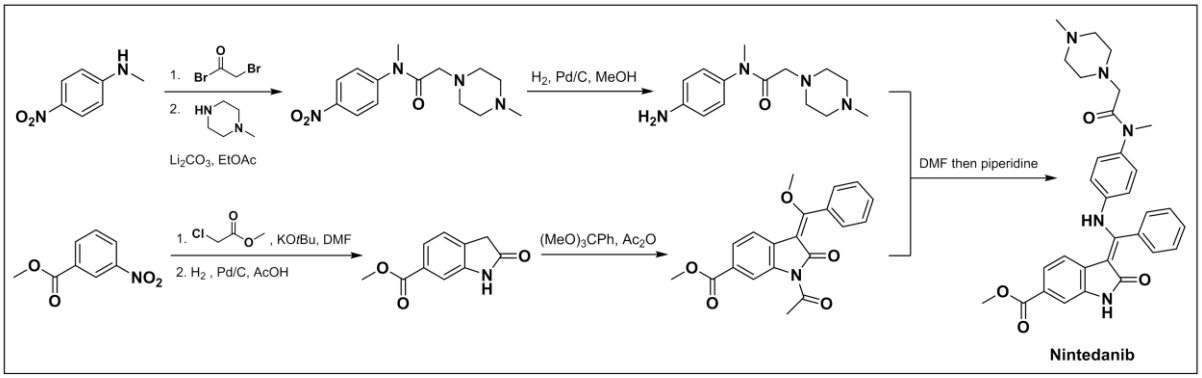

Figure 9. General scheme for the synthesis of nintedanib.[60]

2.1.4. Nintedanib

Nintedanib received FDA approval in 2014 to treat idiopathic pulmonary fibrosis,[53] followed by approvals in 2019 and 2020 for the treatment of interstitial lung diseases.[54] Nintedanib, an oxindole-based non-selective kinase inhibitor (a general scheme for synthesis is outlined in **Figure 9**), shows potent activity towards several kinases, including VEGFR, FGFR, PDGFR, SRC, and FLT3 kinases.[55] The binding mode of nintedanib is similar to that of other type I FLT3 inhibitors as it competes with ATP for binding at the adenosine binding site in the enzyme, preventing autophosphorylation and blocking downstream signalling cascades.[56] The co-crystal structure of nintedanib and FGFR-1 showed that nintedanib occupied the ATP binding site by forming hydrogen bonds with the amino acids in the hinge region and with the aspartate residue of the DFG motif (**Figure 4-D**).[57] The reported IC_{50} of nintedanib against FLT3-WT was 26 nM[56] and in addition, it displayed potent activity in binding assays against FLT3-ITD (K_d = 0.7 nM) and FLT3-TKD-D835Y (K_d = 0.42 nM) relative to the wild enzyme (K_d = 3.8 nM).[58] Furthermore, it showed cytotoxic effect against MV4-11 cell line with an IC_{50} value of 53 nM indicating that it has the ability to target FLT3-ITD$^+$ cell lines.[59] Nintedanib was evaluated in three clinical trials for different AML indications,[51] where two studies were completed, and one is ongoing. In a phase II study to evaluate a combination of nintedanib and cytarabine in elderly patients with AML unfit for intensive chemotherapy, nintedanib failed to show any beneficial therapeutic activity as compared to placebo.[55]

2.1.5. Fedratinib

Fedratinib was approved in 2019 by the FDA for the treatment of adults with myelofibrosis.[61] It is a dual JAK2/FLT3 diaminopyrimidine-based kinase inhibitor (a general scheme for synthesis is outlined in **Figure 10**) which inhibits both mutant and wild-type FLT3 and exhibits higher selectivity for JAK2 over closely related kinase family members.[62] Based on its binding mode to JAK2 enzyme, fedratinib is a type I kinase inhibitor that binds to the ATP site, where the diaminopyrimidine moiety fits in the hinge region and forms two hydrogen bonds (**Figure 4-E**).[63] Fedratinib inhibited both FLT3 and JAK2 with IC_{50} values of 15 nM and 3 nM, respectively.[61] Moreover, it displayed potent activity in binding assays against FLT3-ITD (K_d = 16 nM) and FLT3-TKD-D835Y (K_d = 6.4 nM) relative to the wild enzyme (K_d = 13 nM).[58] In addition, fedratinib exhibited antiproliferative activity against the FLT3-ITD$^+$ cells lines, MV4-11 (EC_{50} = 57 nM) and MOLM-13 (EC_{50} = 69 nM).[62] To date, no clinical trials exist for fedratinib for any AML indications.[51]

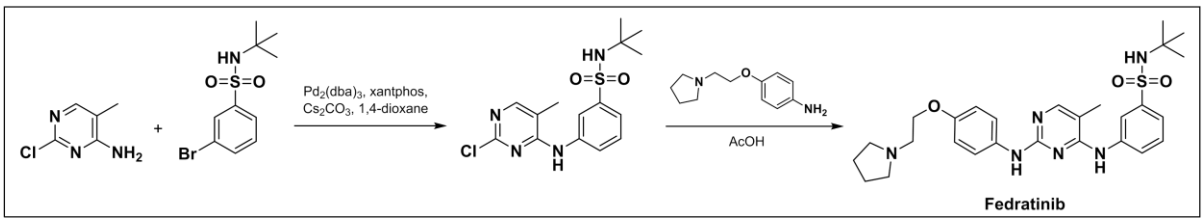

Figure 10. General scheme for the synthesis of fedratinib.[64]

2.1.6. Pacritinib

Pacritinib has been approved by the FDA for the treatment of adults with myelofibrosis in 2022.[65] It is a dual JAK2/FLT3 2-aminopyrimidine-based kinase inhibitor (a general scheme for synthesis is outlined in **Figure 11**). According to docking studies on FLT3, pacritinib is a type I kinase inhibitor, where it binds to the ATP-binding site and its 2-aminopyrimidine moiety forms two hydrogen bonds with the hinge region amino acids (**Figure 4-F**).[66] The IC_{50} values of pacritinib against JAK2-WT, FLT3-WT, FLT3-ITD, and FLT3-TKD-D835Y are 23 nM, 22 nM, 9 nM and 3.1 nM, respectively.[32,67] Furthermore, pacritinib demonstrated cytotoxic activity against FLT3-ITD$^+$ AML cell lines (MV4-11 and MOLM-13) with IC_{50} values of 33 nM and 73 nM, respectively.[67]

Pacritinib was evaluated clinically as combination therapy in phase 1/2 studies for different AML indications. Two of these studies were terminated and one was completed.[51] There is considerable evidence for including pacritinib in AML therapy, especially in patients resistant to FLT3-tyrosine kinase inhibitor therapy as the existence of alternative survival pathways such as the JAK-STAT pathway can allow leukemic cells to evade FLT3 mono-inhibition. The dual JAK2/FLT3 activity of pacritinib can potentially address this resistance and thus provides a rationale for clinical evaluation of pacritinib in AML.[68]

2.1.7. Crenolanib

Crenolanib is an investigational drug that has not yet received FDA approval but was granted fast track designation in 2017 for FLT3-positive relapsed or refractory AML indication.[69] It is a dual FLT3/PDGFR benzimidazole-based kinase inhibitor (a general scheme for synthesis is outlined in **Figure 12**) with potent activity and higher selectivity against wild-type and mutant isoforms of FLT3 and PDGFRα-β than other closely related protein kinases (i.e., KIT).[70] Crenolanib is a type I kinase inhibitor as it binds to the ATP domain of the kinase enzyme while in DFG-in conformation as indicated by its crystal structure with PDGFRα (**Figure 4-G**).[71] The benzimidazole nitrogen forms hydrogen bond within the hinge region, while the quinoline moiety interacts with the gatekeeper Phe691 forming aromatic interactions, so it is expected that the gatekeeper mutations would affect crenolanib potency.[72] Owing to its binding mode as a type I kinase inhibitor, crenolanib can overcome the resistance that develops against type II kinase inhibitors as in the case of quizartinib- and sorafenib-resistant AML either with FLT-ITD or FLT3-D835 secondary mutations. These mutations stabilize FLT3 in the active conformation, preventing type II kinase inhibitor binding.[72]

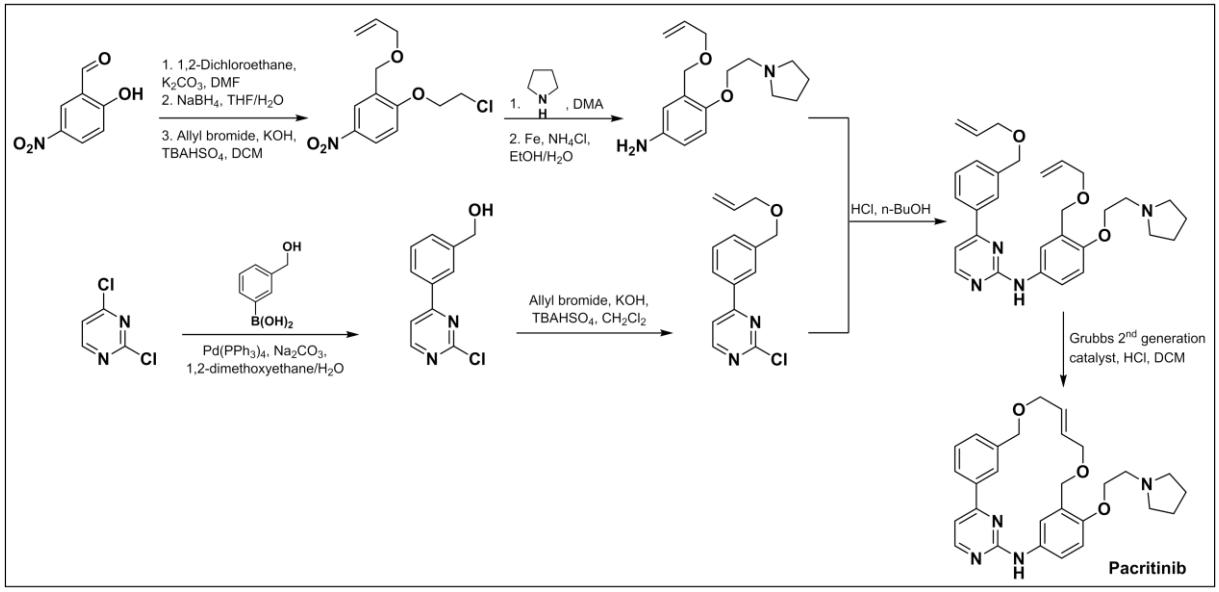

Figure 11. General scheme for the synthesis of pacritinib.[32]

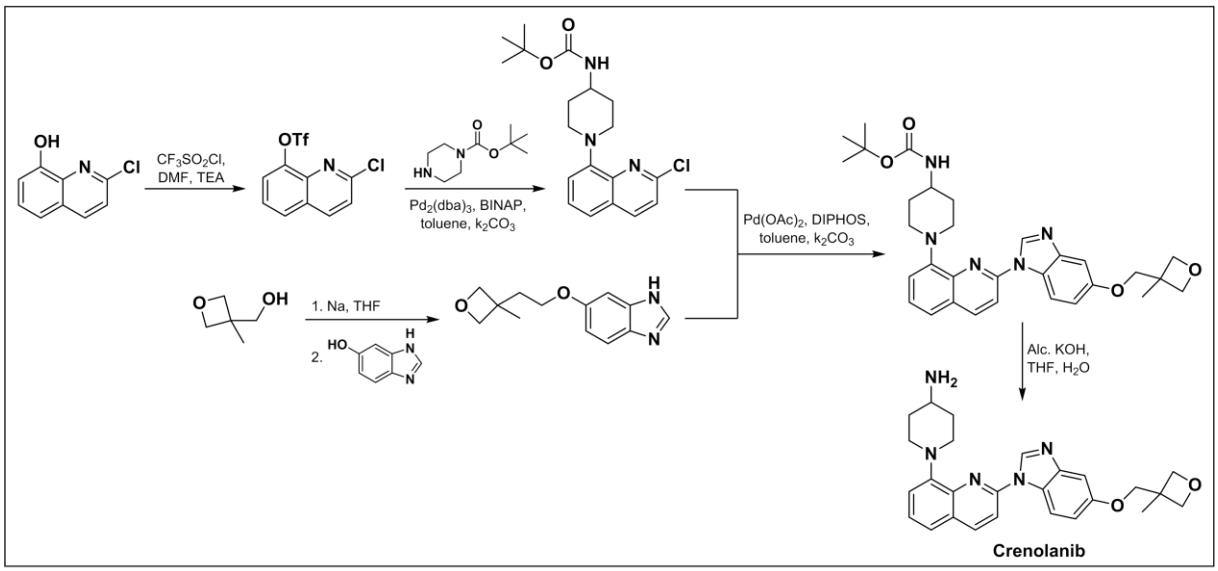

Figure 12. General scheme for the synthesis of crenolanib.[75]

When evaluated in cell-based assays, crenolanib exhibited nanomolar inhibitory activity against wild-type FLT3 (IC_{50} = 2 nM) and different FLT3 mutations including FLT3-ITD (IC_{50} = 1.3 nM) and FLT3-TKD-D835Y (IC_{50} = 6.9 nM). As expected, mutations in the gatekeeper Phe691 contributed to the reduced activity of crenolanib (IC_{50} = 67.8 nM).[73] In addition, crenolanib demonstrated potent cytotoxicity against MV4-11 (IC_{50} = 1.3 nM) and MOLM-13 cell lines (IC_{50} = 4.9 nM).[70] Furthermore, it is significantly more selective against KIT (about a 100 times) which might contribute to a lower myelosuppression side effect.[72]

Crenolanib has reached phase III trials and has shown significant clinical efficacy either alone or in combination therapy for different AML indications.[74] More than ten clinical studies were conducted for crenolanib, of these six were completed, and three are ongoing.[51]

2.1.8. Lestaurtinib

Lestaurtinib has been designated an orphan drug status by the FDA in 2006 for the treatment of AML, however it wasn't approved for this orphan indication.[76,77] It is a non-selective kinase inhibitor that was basically developed as a pan-TRK inhibitor.[78] However, it showed potent activity against JAK2,[79] and wild-type and mutant isoforms of FLT3.[80] Lestaurtinib (previously known as CEP-701) is an orally bioavailable indolocarbazole alkaloid compound (a general scheme for synthesis is outlined in **Figure 13**) that was derived from K-252a, an alkaloid originally isolated from *Nocardiopsis* bacteria.[81] Lestaurtinib is a type I kinase inhibitor that binds to the ATP domain in a very similar mode to that of midostaurin (**Figure 4-H**).[82,83]

In cell-based assays, lestaurtinib exhibited potent activity against FLT3-WT and FLT3-ITD mutation

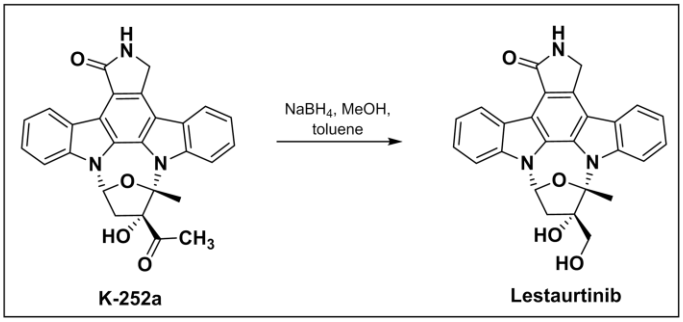

Figure 13. The preparation of lestaurtinib by reduction of the alkaloid K-252a with sodium borohydride in methanol and toluene.[88]

with IC_{50} values of 2.6 nM and 1.5 nM, respectively.[37] On the other hand, F691L mutation imparted resistance against lestaurtinib when tested in BaF3-ITD-F691L mutant cells, where lestaurtinib demonstrated a four-fold increase in IC_{50} against BaF3-ITD-F691L cells (8 nM) as compared to BaF3-ITD cells (2 nM).[83] Notably, lestaurtinib exhibited weak activity against KIT kinase (IC_{50} > 500 nM) suggesting a lower incidence of myelosuppression.[84] In addition, lestaurtinib exhibited potent antiproliferative activity against MV4-11 cell line with an IC_{50} value of 2.1 nM.[37]

Based on the encouraging preclinical data, lestaurtinib was tested as monotherapy or combination treatment in phase I and II clinical trials for several AML indications, including older patients not considered fit for intensive chemotherapy,[81] after salvage chemotherapy for FLT3-mutant AML patients in first relapse,[85] or for patients with relapsed or refractory AML.[84] However, lestaurtinib showed transient responses with limited clinical efficiency in phase I and II trials and no overall clinical benefit was achieved, therefore, further development and testing has been discontinued.[81,84–87]

2.1.9. Dovitinib

Dovitinib is an investigational drug for which a new drug application (NDA) was submitted to the FDA in 2021 for third-line treatment of renal cell carcinoma patients, but the NDA was refused later in 2022.[89,90] Dovitinib is a non-selective benzimidazole- quinolinone-based kinase inhibitor (a general scheme for synthesis is outlined in **Figure 14**) with potent activity against FLT3, KIT, FGFR1, FGFR3, and VEGFR2 (IC_{50} values of 1 nM, 2 nM, 8 nM, 9 nM, and 13 nM, respectively).[91] In reference to its crystal structure with FGFR1, dovitinib is a type I kinase inhibitor that binds to the ATP binding site while in DFG-in conformation. The quinolinone moiety forms two hydrogen bonds with the hinge region, while the phenyl ring of quinolinone engages in hydrophobic interaction with the gatekeeper amino acid. In addition, the hydrophilic 5-(4-methylpiperazin-1-yl)benzimidazole moiety extends into the front pocket (**Figure 4-I**).[92,93]

In binding assays, dovitinib demonstrated reduced activity against FLT3-ITD (K_d = 3.6 nM) and FLT3-TKD-D835Y (K_d = 5.2 nM) relative to the wild enzyme (K_d = 0.64 nM).[94] On the other hand, it exhibited potent cytotoxicity against MOLM-13 and MV4-11 AML cell lines with IC_{50} values of 5 nM and 4 nM, respectively.[95] To date, no clinical trials exist for dovitinib for any AML indications.[51]

2.2. Type II FLT3 kinase inhibitors

2.2.1. Sorafenib

Sorafenib is a multitargeted kinase inhibitor with broad clinical activity against various tumor types.[97] In 2005, sorafenib received its first FDA approval for advanced renal cell carcinoma, then in 2007, it was approved for unresectable hepatocellular carcinoma, later in 2013, it was approved for metastatic differentiated thyroid cancer.[98] Sorafenib is a picolinamide-based kinase inhibitor (a general scheme for synthesis is outlined in **Figure 15**) with potent activity against many kinases comprising, VEGFR, RAF, FLT3, KIT, RET, and PDGFRβ.[99] Sorafenib is a type II kinase inhibitor which, in addition to occupying the ATP binding site, also extends to the hydrophobic allosteric site close to the hinge region. This causes the "DFG" motif to be shifted into the "DFG-out" conformation, in which the sidechain of the phenylalanine flips and points to the hinge.[49] Based on modelling studies, and the binding mode of sorafenib to VEGFR2 enzyme, the picolinamide moiety forms hydrogen bonds with the hinge region while the bi-aryl urea extended into the allosteric pocket region (**Figure 5-A**).[100,101]

Preclinical studies revealed that sorafenib is a potent inhibitor of FLT3-WT and ITD mutation with IC_{50} values of 32.6 nM, and 2.8 nM, respectively. As expected, sorafenib, being a type II kinase inhibitor, exhibited lower sensitivity towards FLT3-TKD mutations with a high IC_{50} of 103.5 nM against FLT3-

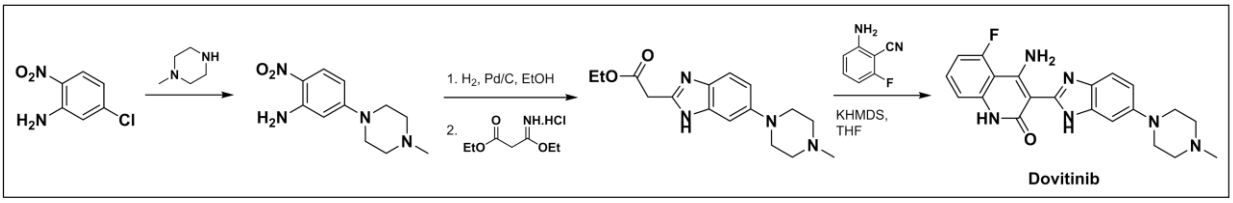

Figure 14. General scheme for the synthesis of dovitinib.[96]

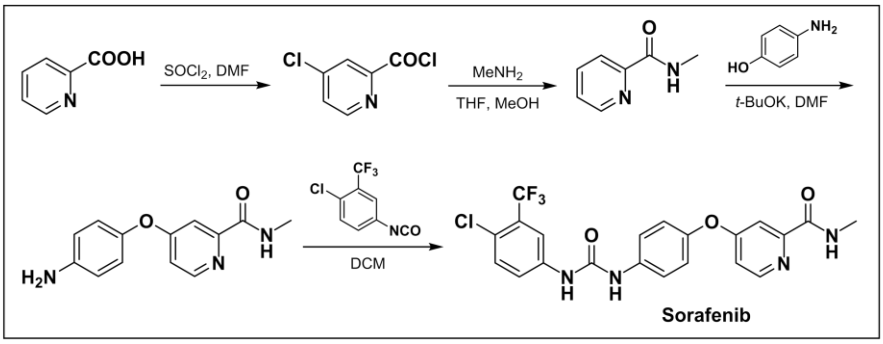

Figure 15. General scheme for the synthesis of sorafenib.[108]

D835Y mutation.[102] In cellular assays, sorafenib demonstrated preferential antiproliferative activities against FLT3-WT-overexpressing (EOL-1) and FLT3-ITD$^+$ (MV4-11) AML cell lines with potent IC_{50} values of 0.033 nM and 0.88 nM, respectively, while lacking activity against FLT3-independent RS4;11 cell line (IC_{50} = 12 μM).[102]

Sorafenib has been evaluated, alone or in combination therapy, in many clinical studies[51] for various AML indications including, patients with newly diagnosed acute myeloid leukaemia,[103] patients with relapsed or refractory FLT3-ITD$^+$ AML,[104] or as salvage treatment for FLT3-ITD$^+$ AML after allogeneic stem cell transplantation.[105] These studies reported conflicting findings, where in some cases, sorafenib monotherapy showed transient favourable responses followed by loss of clinical efficiency which might be attributed to the development of resistant mutations or the upregulation of compensating pathways.[103,104,106] On the other hand, combination therapy proved effective and well tolerated in some AML indications. For example, azacytidine and sorafenib combination therapy can benefit patients with relapsed/refractory FLT3-ITD$^+$ AML.[107]

Ponatinib is a third-generation pan-BCR-ABL kinase inhibitor approved by the FDA in 2012 for chronic-phase chronic myeloid leukemia (CML) and Philadelphia chromosome-positive acute leukemia (Ph+ ALL).[109,110] Ponatinib is an imidazo[1,2-*b*]pyridazine-based non-selective kinase inhibitor (a general scheme for synthesis is outlined in **Figure 16**) with potent nanomolar activity against various kinases in addition to BCR-ABL including, FGFR1, PDGFRα, VEGFR2, FLT3, and KIT.[111] Based on the crystal structure of ponatinib with KIT enzyme and the docking studies with FLT3,[28,112,113] it is clear that ponatinib binds to the inactive form of FLT3 in a similar mode to other type II kinase inhibitors, where the imidazopyridazine ring fits within the hinge region, and the phenyl moiety occupies the hydrophobic pocket located behind the gatekeeper and the rest of the molecule extends into the allosteric pocket near the DFG motif (**Figure 5-B**).[113] In addition, FLT3 model with F691L mutation demonstrated minor steric clashes with ponatinib, which corresponds to a moderate reduction in ponatinib cellular potency when evaluated against Ba/F3 FLT3-ITD-F691L (IC_{50} = 52 nM) as compared to Ba/F3 FLT3-ITD cells (IC_{50} = 3 nM).[28,113] Furthermore, ponatinib showed diminished activity when evaluated against Ba/F3 cells

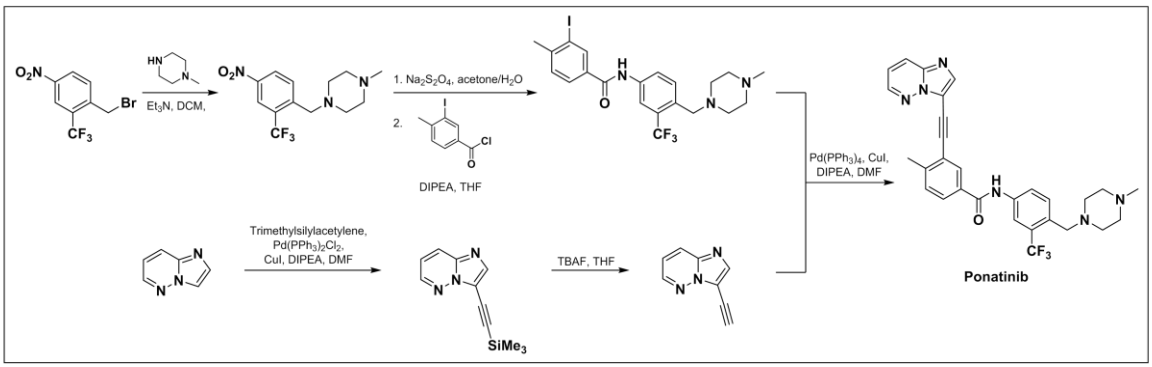

Figure 16. General scheme for the synthesis of ponatinib.[117]

2.2.2. Ponatinib

expressing FLT3-TKD mutations as observed with all type II kinase inhibitors.[113] In cellular assays, ponatinib exhibited potent antiproliferative activity against MV4-11 cell line with an IC_{50} value of 2 nM.[114]

Ponatinib has been investigated in phase I clinical studies for relapsed or refractory AML indication. The use of ponatinib alone or in combination with azacitidine demonstrated preliminary clinical efficiency warranting further investigations.[115,116]

2.2.3. Pexidartinib

Pexidartinib was approved by the FDA in 2019 for the treatment of adult patients with symptomatic tenosynovial giant cell tumor that is associated with severe morbidity and is unresponsive to surgery.[118,119] Pexidartinib is an azaindole-based multitargeted kinase inhibitor (a general scheme for synthesis is outlined in **Figure 17**) with high potency against CSF1R, KIT, and FLT3-ITD enzymes with IC_{50} values of 13 nM, 27 nM, and 11 nM, respectively.[28] As inferred from its crystal structure with CSF1R, pexidartinib binds to the ATP binding site and extends to the adjacent allosteric pocket in a similar mode to other type II kinase inhibitors (**Figure 5-C**).[120] Noteworthy, pertaining to its novel design comprising a pyridine ring instead of the common phenyl ring interacting with the hydrophobic pocket and a methyl amine linker instead of the common urea or amide linkers used in type II inhibitors, pexidartinib successfully retained its activity against the gatekeeper F691L mutation.[28,121] On the other hand, similar to other type II kinase inhibitors, pexidartinib was liable to FLT3-TKD mutations.[28] In cellular assays, pexidartinib exhibited moderate activity against MV4-11 and MOLM-14 cell lines with IC_{50} values of 200 nM and 350 nM, respectively.[28]

Pertaining to its promising preclinical profile, pexidartinib was evaluated in a phase I/II clinical study in adults with relapsed/refractory FLT3-ITD$^+$ AML, where it demonstrated safety, well-tolerability, and clinical efficacy warranting further investigations in patients with FLT3-F691L mutations.[122]

2.2.4. Cabozantinib

Cabozantinib, a multitargeted kinase inhibitor, has obtained multiple FDA approvals due to its activity against a broad range of targets. In 2016, the FDA approved cabozantinib for patients with advanced renal cell carcinoma post anti-angiogenic therapy.[124] In 2017, it received a second approval as first-line treatment of advanced renal cell carcinoma.[125] The third approval came in 2019, for patients with hepatocellular carcinoma.[126] In early 2021, the FDA approved nivolumab in combination with cabozantinib as first-line therapy for patients with advanced renal cell carcinoma.[127] Later, in the same year, cabozantinib received approval for patients with differentiated thyroid cancer.[128] Cabozantinib is a quinoline-based non-selective kinase inhibitor (a general scheme for synthesis is outlined in **Figure 18**) with potent activity against several kinases, such as MET, VEGFR2, RET, KIT, AXL, and FLT3 enzymes.[129] Based on docking studies, cabozantinib

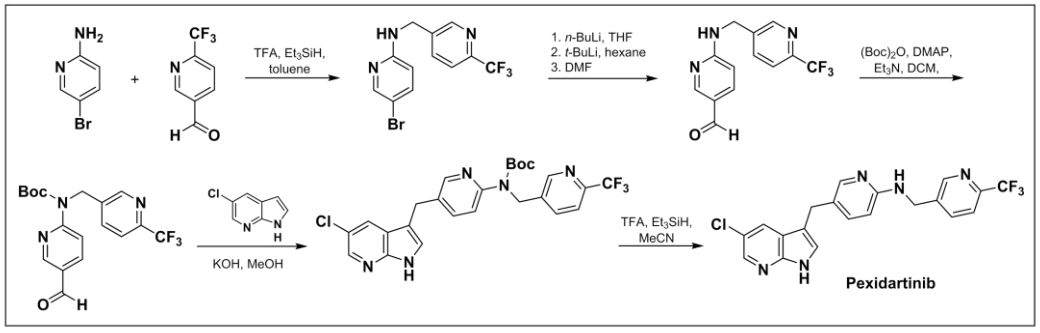

Figure 17. General scheme for the synthesis of pexidartinib.[123]

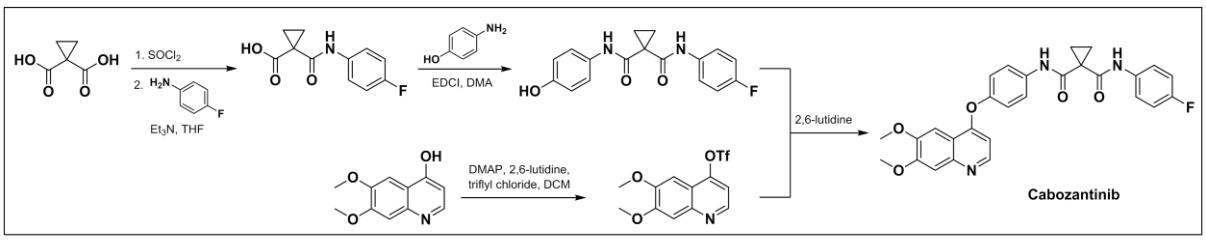

Figure 18. General scheme for the synthesis of cabozantinib.[132]

exhibits the same binding mode as type II kinase inhibitors, where it binds to the inactive conformation of the enzyme (DFG-out). The quinoline moiety occupies the adenine binding site and the dicarboxamide and fluorophenyl moieties extends into the allosteric hydrophobic pocket (**Figure 5-D**).[33]

Cabozantinib exhibited potent enzymatic activity against FLT3-WT (IC_{50} = 11.3 nM),[129] but no data was reported on its activity against FLT3 mutant forms. Furthermore, antiproliferative activities of cabozantinib were promising, where it demonstrated a selective profile against leukemic cell lines, as it only inhibited FLT3-ITD$^+$ cell lines as MV4-11 (IC_{50} = 2.4 nM) and MOLM-13 (IC_{50} = 2 nM), while lacking activity against normal and FLT3-independent cell lines.[130]

Cabozantinib has been evaluated for clinical efficiency in a phase I clinical trial for adult patients with relapsed/refractory AML or older patients with newly diagnosed AML not eligible for conventional therapy. It was well tolerated and effectively inhibited Ba/F3 FLT3-ITD-F691 mutation, while lacking activity against FLT3-TKD-D835 mutations as expected of type II kinase inhibitors.[131]

2.2.5. Quizartinib

Quizartinib was approved recently by the FDA for the treatment of adult patients with newly diagnosed FLT3-ITD$^+$ AML.[133] Quizartinib, an imidazobenzothiazole-based drug (a general scheme for synthesis is outlined in **Figure 19**), is a highly selective second-generation FLT3 kinase inhibitor.[134] The co-crystal structure of quizartinib with FLT3 revealed that quizartinib occupies the adenine-binding site with the imidazobenzothiazole moiety forming hydrogen bonds through a water bridge within the hinge region, while the *t*-butyl-isoxazole resides in the allosteric back pocket, forcing the DFG motif to flip with phenylalanine residue pointing towards the hinge (DFG-out conformation). The urea linker in quizartinib forms hydrogen bonds with the DFG motif, in a way similar to other urea- and amide-containing type II kinase inhibitors. There are two important edge-to-face interactions that form between the middle phenyl ring of quizartinib and both phenylalanine residues of the gatekeeper F691 and the highly conserved DFG motif F830 (**Figure 7-E**).[28,135]

Quizartinib showed potent inhibition in cell-based assays against FLT3-WT and FLT3-ITD mutation with IC_{50} values of 4.2 nM and 1.1 nM, respectively.[37] In addition, quizartinib exhibited preferential antiproliferative activity against FLT3-ITD$^+$ AML cell lines, where it inhibited MV4-11, MOLM-13, and MOLM-14 cells growth, with IC_{50} values of 0.40 nM, 0.89 nM, and 0.73 nM, respectively.[134] Unfortunately, quizartinib exhibited potent inhibition against KIT kinase enzyme which resulted in myelosuppression in treated patients.[136]

Clinical resistance of FLT3 to quizartinib is linked to single point mutations in either the gatekeeper residue or the TKD residues. The substitution of the phenylalanine residue in the gatekeeper with a non-aromatic moiety as leucine (F691L) leads to a significant drop in activity due to the loss of critical interactions with the middle phenyl ring of quizartinib, while mutations that affect the kinase activation loop residues, D835 and Y842, affects quizartinib in a manner similar to other type II kinase inhibitors.[28,135]

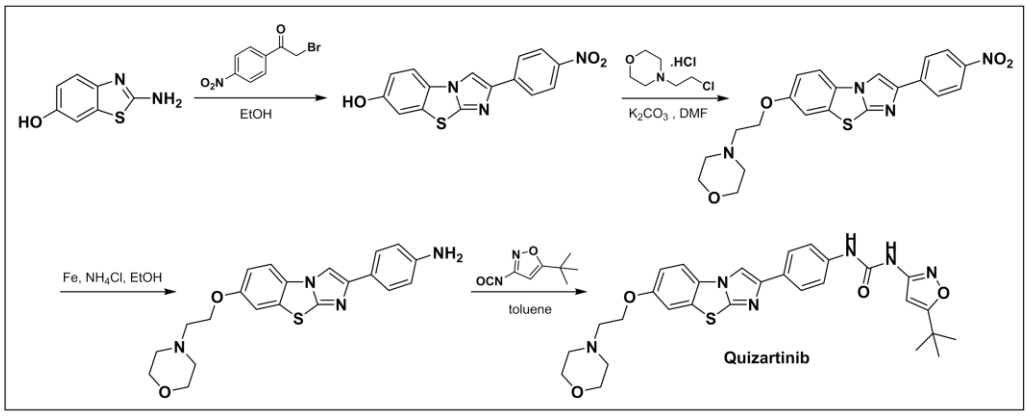

Figure 19. General scheme for the synthesis of quizartinib.[137]

2.2.6. Tandutinib

Tandutinib is an investigational drug that has been granted fast-track status by the FDA to treat AML patients due to its high selectivity towards FLT3 rather than other kinases.[138] Tandutinib is a quinazoline-based (a general scheme for synthesis is outlined in **Figure 20**) selective kinase inhibitor with potent inhibitory activity against type III receptor tyrosine kinases, including FLT3, PDGFR, and KIT.[139,140] Based on docking studies, tandutinib binds to FLT3 kinase in a similar mode to other type II kinase inhibitors, where the quinazoline moiety fits in the adenine binding pocket and the 4-isopropoxy phenyl urea reaches into the allosteric back pocket.[34]

In cellular assays, tandutinib inhibited FLT3-ITD mutant enzyme more potently than FLT3-WT enzyme (IC_{50} = 33 nM and 170 nM, respectively). Moreover, it exhibited strong antiproliferative activity against MV4-11 cell line with IC_{50} value of 60 nM.[37] However, tandutinib, in line with most type II kinase inhibitors, lacks activity against FLT3-TKD mutations.[141] Furthermore, due to its KIT inhibitory activity, tandutinib is expected to cause myelosuppression.[139,142]

Clinical evaluation of tandutinib alone in a phase I clinical study in adult patients with relapsed/refractory AML or newly diagnosed AML, revealed a limited clinical efficiency with no complete or partial remissions observed.[139] On the other hand, in a phase 1/2 study of tandutinib in combination with standard induction chemotherapy in newly diagnosed AML patients, tandutinib was well tolerated, but no data on clinical efficacy was presented.[143] A phase II clinical study of tandutinib in patients with newly diagnosed AML was withdrawn prior to enrollment and no further data on the clinical status of tandutinib is available.[51]

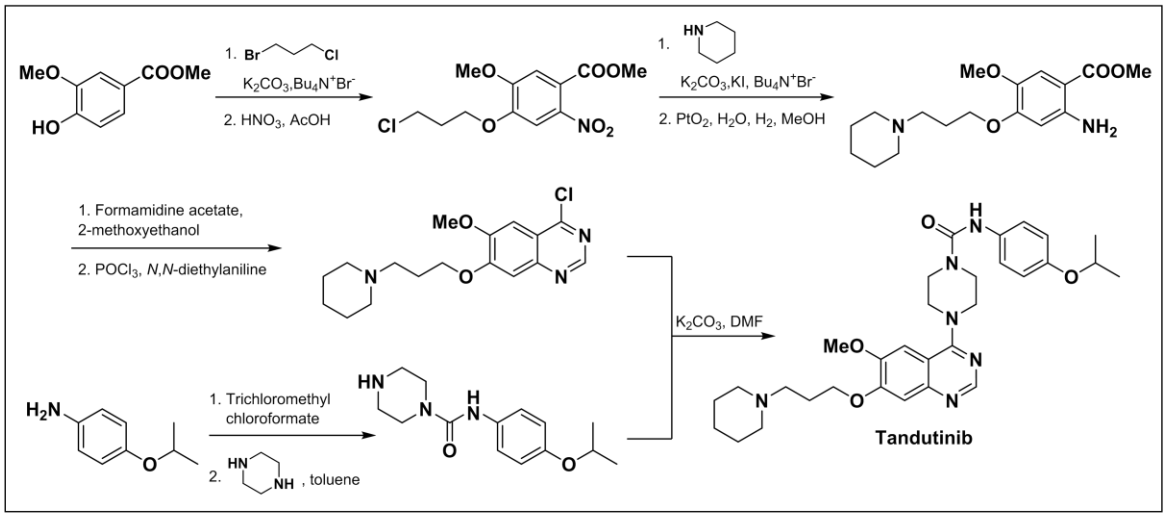

Figure 20. General scheme for the synthesis of tandutinib.[144]

3. Conclusion

Understanding the pathogenesis of AML has allowed for the identification of FLT3 mutations, which are known to be associated with poor prognosis and low survival rates. Subsequently, the development of FLT3 inhibitors as targeted therapies for AML patients harboring FLT3 mutations has shown great promise. Approved and under review anticancer agents represent a wealthy source for investigation and further development for different clinical indications as they have already been tested in humans for safety and thus can bypass several drug discovery hurdles and enter clinical trials readily. First- and second-generation FLT3 inhibitors, either those approved by the FDA or others that are still under review, have shown promising results in clinical trials for both initial treatment and cases of relapse or refractory disease. However, challenges remain, including drug resistance and limitations in the selectivity of some inhibitors. Ongoing research and clinical trials are focused on identifying optimal treatment strategies, combination therapies, and developing the next-generation FLT3 inhibitors to further enhance treatment efficacy and overcome resistance mechanisms.

Abbreviations

AML, Acute myeloid leukemia; AXL, Anexelekto kinase; BCR-ABL, Breakpoint cluster region-Abelson kinase; CML, chronic myeloid leukemia; CSF1R,

Colony stimulating factor 1 receptor kinase; FGFR, Fibroblast growth factor receptor kinase; FLT3, FMS-like tyrosine kinase 3; ITD, Internal tandem duplication; JAK2, Janus kinase 2; KIT, KIT receptor tyrosine kinase; MET, Mesenchymal-epithelial transition factor kinase; NDA, New drug application; PDGFR, Platelet-derived growth factor receptor kinase; Ph+ ALL, Philadelphia chromosome-positive acute leukemia; PKC, Protein kinase C; RAF, Rapidly accelerated fibrosarcoma kinase; RAS, Rat sarcoma virus proteins; RET, Rearranged during transfection kinase; SRC, SRC receptor tyrosine kinase; STAT, Signal transducers and activators of transcription proteins; SYK, Spleen tyrosine kinase; TKD, Tyrosine kinase domain; TRK, Tropomyosin receptor kinase; VEGFR2, Vascular endothelial growth factor receptor 2 kinase; WT, Wild-type.

4. Conflicts of interest

There are no conflicts to declare.

5. Acknowledgments

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