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The antitumor promise of furo[2,3-*d*]pyrimidine: a 2016–2025 review

Mai A. Mansour, *[a] Haya A. Elshafei,[a] Alaa S. Sayed,[a] Aya A. Ashour,[a] Nadia E. Hussein,[a] Marwan M. Abdel Karim,[a] Fares M. Kamel,[a] Nada T. Elsayed,[a] Mahmoud R. Ahmed,[a] Mohamed T. Seleem[a] and Rania M. Gomaa[ab]

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The furopyrimidine scaffold represents a promising core, integrated into numerous compounds targeting cancer and viral infections. Its appeal derives from efficient, accessible synthetic methods. Furthermore, the fused heterocyclic framework acts as a bio-isostere for purines, facilitating interactions across diverse biological pathways. Herein, we review the latest synthetic strategies for the furo[2,3-*d*]pyrimidine core over the past decade, alongside their established anticancer potential, including the structure–activity relationship and probable mechanism of action, and how they have advanced to preclinical and early research stages.

1 Introduction

N-Heterocyclic scaffolds have attracted considerable attention due to their broad spectrum of bioactivities,[1–5] rendering them among the most valuable cores in drug design and discovery. Notably, the pyrimidine ring fused with a five-membered scaffold has prevailed in significant pharmacological interventions.[6,7] Due to its ability to modulate solubility and the hydrophilic-lipophilic balance, pyrimidines enhance binding affinity to enzymes or receptors through hydrogen bonding while mimicking natural substrates. This structural feature significantly enhances druggability and pharmacokinetic profile.[8] The improved ADMET qualities of the target scaffold make it a potential therapeutic candidate compared to analogues lacking such features.[9,10] This structural advantage enables pyrimidine derivatives to engage with RNAs, DNAs, enzymes, and other biopolymeric entities in cells.[11] The lipophilic character of these compounds regulates their interaction with molecular targets and facilitates passive diffusion across biological membranes.[12]

Specifically, for furopyrimidines, the scaffold is well-known for its utility in kinase inhibitor development, offering at least three discrete pharmacophoric features.[13] The structural similarity between pyrimidines and ATP's adenine moiety enables them to replicate hinge-region binding within kinase active sites, making them valuable pharmacophores for kinase inhibition in anticancer drug discovery.[14] Recent studies have demonstrated that pyrimidine-incorporating compounds can create polyheterocycles with enhanced 3D structural diversity, which not only extend beyond traditional linear or bicyclic forms, but also offer promising tools for modulating protein–protein interactions.[15] Therefore, furopyrimidine scaffolds possess a broad spectrum of biological activities, such as anticancer, antiviral, anti-type 2 diabetes, anti-Alzheimer's, and anti-neurodegenerative effects *via* glycogen synthase kinase inhibition.[16] Herein, we examine the synthetic chemistry of furopyrimidines and evaluate their spectrum of biological activities, focusing on their anticancer properties.

2 Synthesis

In 1978, the furo[2,3-*d*]pyrimidine (**I**) ring was successfully synthesized by reacting chloroacetone (**II**) with 2,6-diamino-4-pyrimidinone (**III**)[17] in DMF at 50 °C. This method was subsequently employed in the preparation of several furopyrimidine-based derivatives using dichloroacetone (**II**) in DMF at room temperature.[18–20] Farid *et al.* successfully synthesized the furo[2,3-*d*]pyrimidine ring from 2-amino-4,6-dihydroxypyrimidines (**IV**) instead by refluxing with 2-chloro-2-nitroethenylbenzenes (**V**) in a mixture of ethanol and butanone, using catalytic 1,8-diazabicycloundec-7-ene (DBU).[21] Zhao and coworkers applied the same procedure with diverse substituted 4,6-dihydroxypyrimidines at 120 °C.[22] (Fig. 1).

Subsequently, 5-iodouracil (**VI**) derivatives were coupled with numerous terminal alkynes (**VII**) to prepare furo[2,3-*d*]pyrimidin-2(3*H*)-ones through two *in situ* steps: first, the Sonogashira coupling reaction, followed by Cu(I)-catalyzed intramolecular cyclization.[23] Moreover, intramolecular cyclization of 5-(prop-2-yn-1-yl)-1,6-dihydropyrimidine-4,6-diol (**VIII**) into furo[2,3-*d*]pyrimidinone was efficiently accomplished using concentrated H_2SO_4 at room temperature.[24] The

[a]*Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Badr University in Cairo, Cairo, 11829, Egypt. E-mail: Mai.aly@buc.edu.eg*
[b]*Department of Pharmaceutical Organic Chemistry, Faculty of Pharmacy, Mansoura University, Mansoura, 35516, Egypt*

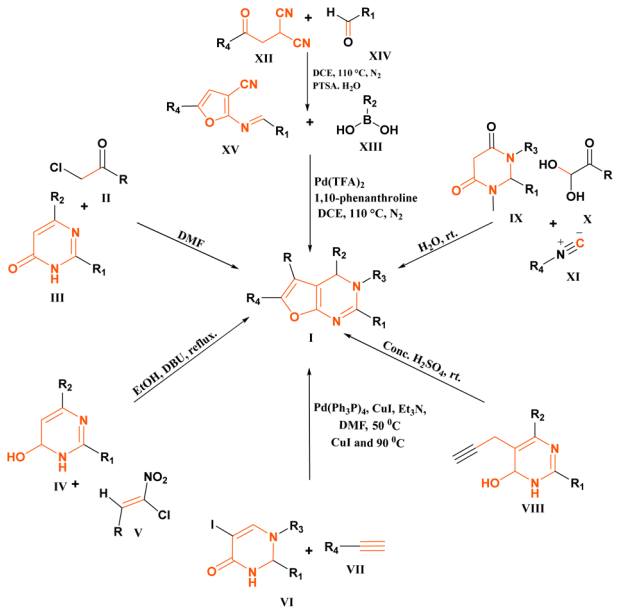

Fig. 1 Synthetic routes for furo[2,3-*d*]pyrimidines.

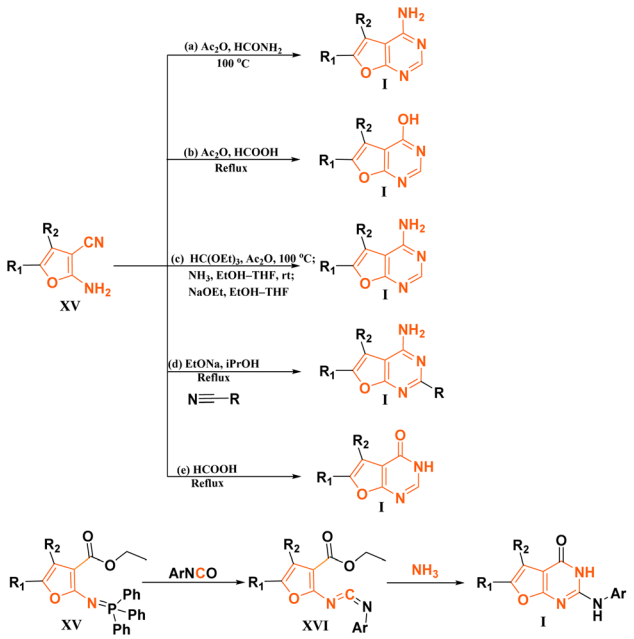

Fig. 2 Synthetic routes for furo[2,3-*d*]pyrimidines starting with furan-based compounds.

postulated reaction mechanism was presumed to proceed *via* nucleophilic attack by the hydroxyl moiety, which, in turn, underwent acidification and rearrangement to produce oxygen-containing heterocycle derivatives.[25] Furthermore, an eco-friendly route was employed, utilizing water as a green solvent, in the synthesis of the furo[2,3-*d*]pyrimidine ring. This regioselective reaction involved the condensation between a one-pot three-component system: 1,3-dimethylbarbituric acid (**IX**), aryl or heteroaryl glyoxal monohydrates (**X**), and alkyl isocyanides (**XI**), in the presence of a minute amount of catalytic $ZrOCl_2 \cdot 8H_2O$ at 50 °C.[26] A similar procedure was also reported, whereas aryl aldehydes were used instead of the glyoxal monohydrate at room temperature.[27]

Recently, in 2023, attempts to synthesize the target heterocyclic ring (**I**) resulted in a three-component protocol comprising a β-ketodinitrile (**XII**), substituted phenylboronic or polyaromatic boronic acids (**XIII**), and an aryl or aliphatic aldehyde (**XIV**), which yielded 2,4,6-trisubstituted furo[2,3-*d*]pyrimidines.[28] This reaction was carried out in the presence of 1,10-phenanthroline and *p*-toluenesulfonic acid, using 1,2-dichloroethane as the solvent at 110 °C under an inert atmosphere, proceeding *via* the formation of an imine intermediate (**XV**).

Efforts to synthesize the furo[2,3-*d*]pyrimidine (**I**) ring from substituted furan systems were primarily and effectively achieved by condensing diethyl 2-amino-5-(4-nitrophenyl)furan-3,4-dicarboxylate with formamide (Fig. 2). The reaction was facilitated by the presence of an electron-withdrawing substituent (EWG) at the carbon atom adjacent to the carbonyl group, such as an ester, in the presence of DMF and formic acid.[29] Kim and coworkers synthesized 4-aminofuro[2,3-*d*]pyrimidine (**I**) from 2-amino-3-cyano-3,4-disubstituted furans (**XV**) with acetic anhydride in formamide (route **a**).[30]

Consequently, 2-amino-3-cyanofuran (**XV**) served as a versatile starting material to access various furopyrimidines, including furo[2,3-*d*]pyrimidin-4-one, when reacted with acetic anhydride and formic acid (route **b**), or 5-substituted-4-aminofuropyrimidine upon treatment with triethylorthoformate (route **c**), in the presence of sodium ethoxide, a strong base, to facilitate amination and cyclization.[31] To attain 2-substituted furopyrimidines from the 2-amino-3-cyanofuran, nitrile derivatives can be incorporated into reflux with sodium methoxide and isopropanol (route **d**).[32] Besides, derivative (**XV**) underwent further annulation when refluxed in neat formic acid[32] (route **e**).

Carbodiimides (**XVI**), prepared *via* aza-Wittig reaction through coupling iminophosphorane (**XV**) with aromatic isocyanates at 0–5 °C, were also used in the synthesis of 2-aminofuro[2,3-*d*]pyrimidin-4(3*H*)-ones with the aid of a catalytic amount of sodium ethoxide.[33] The reaction was carried out at room temperature, in the presence of ammonium hydroxide.[34,35] out at room temperature, in the presence of ammonium hydroxide.[34,35]

3 Furo[2,3-*d*]pyrimidine as anticancer agents

3.1. Miscellaneous agents

In an attempt to discover furopyrimidine-based compounds as anticancer agents, a series of 5-(arylaminomethyl)furo[2,3-*d*]pyrimidines was synthesized and assessed for antiproliferative activity[36] by targeting the folate cycle. These compounds were designed with a methylenamino bridge linking a phenyl ring to the furo[2,3-*d*]pyrimidine scaffold. Various substituents were introduced on the phenyl ring; however, all derivatives except

compound **1** failed to exhibit significant antiproliferative effects. Compound **1** showed moderate growth inhibition with a GI_{50} of 86 μM against the WiDr (colon) cancer cell line. Other derivatives were inactive across all tested cell lines (Fig. 3).

Afterwards, in 2016, 5-methyl-furo[2,3-*d*] pyrimidine derivatives **2–4** were designed and synthesized as microtubule-depolymerizing anticancer agents by targeting the colchicine binding site of tubulin (Fig. 3).[37] Using verubulin and the potent, cyclopenta[2,3-*d*]pyrimidine-based derivative as lead compounds, compound **2** achieved the optimal binding orientation and exhibited the highest microtubule depolymerizing and antiproliferative activities with an EC_{50} of 24 nM and an IC_{50} of 4.3 nM against MDA-MB-435, respectively. Later on, the same research group tested the antiangiogenic properties of compound **2** by assaying its multi-kinase inhibitory activity[38] against EGFR, VEGFR, and PDGFR-β. These inhibitory activities lead to synergistic antitumor effects by disrupting multiple signaling pathways, including angiogenesis.[39] These multi-kinase inhibitors and their SAR will be discussed in detail in subsequent sections.

In 2017, furo[2,3-*d*]pyrimidine-2-one-1,2,3-triazole hybrids were synthesized *via* Pd/Cu-catalyzed reactions.[40] Among the target derivatives, compound **5**, bearing a 5-cyclopropylethynyl moiety, was the most potent, exhibiting the strongest cytostatic effect (IC_{50} = 2.67 μM) against HepG2 cells (Fig. 4). Unfortunately, compounds displaying cytostatic activity against cancer cells were similarly cytotoxic to normal cell lines. Subsequently, further modification yielded compound **6**, which established its cytostatic activity against the Raji lymphoma cell line solely (IC_{50} = 7.9 μM) without affecting normal cell lines (Fig. 4).[41]

Song and co-workers[42] successfully synthesized various series of novel tricyclic furopyrimidines. The tetrahydro-4*H*-furo[2,3-*d*]pyrido[1,2-*a*]pyrimidin-4-one core showed the highest anticancer activity among the synthesized compounds, offering moderate growth inhibitory activity against the HeLa cervical cell line with an IC_{50} value of 10.93 and 17.13 μM for compounds **7** and **8** displayed respectively. In contrast, compound **9** exhibited anticancer activity against MCF-7 breast cancer cells (IC_{50} = 15.0 μM) but not against other cell lines (Fig. 4).

Knowing that chalcones are naturally occurring phytochemicals that are affordable, easily accessible, and typically recognized as safe.[43] This (*E*)-1,3-diphenyl-2-propen-1-one framework features two aromatic rings linked through an α,β-unsaturated carbonyl system.[44] This conjugated enone component enables electron delocalization throughout the entire structure, thereby enhancing its reactivity and biological effects. The α,β-unsaturated carbonyl group also serves as a versatile reactive center that readily interacts with various nucleophilic biological proteins.[45]

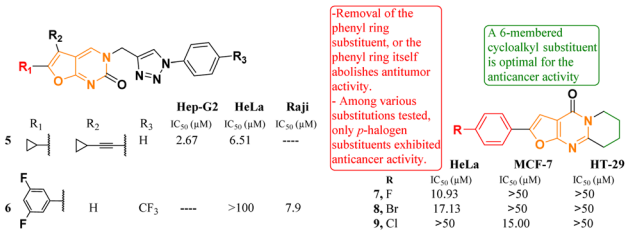

Fig. 4 Furo[2,3-*d*]pyrimidine-based compounds **5–9** as anticancer agents.

In 2022, researchers investigated heterocyclic chalcones as potential anticancer agents.[46] The synthesized series of furo[2,3-*d*]pyrimidine-based chalcones incorporated different substituents, including halogens, to evaluate their anticancer potential. Among these, compounds **MMK-1931** (**10**) and **11** displayed the strongest antiproliferative effects across multiple human cancer cell lines (Fig. 5). Their anticancer activity was assessed using the *in vitro* five-dose NCI60 cell panel assay, demonstrating GI_{50} values ranging from 1.09 to 5.09 μM and 0.51 to 4.46 μM, respectively, with the most potent effects observed across nine tumor subpanels.

The cytotoxic potential of compounds **MMK-1931** and **10** was further confirmed against MCF-7-ADR doxorubicin-resistant cells. When tested on this resistant cell line, both compounds displayed lower IC_{50} values (1.2 μM for **10** and 1.9 μM for **11**) than doxorubicin (IC_{50} = 3.3 μM). *In vivo* studies using a murine Ehrlich ascites carcinoma (EAC) solid tumor model demonstrated the efficacy and safety of compounds **10** and **11**, confirming their potential as anticancer agents at a dose of 5 mg kg^{-1} daily. Due to the potent anticancer activity of compound **MMK-1931**, it was encapsulated in chitosomes to enable oral delivery as an anticancer nanomedicine.[47] This formulation activated apoptotic pathways by upregulating Bax and caspase-9 while downregulating Bcl-2. In addition, it modulated oncogenic signaling by reducing cyclin D and MDM2 levels and enhancing p53 and PTEN expression.

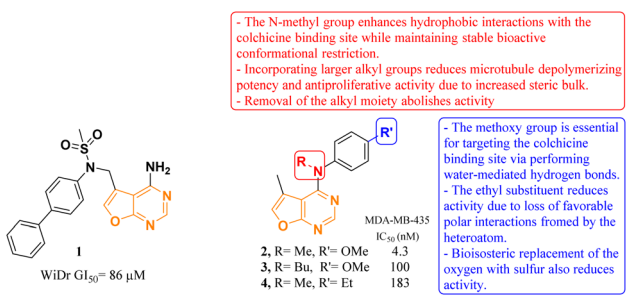

Fig. 3 Furo[2,3-*d*]pyrimidine-based compounds **1–4** as anticancer agents.

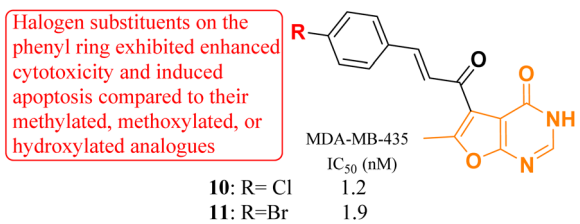

Fig. 5 Furo[2,3-*d*]pyrimidine-chalcone hybrids 10, 11 as anticancer agents.

Recent advances in anticancer drug discovery have highlighted the potential of hybrid molecules as promising therapeutic agents.[48] Among these, ibuprofen-furo[2,3-*d*]pyrimidine hybrids **12–15**, synthesized by Liao *et al.*,[49] have attracted considerable attention due to their notable antitumor properties and favorable biological profiles (Fig. 6). This research investigates the synthesis and biological assessment of a series of ibuprofen-furo[2,3-*d*]pyrimidine derivatives incorporating triazole, hydrazide, and oxadiazole functionalities.

HepG2 and A549 served as standard models for evaluating the cytotoxic, antiproliferative, and apoptotic effects of the novel compounds *in vitro*. Derivatives featuring a triazole group consistently demonstrated the highest potency, underscoring the critical contribution of this moiety to biological activity. In contrast, hydrazide-bearing analogs showed moderate effects, while those containing oxadiazole exhibited the lowest antitumor activity.

Substitution at the C-4 position of the pyrimidine ring served a crucial function in modulating biological outcomes. The observed order of potency was piperidin-1-yl > morpholin-1-yl > diethylamino > di-*n*-propyl amino, highlighting the significance of substituent selection for maximizing antitumor potential. Notably, compound **12** emerged as the most effective, with IC_{50} values of 0.144 μM (HepG2) and 0.068 μM (A549). Further studies confirmed that **12** induces apoptosis in a dose-dependent manner, reinforcing its cytotoxic profile. Target prediction analyses suggest that **12** may inhibit the G protein-coupled receptor C–C chemokine receptor type 3 (CCR3), providing a plausible mechanistic basis for its potential participation in modulating signaling pathways involved in apoptosis regulation.

Similarly, a series of coumarin-furo[2,3-*d*]pyrimidinone hybrids **16–18**, bearing the hydrazide linker, exhibited potent antiproliferative activity against HepG2 and HeLa cell lines, confirming their potential as anticancer agents (Fig. 6).[50] The integration of the coumarin scaffold into the hybrid system enhances the pharmacological profile, with certain derivatives demonstrating moderate dual inhibitory activity against diverse kinases, suggesting their utility as multi-target anticancer agents. Among the tested compounds, compound **16** emerged as the most active antitumor agent, exhibiting significant antiproliferative effects against HepG2 and HeLa cells with IC_{50} values of 4.87 μM and 8.75 μM, respectively. It induces apoptosis in HepG2 cells in a concentration-dependent manner and strongly inhibits cell migration and invasion. Kinase screening revealed that **16** acts as a multi-target inhibitor, showing inhibition rates of 20–40% against RON (37.99%), ABL (26.98%), EGFR, and ITK at 1 μM. In contrast, compounds **17** and **18** also demonstrate notable antiproliferative activity, although their potency is lower than that of **16**.

Generally, the 1*H*-pyrazol–furo[2,3-*d*]pyrimidine scaffold provides a versatile framework for designing novel antitumor agents, offering opportunities for targeted interactions with diverse cancer-relevant proteins. This structural platform serves as the basis for developing compounds with enhanced cytotoxicity and potential therapeutic efficacy.

A series of novel 1*H*-pyrazol–furo[2,3-*d*]pyrimidines **19–23** was synthesized *via* a chalcone-mediated rearrangement reaction (Fig. 7).[35] The cytotoxic effects of these compounds against HepG2 cells were evaluated, yielding IC_{50} values from 0.17 to 30.78 μM, indicating a wide range of potency. Among them, compound **21** exhibited the greatest cytotoxicity (IC_{50} = 0.17 μM) and was further assessed for apoptosis induction. Annexin V-FITC/PI staining demonstrated that **21** promotes early apoptosis in a concentration-dependent manner, with apoptotic rates of 7.59%, 10.69%, 30.40%, and 64.05% at 0, 5.09, 10.17, and 20.35 μM, respectively, highlighting its potential as a targeted anticancer agent.

Another series of furopyrimidine-pyrazole hybrids (**24–26**) was investigated for anticancer activity (Fig. 7).[51] Their antiproliferative effects were evaluated using the NCI60 cell line panel, which revealed the potency of compound **24**. This compound exhibited notable anticancer activity across sixty human tumor cell lines, with a mean GI_{50} value of 8.39 μM. Subsequently, compound **24**, along with its pyrazoline and pyrazole analogues, was tested on two cell lines, HCT-116 and MCF-7, both of which harbor wild-type p53, to assess their potential to inhibit the p53-MDM2 protein–protein interaction. Compound **25** showed ELISA-based biochemical inhibitory activity against MDM2 with an IC_{50} value of 13.8 μM.

3.2. Furo[2,3-*d*]pyrimidine as kinase inhibitors

Small-molecule kinase inhibitors are categorized into seven types based on their interactions with target kinases and the

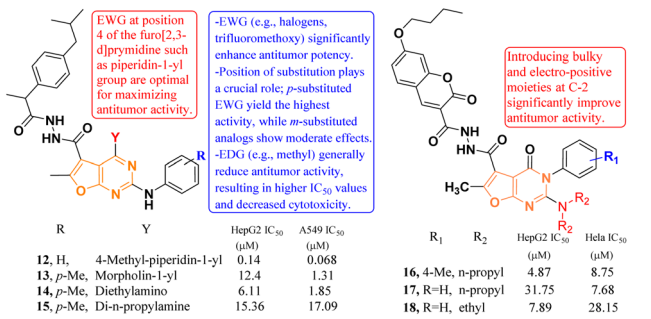

Fig. 6 Furo[2,3-*d*]pyrimidine-based compounds **12–18** as anticancer agents.

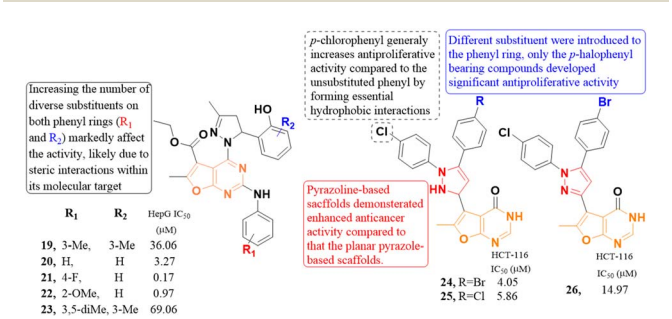

Fig. 7 Furo[2,3-*d*]pyrimidine-based compounds **19–26** as anticancer agents.

conformational state of the ATP-binding site. Type I inhibitors bind to the ATP-binding pocket or hinge region while the kinase is in the active DFG-in state. This represents the largest subclass of inhibitors.[52] Type II inhibitors, on the other hand, preferentially engage the inactive DFG-out conformation, regardless of whether the C-helix is positioned in or out. Because the inactive state exhibits greater structural diversity than the conserved active configuration. Type II agents often demonstrate higher selectivity, *via* binding to the inactive DFG-out form, occupying both the ATP site and the hydrophobic pocket exposed in this conformation. Type III allosteric inhibitors target a regulatory pocket situated adjacent to the ATP-binding cleft. This location generally offers greater selectivity compared to ATP-competitive inhibitors. They function as allosteric modulators by attaching to regulatory sites that are spatially separate from the ATP pocket.[53]

In contrast, Type IV inhibitors interact with more distant and structurally independent allosteric sites that modulate the kinase's conformation without affecting the ATP region. While both Type III and Type IV inhibitors are allosteric, Type IV inhibitors target distinct regions compared to Type III inhibitors.[54] Type V inhibitors are often designed as bivalent linked molecules, enabling them to engage two different regions of the kinase simultaneously to enhance specificity and affinity.[55] Type VI inhibitors also exert their effects through covalent attachment to nucleophilic amino acids, primarily cysteine residues, within the kinase active site, leading to irreversible inhibition. Finally, Type VII inhibitors are nonclassical allosteric agents that interact with the extracellular domains of receptor tyrosine kinases rather than the intracellular catalytic domain, thereby modulating signaling through an alternative mechanism.[56]

3.2.1. EGFR inhibitors. Epidermal Growth Factor Receptor (EGFR) is a transmembrane protein located on the surface of many human cells. It acts as a receptor for specific growth factor ligands such as epidermal growth factor (EGF). Upon binding these ligands, EGFR undergoes activation by dimerizing (pairing with another EGFR or related receptor), which triggers its intrinsic tyrosine kinase activity inside the cell. This activation initiates a cascade of intracellular signaling pathways that control essential cellular processes, together with cell growth, differentiation, migration, and survival.[57–59] EGFR is particularly important in cancer biology because it is frequently overexpressed or mutated in many cancer types, leading to uncontrolled cell proliferation and tumor development. Its abnormal activation correlates with poor prognosis in tumors such as non-small cell lung cancer (NSCLC), breast cancer, and others.[60–62] Due to its key role in driving cancer progression, EGFR is a major target for anticancer drug development aimed at inhibiting its kinase activity or blocking ligand binding to stop malignant cell growth and promote cancer cell death.[63,64]

4-Anilino-furo[2,3-*d*]pyrimidine-based scaffolds were synthesized as dual inhibitors targeting EGFR and HER2 (Human Epidermal Growth Factor Receptor 2) tyrosine kinases.[65] Modifications at the solvent-accessible 5-position side chain of the furo[2,3-*d*]pyrimidine scaffold impact the inhibitory activity of these compounds against EGFR and HER2, as well as their anticancer effects *in vitro* and *in vivo*. The 4-anilino-furo[2,3-*d*]pyrimidines were synthesized with various side chains at the 5-position, including esters, acids, amides, and alcohols, which affected their hydrophilicity and inhibitory potency (Fig. 8).

In vitro enzymatic assays confirmed potent EGFR inhibitory activity, particularly the acid derivative **27** with an IC_{50} of 0.75 μM. On the other hand, cellular assays revealed that compound **28** had potent antiproliferative effects on the A549 lung cancer cell line, likely due to its prodrug nature. *In vivo* antitumor activity in a mouse model showed that compounds **27** and **28** had tumor growth inhibition comparable to the clinically used drug gefitinib. In another study, Faggal *et al.*[66] have incorporated different substituents on the 4-aniline ring. With the aid of the hydrophobic tail created by the ethyl carboxylate group, compound **29** exhibited enhanced antiproliferative activity (GI_{50} = 1.29–19.70 μM). Such an activity was attributable to the carboxylic acid moiety on the phenyl ring *via* three hydrogen bonds with Lys721 and DFG-Asp831,[67] subsequently, displaying strong EGFR inhibition, with an IC_{50} value of 0.121 μM. In contrast, compounds bearing the flexible hydrazide spacer did not show meaningful antiproliferative activity.

In 2016, Jin Han *et al.*[68] made a comparative analysis between the furopyrimidines scaffolds and their thienopyrimidine counterparts, which demonstrated that the furopyrimidines generally present greater potency as EGFR inhibitors. Alterations (Fig. 9) were mainly focused on the 4-amino group (Fragment A), the *R*′ position, and the 6-aryl group (Fragment B) to explore their structure–activity relationships in relation to EGFR inhibition. Many of the analogues (**30–32**) exhibited a consistent binding mode defined by a H-bond between N-1 and Met793, a water-mediated bonding between N-3 and Thr854, and a cation-π interaction linking the aromatic moiety of the 4-amino substituent to Lys745. Among these, compound **30** was identified as the most potent derivative (IC_{50} = 0.4 nM), demonstrating activity similar to that of the EGFR inhibitor erlotinib.

Shu-Yu Lin and coworkers[69] optimized furopyrimidine-based EGFR inhibitors through scaffold hopping and modifications of the covalent warhead to enhance both potency and pharmacokinetic performance (Fig. 10). The designed compounds (**33–36**) integrate the furopyrimidine core with an (*S*)-2-phenylglycinol moiety, in which the hydroxyl group establishes an additional

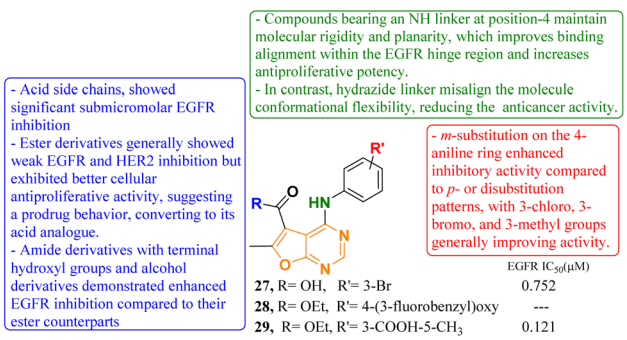

Fig. 8 Furo[2,3-*d*]pyrimidine-based compounds **27–29** as EGFR inhibitors.

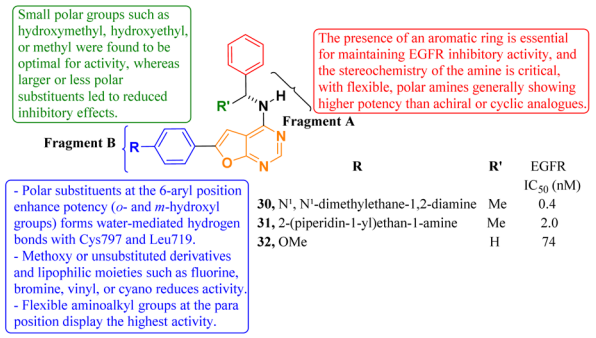

Fig. 9 Furo[2,3-*d*]pyrimidine-based compounds **30–32** as EGFR inhibitors.

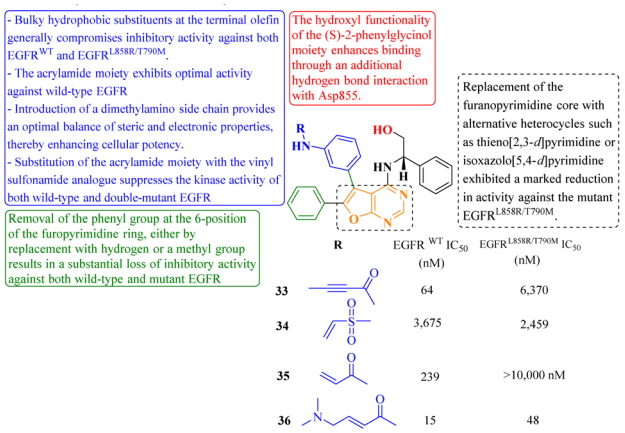

Fig. 10 Furo[2,3-*d*]pyrimidine-based compounds **33–36** as EGFR inhibitors.

hydrogen bond with Asp855, thereby enhancing binding affinity. An acrylamide group was introduced as a Michael acceptor, and further optimization through the attachment of an *N*,*N*-dimethylamino side chain resulted in the identification of the EGFR-targeted candidate **DBPR112** (**36**), which has progressed into Phase I clinical trials.[70] Molecular modeling revealed that the furopyrimidine scaffold, in conjunction with three phenyl substituents, interacts closely with key residues, including Val726, Ala743, Lys745, Leu788, Leu718, and Thr790, through σ–π hydrophobic interactions, which are essential for effective EGFR inhibition.

Structurally, the 6-phenyl ring adopts a perpendicular orientation relative to the 5-phenyl ring, while proper spatial alignment of the acrylamide warhead toward the thiol group of Cys797 is critical for covalent linkage establishment. High inhibitory activity against the EGFR$^{L858R/T790M}$ mutant is achieved only when the acrylamide moiety is optimally directed toward Cys797 within the binding pocket. This finding confirms that the furanopyrimidine scaffold, in combination with phenyl rings at both the 5- and 6-positions, owns a type V inhibitor conformation.[71,72] Moreover, stereochemical investigation revealed that the (*S*)-configuration of the 2-phenylglycinol side chain is crucial for potent EGFR inhibition. Among the synthesized derivatives, compound **36**, **DBPR112**, bearing the dimethylamino substituent, exhibited the most potent antiproliferative activity against HCC827 (CC_{50} = 25 nM) and H1975 (CC_{50} = 620 nM) cell lines.

In 2023, the same research group reported the development of a new series of orally bioavailable, third-generation furanopyrimidine-based EGFR inhibitors, designed to address the dose-limiting toxicities of the previously synthesized compounds.[73] Initially, structural optimization was achieved by replacing the (*S*)-2-phenylglycinol moiety with alkyl substituents to enhance selectivity. The aromatic side chain was not essential for EGFR inhibition, a concept further supported by compound **37**, in which the phenyl group was entirely removed and replaced with a hydrogen atom. Remarkably, compound **37** maintained strong EGFR inhibitory activity and demonstrated over a 10-fold selectivity for the mutant EGFR$^{L858R/T790M}$ compared to the wild-type kinase (Fig. 11). Despite the promising enzymatic profile, limited cellular potency was observed in antiproliferative assays due to an imbalance between enzymatic inhibition and favorable physicochemical properties.

Guided by insights from molecular modeling, the focus of further optimization was on enhancing cellular efficacy and physicochemical properties by introducing various solubilizing substituents on the phenyl rings at positions 5 and 6 of the furopyrimidine core (**38–42**) (Fig. 11). This approach also aimed to improve selectivity toward mutant EGFR. Introducing an *N*,*N*,*N*′-trimethylethylamino side chain at position 5 produced compound **40**. This compound retained strong and mutant-selective EGFR inhibition but demonstrated weak cellular potency in both A431 and H1975 cell lines (CC_{50} > 1 μM). Other attempts to enhance the cellular potency of compound **38** resulted in compound **39**, whereas the incorporation of an *N*-methyl piperazine substituent to the phenyl ring at the 6 position resulted in an enhanced CC_{50} of 685 nM in H1975 cells. Notably, it was considerably less active in A431 cells (CC_{50} =

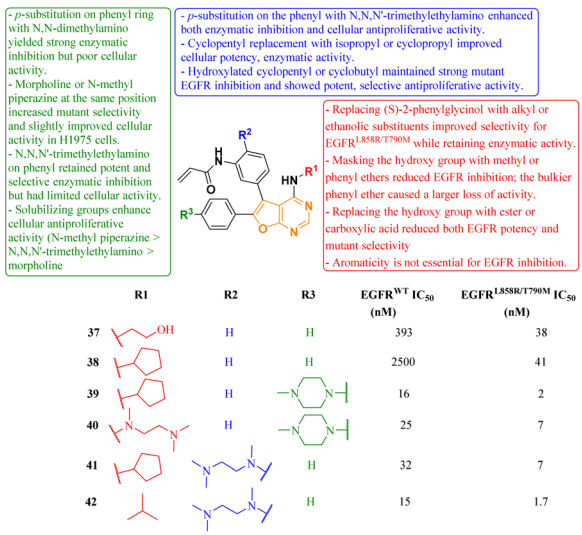

Fig. 11 Furo[2,3-*d*]pyrimidine-based compounds **37–42** as EGFR inhibitors.

3961 nM), indicating approximately 8-fold selectivity toward mutant EGFR over the wild-type receptor.

Introduction of the *N*,*N*,*N*′-trimethylethylamino group at the *p*-position of the phenyl ring at position 5 of the furopyrimidine scaffold led to the creation of compound **41**. This compound showed strong inhibition of the mutant $EGFR^{L858R/T790M}$, with a 5-fold selectivity over the wild-type enzyme. Remarkably, compound **41** specifically inhibited the growth of H1975 NSCLC cells, possessing the double mutant EGFR, thereby yielding a CC_{50} value of 310 nM and exhibiting a 13-fold selectivity compared to A431 cells that overexpress $EGFR^{WT}$. Motivated by these encouraging findings, new compounds were developed by substituting the cyclopentyl group with an isopropyl group. Among these new derivatives, compound **42** exhibited significant enzymatic inhibition, notable antiproliferative activity in cells, and distinct $EGFR^{WT}$-sparing characteristics. Compound **42** displayed over eight-fold selectivity for H1975 cells over A431 cells, optimal drug metabolism, and pharmacokinetics upon *in vivo* oral administration, establishing it as a novel preclinical candidate.

3.2.2. VEGFR inhibitors. VEGFR is a receptor tyrosine kinase and the principal mediator of the biological actions of vascular endothelial growth factor. It serves a pivotal function in regulating angiogenesis, including endothelial cell division, migration, survival, and vascular permeability.[74] Because tumors depend heavily on neovascularization for growth and metastasis, VEGFR-2 has become a validated and highly attractive therapeutic target in anticancer drug development.[75]

Structurally, VEGFR-2 features an ATP-binding hinge region (Cys919), an activation loop that contains the DFG motif Asp1046, and a well-defined allosteric hydrophobic back pocket (DFG-out). This pocket is suitable for accommodating type III inhibitors, providing superior selectivity. Heterocyclic scaffolds, such as furo[2,3-*d*]pyrimidines, fit efficiently within this pocket through hydrogen bonds and hydrophobic interactions and are therefore excellent building blocks for designing novel VEGFR inhibitors.[74]

Sorafenib is a multikinase inhibitor that can inhibit VEGFR-2 in its inactive conformation.[76,77] Sorafenib was used as a lead compound in designing different furo[2,3-*d*]pyrimidine series by introducing its diphenyl urea group that stabilizes the inactive DFG-out conformation. Compounds **43–45** were synthesized and optimized by Aziz *et al.*[65] as a VEGFR inhibitor where its furo[2,3-*d*]pyrimidine scaffold acted as a hinge-binding core, enabling a crucial hydrogen bond interaction with the VEGFR hinge region (Fig. 12). The NH linker in compound **43** was replaced with an ether-linked side chain that subsequently provided enhanced conformational flexibility and improved binding orientation. This offered compound **45** that exhibited a strong VEGFR-2 inhibitory activity with an IC_{50} value of 122 nM.

Abd El-Mageed *et al.*[78] designed and synthesized furo[2,3-*d*] pyrimidine (**46,47**) and furo[3,2-*e*] [1,2,4]triazolo[1,5-*c*]pyrimidine (**48–50**) targeting the VEGFR (Fig. 13). Among these, compounds **47** and **49** exhibited the most potent VEGFR inhibitory activities. In contrast, benzamide-incorporating compounds showed inferior inhibitory activity compared to

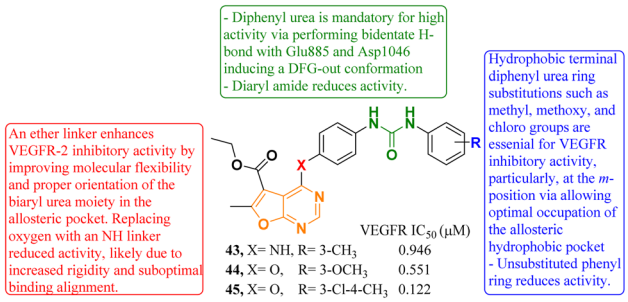

Fig. 12 Furo[2,3-*d*]pyrimidine-based compounds **43–45** as VEGFR inhibitors.

their benzylidene amino derivatives counterparts (**46,47**), likely due to less optimal binding interactions. Consequently, compound **49** displayed the lowest IC_{50} value (38.72 nM), surpassing that of sorafenib (IC_{50} = 41.24 nM), which was attributed to its more favorable conformation and hydrogen-bonding orientation in the VEGFR hydrophobic back pocket.

Compounds **51** and **52** are another benzamide-furo[2,3-*d*] pyrimidine hybrids belonging to a comprehensive series of newly synthesized furan-based compounds designed to target the VEGFR-2 kinase domain (Fig. 13). Among this series, compound **51** emerged as the most potent furopyrimidine analogue, exhibiting moderate antiproliferative activity with IC_{50} values of 13.1, 11.4, 14.5, 21.4, and 22.1 μM against HepG2, MCF-7, A549, HT-29, and PC3 cell lines, respectively, highlighting its potential as a promising anti-angiogenic lead compound.

3.2.3. PI3K inhibitors. The PI3K/Akt signaling cascade is a central pathway involved in numerous cancers, where it regulates key malignant behaviors such as survival, spread, and metabolic adaptation.[79] It also has significant functions within the tumor microenvironment, influencing blood vessel formation and the attraction of inflammatory cells.[80] Three distinct classes of PI3Ks (class I, II, and III) have been characterized, each featuring specific substrates and effectors, in addition to the common substrate Akt.[81]

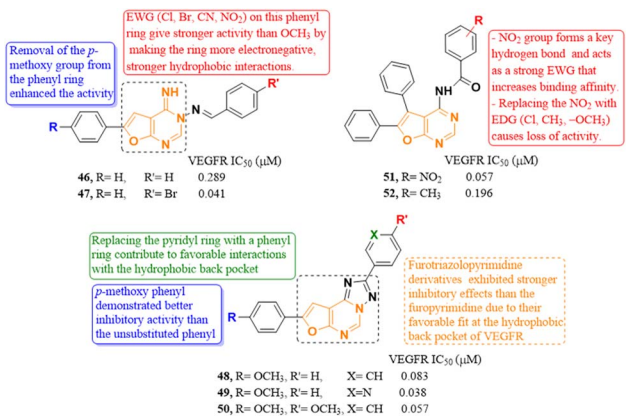

Fig. 13 Furo[2,3-*d*]pyrimidine-based compounds **46–52** as VEGFR inhibitor.

The heterodimeric class I PI3Ks, comprising p110 catalytic and p85 regulatory subunits, signal through downstream tyrosine kinases such as GPCRs and small monomeric GTPases.[82] Their catalytic isoforms include p110α (PIK3CA), p110β (PIK3CB), p110γ (PIK3CG), and p110δ (PIK3CD).[83] Class I PI3Ks play a significant role in cancer development by regulating downstream effectors.[84] Advances in understanding this pathway have led to the development of drugs that inhibit various steps in the network by targeting various enzymatic and cellular pathways, including the inhibition of the enzymes PI3Kα and its downstream effector, AKT-1,[85] as well as inducing apoptosis in several human cancer cell lines.[86] Numerous PI3K/Akt pathway inhibitors have been developed, with some already receiving approval for use in cancer treatment.[87]

In 2020, Mansour *et al.*[88] designed and synthesized a set of novel furopyrimidine derivatives (**53,54**) aimed at treating pancreatic cancer by inhibiting PI3K-α, using a structural strategy that mimics the purine segment of adenosine-5′-triphosphate (ATP) (Fig. 14). In this design, incorporating the furo[2,3-*d*]pyrimidine framework was mainly intended to allow a hydrogen-bonding interaction through the oxygen of the fused furan ring. The ester substituent at the third carbon was intentionally retained, as it is well-suited to occupy the ribose-binding pocket. To enhance antitumor potential, a flexible aliphatic piperazine unit was introduced at the fourth position because of its known contribution to kinase inhibition. Derivative **54**, corresponding to 69% PI3K-α inhibition, recorded the highest antiproliferative activity among the synthesized compounds (IC_{50} = 6.00 μM) against the pancreatic cancer cell line (PANC-1). As for compound **53**, bearing the aryloxyacetyl substituent, it established an IC_{50} value of 4.50 μM against the same cell line.

In 2025, sixteen derivatives of furopyrimidine were developed and evaluated for their biological properties, particularly their antiproliferative effects against 60 human cancer cell lines. The combination of the unique 1,3,4-thiadiazole as an anticancer pharmacophore with the furopyrimidine framework revealed a significant enhancement in the anticancer effectiveness of these novel chemical compounds.[89] Compound **55** showed the strongest overall biological activity. It produced potent inhibition of PI3Kα and PI3Kβ as well, offering a substantial antitumor activity against the MDA-MB-231 cell line with an IC_{50} of 3.359 μM. It also inhibited AKT-1 with an IC_{50} of 0.411 μM, confirming its broad enzyme inhibitory profile. Compound **56**, on the other hand, exhibited selective PI3K-β inhibition (IC_{50} = 0.185 μM), indicating a preference for the β-isoform.

3.2.4. FLT-3 kinase inhibitors. A key regulator of immune responses, hematopoiesis, and cellular proliferation, FLT3 belongs to the type III family of receptor tyrosine kinases.[90] The FLT3 protein is comprised of four primary regions: an extracellular ligand-binding domain (ECD), a transmembrane domain (TMD), a juxtamembrane domain (JMD), and a cytoplasmic tyrosine kinase domain (TKD).[91] The FLT3 receptor features two prevalent mutation types. The FLT3-ITD (Internal Tandem Duplication) mutation occurs in about 25% to 30% of individuals with acute myeloid leukemia (AML) and is linked to a poor prognosis and heightened resistance to standard treatments.[90,92]

FLT3 inhibitors are categorized into three types, type I, type II and typeI/II based on their binding mechanisms[93,94] Type II inhibitors engage three essential components of the FLT3 receptor structure: (1) the hinge binding site, which establishes crucial interactions with the Cys694 and Glu692 motifs, (2) the DFG interacting element that binds to the Phe691 residue, and (3) the terminal lipophilic region that connects with the allosteric site formed by DFG displacement.[95]

In 2024, Moradi *et al.*[96] reported that incorporating a 1,3,4-thiadiazole-urea group at position 4 of the quinazoline scaffold enabled the identification of a selective and effective FLT3 inhibitor. This structural unit was subsequently applied as a promising DFG-binding motif across various heterocyclic frameworks, leading to the development of multiple cytotoxic agents. Building on this concept, a series of furo[2,3-*d*]pyrimidin-1,3,4-thiadiazole derivatives (**57–60**) was rationally designed, synthesized, and biologically assessed to identify new FLT3 inhibitors (Fig. 15).

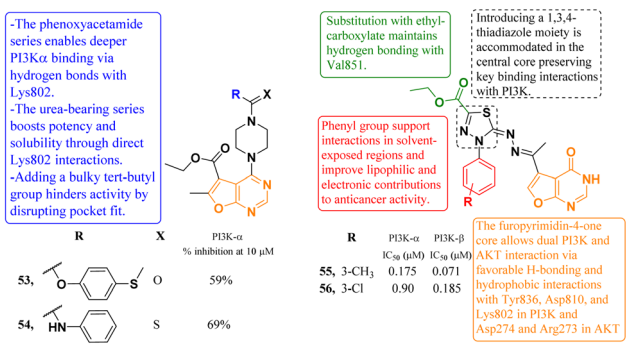

Fig. 14 Furo[2,3-*d*]pyrimidine-based compounds **53–56** as PI3K inhibitors.

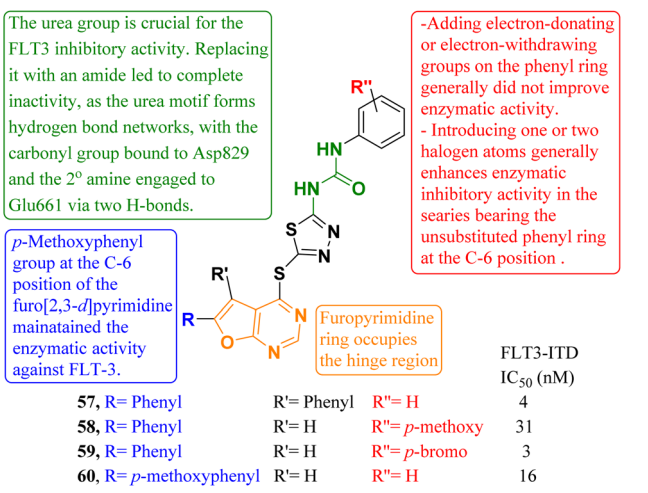

Fig. 15 Furo[2,3-*d*]pyrimidine-based compounds **57–60** as FLT3 inhibitors.

To illustrate the relationships between the structures and their observed activities, the synthesized compounds comprised three diverse series attached to the furo[2,3-*d*] pyrimidine backbone, including an unsubstituted phenyl ring at the position 6, a diphenyl substituent at the C-5 and C-6 positions, and a *p*-methoxy substituted phenyl ring at the C-6 position. Among these three series, compound **57**, incorporating the unsubstituted distal phenyl, showed significant FLT3-ITD inhibitory effectiveness (IC_{50} = 4 nM) and strong antitumor activity (GI_{50} values of 0.074 μM (MV4-11) and 0.110 μM (MOLM-13)).

Compound **59**, incorporating the *p*-bromophenyl group, demonstrated the highest level of inhibitory activity, yet it showed reduced antiproliferative effects against both MOLM-13 and MV4-11 cell lines, with GI_{50} values of 0.57 μM and 1.19 μM, respectively. In contrast, compound **58**, incorporating the *p*-methoxyphenyl ring, enhanced cellular activity and caused significant cell cycle arrest in the G1 phase, exceeding the performance of all other compounds. Meanwhile, among the third series, the *p*-methoxyphenyl bearing compound **60** exhibited the most favorable enzymatic and cellular potencies with an IC_{50} value of 16 nM against FLT3-ITD and GI_{50} values of 0.096 μM and 0.117 μM against MV4-11 and MOLM-13, respectively.

3.2.5. Dual MER/AXL kinase inhibitors. Inhibiting the TAM (TYRO3, AXL, and MER) family of receptor tyrosine kinases (RTKs) results in a positive immune regulation that hinders the suppression of the host's tumor immune responses.[97] Lately, a series of bifunctional furo[2,3-*d*]pyrimidines (**61–64**) were synthesized and assessed against the AXL/MER kinases, initially incorporating 1,3-diketone fragments (Fig. 16).[98] The target compounds adopted a type II binding mode with the MER active site, whereas the N1 of the furopyrimidine core formed a crucial hydrogen bond with Met674 at the hinge region[99] and the oxygen and amide nitrogen from bidentate hydrogen bonds with the backbone of DFG-Asp741. Along with additional hydrophobic interactions, such furopyrimidine-based compounds perfectly implemented the DFG-out conformation. The 1-methyl-1*H*-pyrazol-4-yl bearing compound **62** demonstrated the most promising cellular and dual enzymatic (AXL/MER) inhibitory activity, yet with low oral bioavailability. Attempts to enhance the pharmacokinetics of furo[2,3-*d*] pyrimidine led to **BPR5K230** (**64**), which demonstrated outstanding anticancer activity *in vitro* and in murine syngeneic and xenograft tumor models.

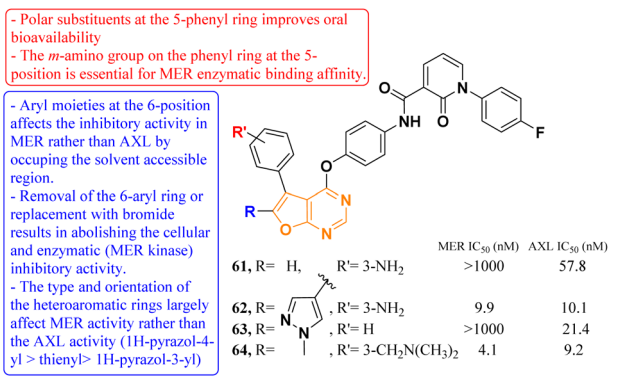

Fig. 16 Furo[2,3-*d*]pyrimidine-based compounds **61–64** as dual MER/AXL inhibitors.

4 Summary

To our knowledge, compounds with furopyrimidine cores remain confined to preclinical or early-stage research, with no entries in FDA approval lists or in DrugBank as approved drugs. Yet they show considerable promise as targeted anticancer agents, selectively inhibiting key kinases such as EGFR, VEGFR, PDGFR, FLT3, and PI3K, involved in cancer pathways over normal tissues. Notably, **DBPR112** (**36**) and **BPR5K230** (**64**) are now being investigated in clinical trials for their potential as potent small-molecule kinase inhibitors (SMKIs) as targeted anticancer agents.

Author contributions

Mai A. Mansour: writing – original draft, writing – review & editing, visualization, Haya A. Elshafei: writing – original draft, visualization, Alaa S. Sayed: writing – original draft, visualization, Aya A. Ashour: writing – original draft, Nadia E. Hussein: writing – original draft, visualization, Marwan M. Abdel Karim: writing – original draft, Fares M. Kamel: writing – original draft, Nada T. Elsayed: writing – original draft, Mahmoud R. Ahmed: writing – original draft, Mohamed T. Seleem: writing – original draft, Rania M. Gomaa: writing – review & editing, supervision.

Conflicts of interest

There are no conflicts to declare.

Abbreviations

ABL	Abelson murine leukemia
AC_2O	Acetic anhydride
Akt	Protein kinase B
AML	Acute myeloid leukemia
Axl	Anexelekto receptor tyrosine kinase
CCR3	chemokine receptor type 3
DBU	1,8-Diazabicycloundec-7-ene
DCE	1,2-Dichloroethane
DFG	Asp-Phe-Gly motif
DMF	Dimethylformaide
EGFR	Epidermal growth factor receptor
ET_3N	Triethylamine
EtOH	Ethanol
EWG	Electron withdrawing group
FLT3	Fms-related tyrosine kinase 3
GPCR	G protein-coupled receptors
$HC(OEt)_3$	Triethyl orthoformate
HER2	Human epidermal growth factor receptor 2
ITK	IL-2-inducible T-cell kinase
MDM2	Mouse double minute 2

MER	*c*-MER proto-oncogene tyrosine kinase
NSCLC	Non-small cell lung cancer
$Pd((Ph)_3P)_4$	Tetrakis(triphenylphosphine)palladium(0)
$Pd(TFA)_2$	Palladium(II) trifluoroacetate
PDGFR-β	Platelet-derived growth factor receptor-beta
PI3K	Phosphoinositide 3-kinase
PTSA	*p*-Toluenesulfonic acid
RTK	Receptor tyrosine kinases
SMKI	Small-molecule kinase inhibitors
VEGFR	Vascular endothelial growth factor receptor
V-FITC/PI	V-Fluorescein isothiocyanate/propidium iodide

Data availability

No primary research results, software or code have been included and no new data were generated or analysed as part of this review.

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