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MEDICINAL CHEMISTRY RESEARCH

REVIEW ARTICLE

Pyrimidine and fused pyrimidine derivatives as promising protein kinase inhibitors for cancer treatment

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Abstract

Pyrimidine ring and its fused derivatives including pyrazolo[3,4-*d*]pyrimidine, pyrido[2,3-*d*]pyrimidine, quinazoline, and furo[2,3-*d*]pyrimidine compounds had received much interest due to their diverse biological potential, in addition fused pyrimidine are considered as bioisosteres with purines and consequently many pyrimidine and fused pyrimidine derivatives as pyrazolo[3,4-*d*]pyrimidine, pyrido[2,3-*d*]pyrimidine, quinazoline, and furo[2,3-*d*]pyrimidine possessed promising anticancer activity. These pyrimidine derivatives exerted their anticancer potential through different action mechanisms; one of these mechanisms is inhibiting protein kinases that are considered as essential enzymes for controlling cell growth, differentiation, migration, and metabolism. The present review sheds the light on the anticancer significance of some privileged pyrimidine and fused pyrimidine derivatives via selective inhibition of protein kinases, revealing structure-activity relationships and some synthetic pathways used for constructing these scaffolds in an attempt to assist medicinal chemists to construct novel pyrimidines with higher selectivity as anticancer agents.

Keywords Anticancer agents · Erlotinib · Pyrazolo[3,4-*d*]pyrimidines · Bioisosteres · Pyrimidine scaffold

Introduction

Cancer is still one of the most fatal diseases, affecting nearly 7 million persons per year all over the world. It is characterized by loss of cell growth control causing a cellular mass called cancer [1–6]. However, death is most often accompanies cancer because of metastasis which is responsible for spreading cancer to another part in the body to establish secondary cancerous growths [7–12]. It was found that strategies for cancer treatment such as surgery and radiation cannot control the spread of tumor; so many scientific trials to treat cancer had been depending on conventional chemotherapy [13–16]. Unfortunately, the conventional chemotherapy did not differentiate between the normal human cells and affected cells, causing many drawbacks [17, 18]. Consequently, to circumvent these drawbacks a new strategy for cancer treatment compromising the use of selective tumor drugs called molecular targeted therapies which inhibits certain receptors and signaling pathways which stimulate tumor cell growth had been developed [19–22]. Protein kinases (PKs) are enzymes that stimulate phosphate transfer from ATP to amino acids tyrosine, serine and/ or threonine residues in protein substrates [23–26]. Also, PKs are important enzymes responsible for cellular signaling processes such as cell growth regulation, differentiation, migration, and metabolism [27–29]. Mutation or overexpression of many PKs had been reported in multiple human cancers [30–33]. Consequently, inhibiting protein kinase has been used as a selective way for targeting cancer cells [34–38]. The literature survey explained that the binding site of kinase inhibitor consists of five essential regions; adenine-binding site, sugar region, phosphate-binding region (hydrophilic channel), hydrophobic region I and hydrophobic region II [39, 40]. Most discovered kinase inhibitors should be small molecules and ATP-competitive inhibitors that exhibited up to three hydrogen bonding interactions with the amino acids present in the target kinase [41–43].

Pyrimidine ring attracted much attention due to its diverse array of biological and pharmacological activities especially anticancer activity [44–49]. Many fused

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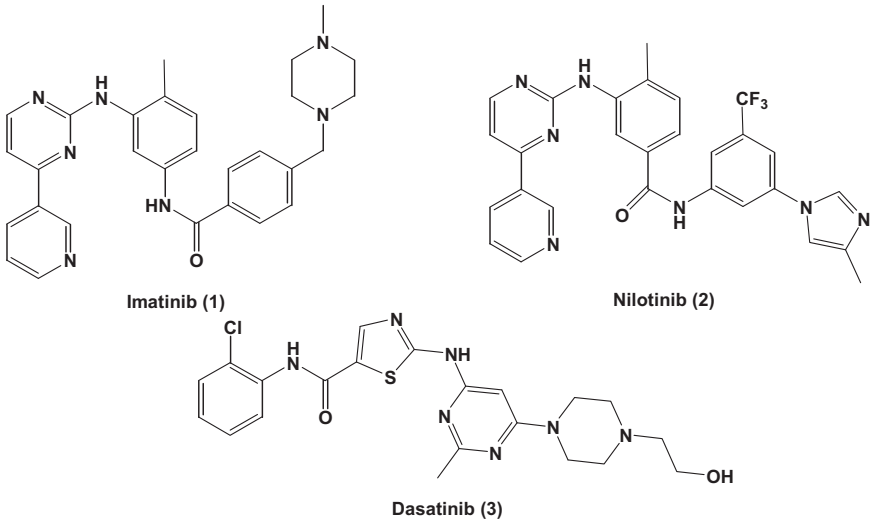


Fig. 1 Chemical structure of tyrosine kinase inhibitors imatinib (**1**), nilotinib(**2**) and dasatinib (**3**)

pyrimidine derivatives exerted their anticancer activity through inhibiting many types of PKs as they are considered as bioisosteres to purine scaffold from which ATP is formed [12, 50–53]. Herein, this review reveals the new approaches and medicinal chemistry efforts in search for new pyrimidine and fused pyrimidine scaffolds as PKs inhibitors.

Pyrimidine derivatives

At the beginning of the twenty-first century, scientist's efforts discovered more potent and selective tyrosine kinase inhibitors, imatinib (Gleevec^{TM}) (**1**) [54, 55], nilotinib (Tasigna^{TM}) (**2**) [56, 57], and dasatinib (Sprycl^{TM}) (3) [58, 59] (Fig. 1). FDA approved these pyrimidine derivatives for treating chronic myelogenous leukemia via inhibiting Bcr-Abl tyrosine kinases [60–62].

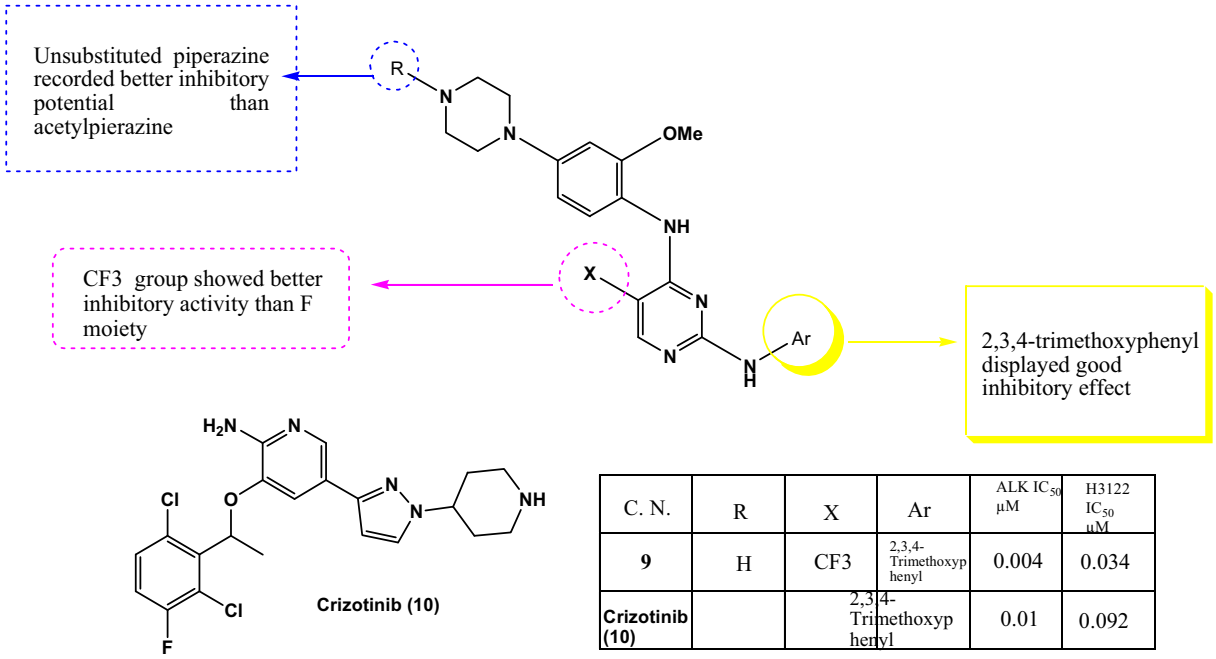
In 2013, a group of investigators designed and synthesized a new series of pyrimidine derivatives as anaplastic lymphoma kinase (ALK) inhibitors with antiproliferative potential against H3122 [63]. From this series, compound **9** ($IC_{50} = 0.004$ μM, $IC_{50} = 0.034$ μM in cell based assay) exhibited 2.5-fold better ALK inhibitory activity and antiproliferative potential than the reference compound crizotinib ($IC_{50} = 0.01$ μM in ALK assay, $IC_{50} = 0.092$ μM in cell based assay) (**10**). SAR study revealing the effect of various substituents is illustrated in Fig. 2.

The target compound **9** was obtained in 75% yield by reacting compound **4** with 4-(*N*-Boc-piperazin-1-yl)-2-methoxyaniline **5** in the presence of diisopropylethylamine, followed by separating the obtained regioisomers (**6&7)** and reacting compound **6** with trimethoxy aniline (Scheme 1).

In 2020, Xu et al. [64] designed and constructed novel 2,4-disubstitutedpyrimidines as Aurora kinase inhibitors. In addition, the prepared derivatives were evaluated for their activity toward A549, HCT-116, and MCF-7 cell lines and SAR of the designed derivatives are depicted in Fig. 3. From these constructed derivatives, compound **11** demonstrated similar antitumor potential (IC_{50} equal to 12.05, 1.31, and 20.53 μM toward A549, HCT-116, and MCF-7, respectively) to that recorded by the standard VX680 (IC_{50} = 3.9, 1.49, and 17.39 μM, respectively). Regarding Aurora suppression activity, this derivative demonstrated suppression potential toward Aurora A ($IC_{50} = 79.4$ μM) and Aurora B ($IC_{50} = 66.3$ μM). SAR studies showed that cyclohexyl moiety at the tail exhibited better antiproliferative than aromatic ring toward HCT-116 cell lines. Replacing NH on the urea group with CH_2 did not affect the anticancer activity on the tested three cell lines.

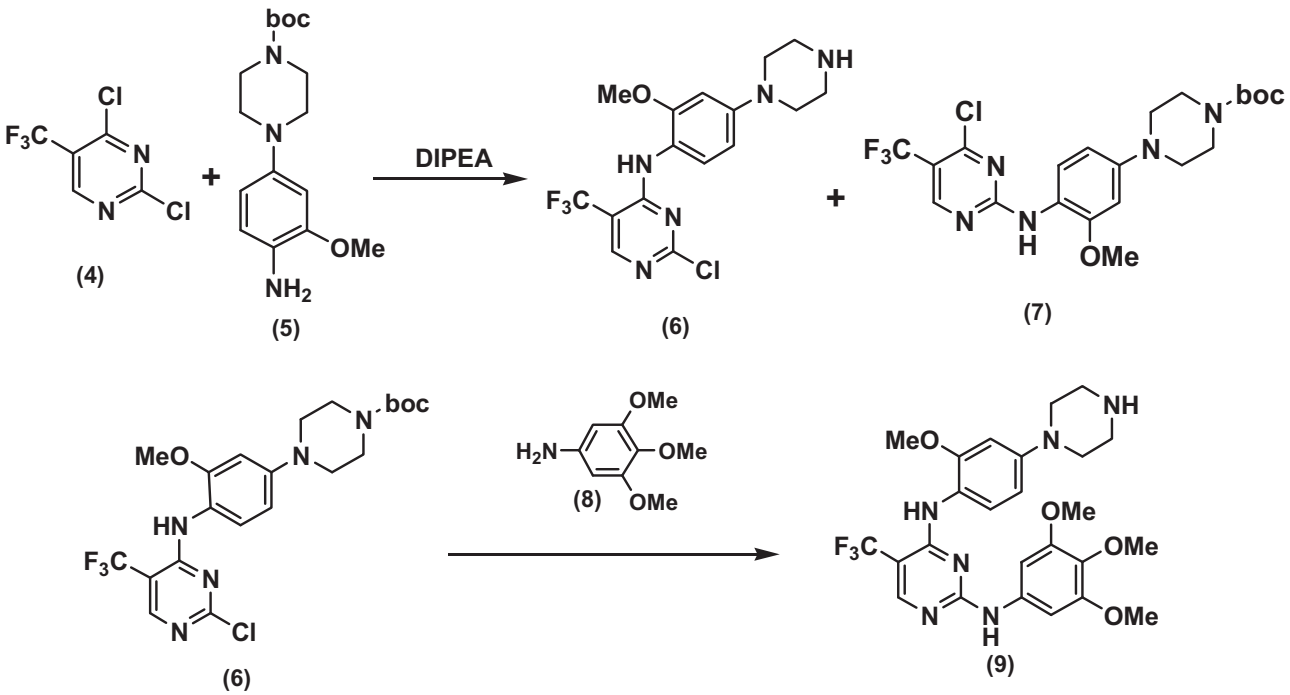
Furthermore, the *N*-(4-(2-(4-(morpholinophenyl)amino) pyrimidin-4-yl)phenyl)acrylamide derivative **12** (Fig. 4) was newly synthesized and showed high JAK3 suppression activity with $IC_{50} = 1.7$ nM with higher selectivity than JAK2 and JAK1 [65]. This selectivity was attributed to the formation of hydrophobic interaction between the aromatic amine moiety and Leu828 and Gly908 amino acids. Moreover, this candidate **12** demonstrated better suppression of T-cell proliferation potential ($IC_{50} = 0.83$ μM) than exhibited by tofacitinib ($IC_{50} = 1.38$ μM). SAR study revealing the effect of various substituents is illustrated in Fig. 4. In addition, the benzoxazolopyrimidine derivative **13** (Fig. 4) showed excellent anticancer potential toward leukemia cell line (RPMI-8226), prostate cancer cell line (PC-3), and renal cancer cell line (A498) with $IC_{50} = 0.72$, 0.7932, and 0.8511 μM, respectively. The mechanism of anticancer potential of this candidate was suggested to be PTK inhibition on MDA-MB-468 cell lines with IC_{50} = 0.07 μM [66].

VX680 (**14**) (Fig. 5) is a small pyrimidine heterocycle reported to suppress Aurora kinases A, B, and C with ki equal to 0.6, 18, and 4.6 nμ, sequentially [67]. This compound **14** has the ability to inhibit many cancer types as ovarian cancer, colon cancer, and leukemia [68]. While,



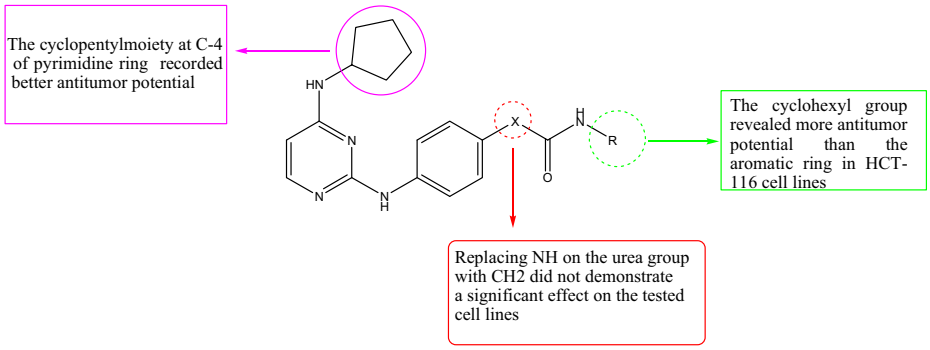
C. N.	R	X	Ar	ALK IC_{50} μM	H3122 IC_{50} μM
9	H	CF3	2,3,4-Trimethoxyphenyl	0.004	0.034
Crizotinib (10)			2,3,4-Trimethoxyphenyl	0.01	0.092

Fig. 2 SAR of pyrimidine derivatives asALK inhibitor, chemical structure of derivative(**9**) and crizotinib (**10**)



Scheme 1 Synthesis of ALK inhibitor (**9**)

ENMD-2076 (**15**) suppress Aurora A selectively with IC_{50} = 14 nM [69]. Luo et al. [70] designed and prepared new C-2, C-4, C-6 trisubstitutedpyrimidines as Aurora A suppressor. The design of these pyrimidine targets was based upon some modifications of both VX680 and ENMD-2076. These modifications include introducing *N*-substituted aniline at C-2 instead of S-substituted moiety in VX680. In addition, modification included replacement of styrene side chain in ENMD-2076 with N-benzylamine. SAR explaining effect of substituent at C-6 on the inhibitory potential on Aurora A is appeared in Fig. 5. From the constructed pyrimidines compound **16** recorded potential inhibitory effect



C. N.	X	R	MCF-7 (IC50 μM)	A549 (IC50 μM	HCT-116(IC50 μM	Aurora A (IC50 μM	Aurora B (IC50 μM
11	CH_2	cyclohexyl	20.53	12.05	1.31	79.4	66.3
VX-680			17.39	3.9	1.49	97.4	98.1

Fig. 3 SAR of some novel pyrimidine derivatives and chemical structure of target pyrimidine **11** as Aurora A and Aurora B inhibitor

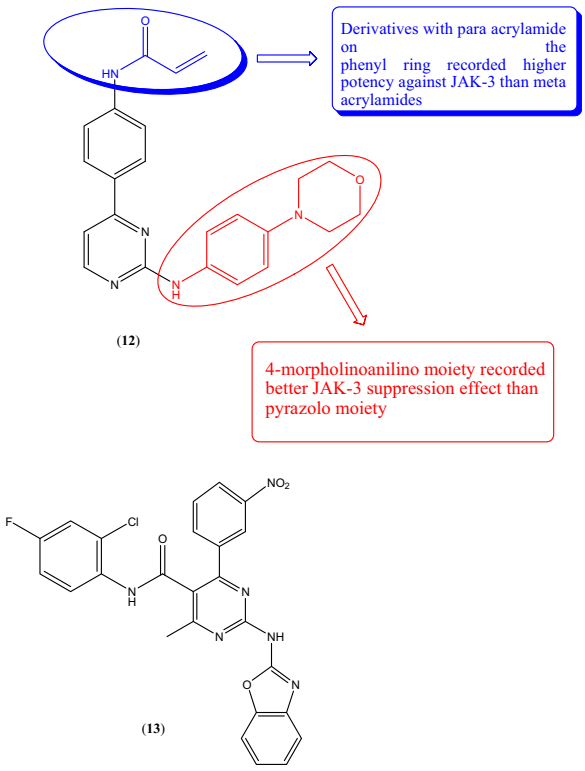


Fig. 4 Chemical structures of pyrimidines **12** and **13**

on aurora A with $IC_{50} = 25$ nM through hydrophobic interaction and three hydrogen bondings with K162, A213, and L139. Moreover, the designed derivatives were assayed for anticancer potential in vitro by the use of VX680 as a standard toward breast cancer cell line as MCF-7, SK-BR-3, MDA-MD-231, and leukemia cell lines as K-562, U937, HL-60, MOLT-4. Results of compounds **16** and **17** are explained in Fig. 5.

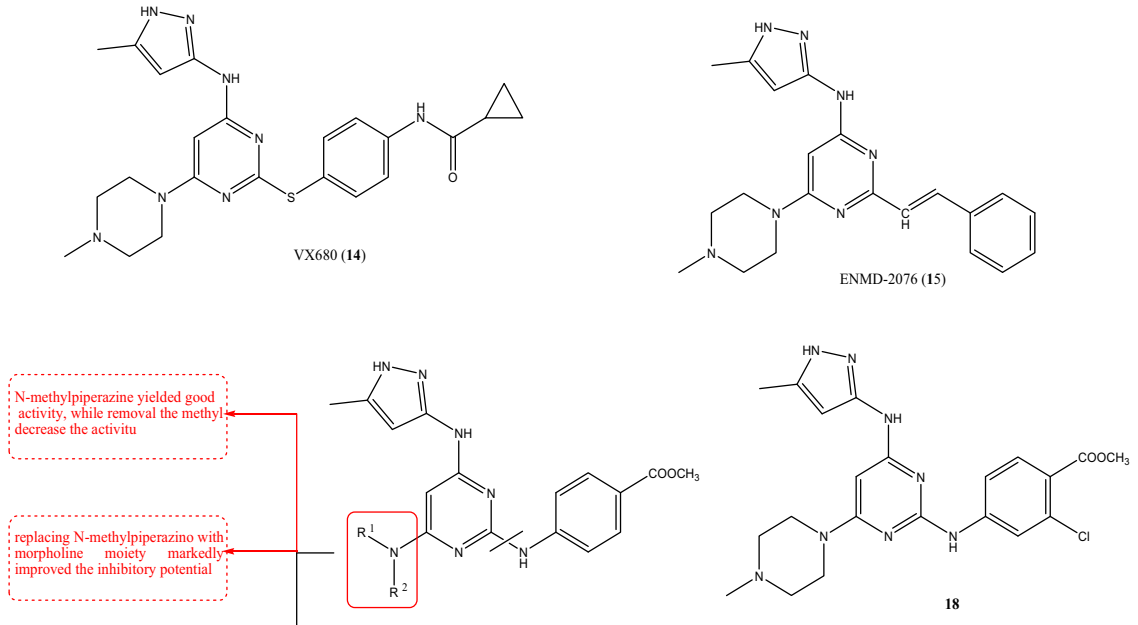
Long et al. [71] in 2018 revealed that the disubstituted anilino moiety at C-2 of pyrimidine nucleus showed higher Aurora A inhibitory potential than the monosubstituted anilino fragment. This is obvious upon comparing compound **18** ($IC_{50} = 7.7$ nM) with 4-aminobenzoate **17** ($IC_{50} = 46$ nM).

Recently, in 2019, novel series of 4,6-diaryl-2-amine derivatives were evaluated for their anticancer potential toward colon cancer cell line (HCT-116) [72]. All the new compounds showed anticancer activity with half maximal cell growth inhibitory concentrations equal to 1.45–40.82 μM. The candidate **19**—the most active anticancer agent ($GI_{50} = 1.45$)—was subjected to kinase assay using 25 cancer-associated kinases applying EMD Millipore Kinase Profiler service assay protocol. This tested compound **19** recorded high selectivity toward Aurora A kinase than other tested kinases. In silico docking of this derivative demonstrated that this derivative performed two hydrogen bondings with Ala213 and Pro214, in addition to seven hydrophobic interactions (Leu263, Arg220, Gly216, Tyr212, Glu211, Leu139, and Arg137) as seen in Fig. 6.

Pyrazolo[3,4-*d*]pyrimidine derivatives

Pyrazolopyrimidine derivatives 1NA-PP1 (**20**) and 1NM-PP1 (**21**) (Fig. 7) were documented to inhibit Src kinase and widely reported as standards for design of many pyrazolo [3,4-*d*]pyrimidine derivatives [73–75].

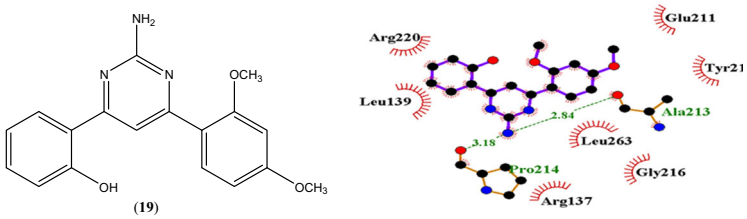
Moreover, novel derivatives of 1,4,6-trisubstituted pyrazolo [3,4-d]pyrimidines were designed based upon some chemical modifications of olomoucine **26** and roscovitine **27**. These chemical modifications include replacing the imidazole ring in olomoucine with a pyrazole ring in addition to introduction different substituents at C-4, C-6, and N-1 of pyrazolopyrimidine. The newly synthesized derivatives were evaluated for their inhibitory activity against CDK2 and for their antiproliferative potential against A431, SNU638, and HCT-116 cell lines. In general, structure–activity relationship (SAR) recorded that compounds having anilino group at C-4 showed



C. N.	NR^1R^2	Aurora kinase A IC50	HL-60	K562	U937	MOLT-4	MCF-7	MDA-MD-231	SK-BR-3
16	morpholine	25 nM	0.750	0.537	0.447	0.302	0.938	0.571	3.18
17	N-methyl Piperazine	46 nM	0.203	0.359	0.119	0.161	1.78	0.359	8.65
VX-680			0.0382	0.0791	0.0360	0.0212	1.30	0.127	9.99

Fig. 5 SAR of some novel pyrimidine derivatives and chemical structure of VX680, ENMD-2076 and target pyrimidine **16**, **17**, and **18** as Aurora kinase inhibitors

Fig. 6 Chemical structure of compound **19** and its binding mode of compound **19** within Aurora A kinase



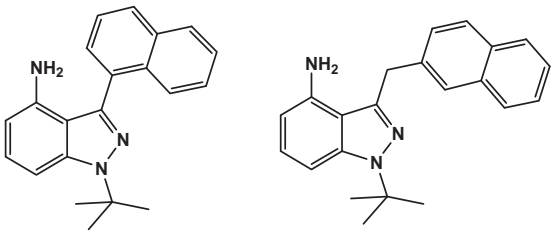
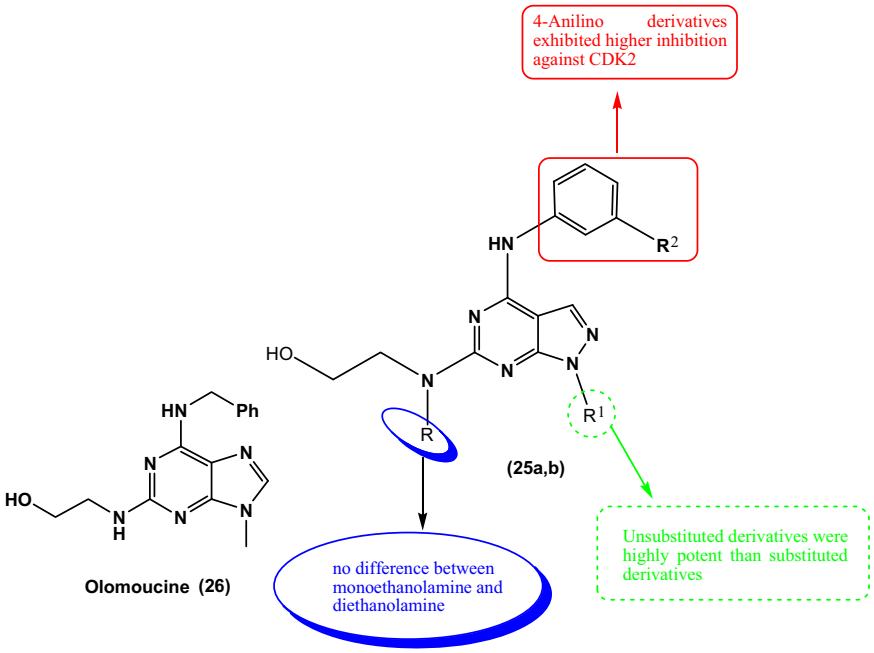


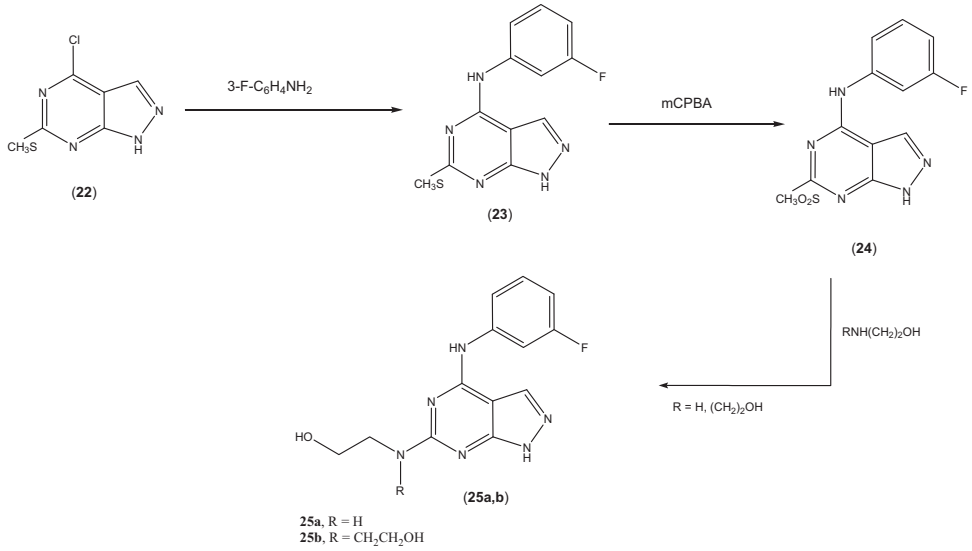
Fig. 7 Chemical structures of 1NM-PP1 (**20**) and 1NM-PP1 (**21**)

higher CDK2 and cell division than 4-benzyl derivatives. Compounds **25a, b** having a 3-fluoroaniline group at C-4 were prepared and revealed comparable or superior cyclin-dependent kinase 2 (CDK2) ($IC_{50} = 0.5$ μM for **33a**, 0.7 μM for **33b**), inhibitory activity to those of olomoucine **26** ($IC_{50} =$ 7 μM) and roscovitine **27** ($IC_{50} = 0.5$ μM) as reference compounds [76]. Moreover, unsubstitution at N-1 recorded higher potency for CDK2 inhibitory effect than substituted analogs. Regarding substitution at C-6, it was found that no difference between monoethanolamine and diethanolamine toward CDK2 activity (Fig. 8). The pyrazolopyrimidine derivatives (**25a,b**) were prepared as illustrated in Scheme 2. Accordingly, the reaction of 4-chloro-6-methylmercaptopyrazolo[3,4-*d*]pyrimidine (**22**) with 3-fluoroaniline in the presence of Hunig's base in n-butanol yielded compound **23** which upon oxidation with m-CPBA followed by nucleophilic displacement of the resulting activated methylsulfonyl groups with

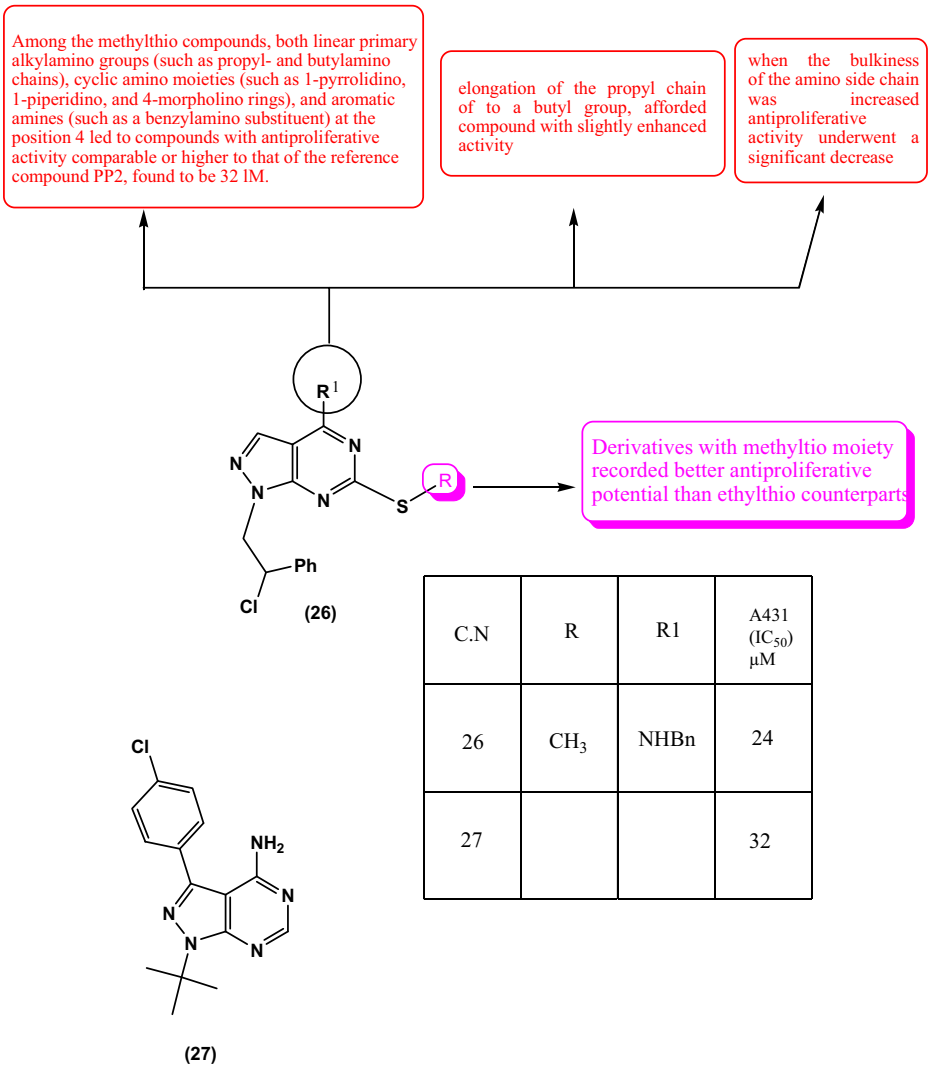


C.N.	R	R^1	R^2	CDK2 IC50	A431	SNU638	HCT116
25a	H	H	F	0.5	28.5	100	100
25b	$(CH_2)_2OH$	H	F	0.9	54.33	100	100
26	–	–	–	7	16.60	16.62	12.05
27	0.5	–	–	–	–	–	–

Fig. 8 Chemical structures of compounds (**25a,b**), olomoucine (**26**) and roscovitine (**27**)



Scheme 2 Synthesis of 1,4,6-trisubstituted pyrazolo[3,4-*d*] pyrimidines **25a,b**



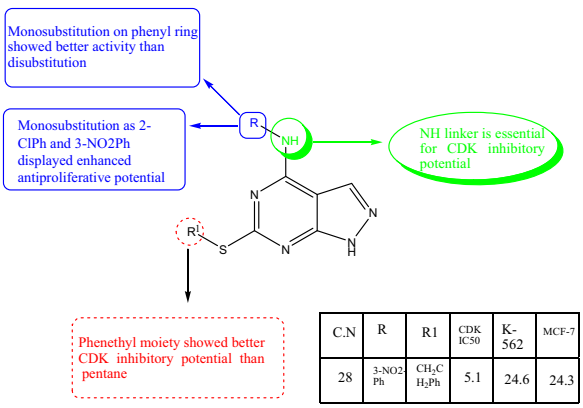
C.N	R	R1	A431 (IC_{50}) µM
26	CH_3	NHBn	24
27			32

Fig. 9 Chemical structures of 1,4-disubstitutedpyrazolo[3,4-*d*] pyrimidine derivatives (**26**) and (**27**)

hydroxylamines gave the target 1,4,6-trisubstituted pyrazolo [3,4-*d*]pyrimidines **25a,b**.

Some 4-aminopyrazolo[3,4-*d*]pyrimidines substituted at position 1 and 6 were prepared and exhibited anticancer activity toward A431 cells, inhibited Src phosphorylation and induced apoptotic cell death. SAR studies of these derivatives are explained in Fig. 9. From the prepared compounds, derivative **26** incorporating a methylthio moiety at position 6 inhibited Src phosphorylation than the reference compound **27** (Fig. 9), so, the size of the alkyl group at position 6 was essential for activity [77].

Recently, novel derivatives of 4,6-disubstituted pyrazolopyrimidines incorporating various anilines at C-4 and thiophenethyl or thiopentane moieties at C-6 had been synthesized [78]. All the synthesized compounds were evaluated for in vitro CDK2/cyclin E and Abl kinase inhibitory activity as well as antiproliferative activity against K-562 (chronic myelogeneous leukemia), and MCF-7 (breast adenocarcinoma) cell lines. The SAR studies are explained in Fig. 10.



C.N	R	R1	CDK IC50	K-562	MCF-7
28	3-NO2-Ph	CH_2CH_2Ph	5.1	24.6	24.3

Fig. 10 SAR of pyrazolopyrimidine derivatives as CDK2 inhibitor and chemical structure of compound **28**

From SAR, it is clear that derivative with thiophenethyl at C-6 with monosubstituted aniline showed better CDK2 inhibitory potential than thiopentane at C-6 and disubstituted anilines.

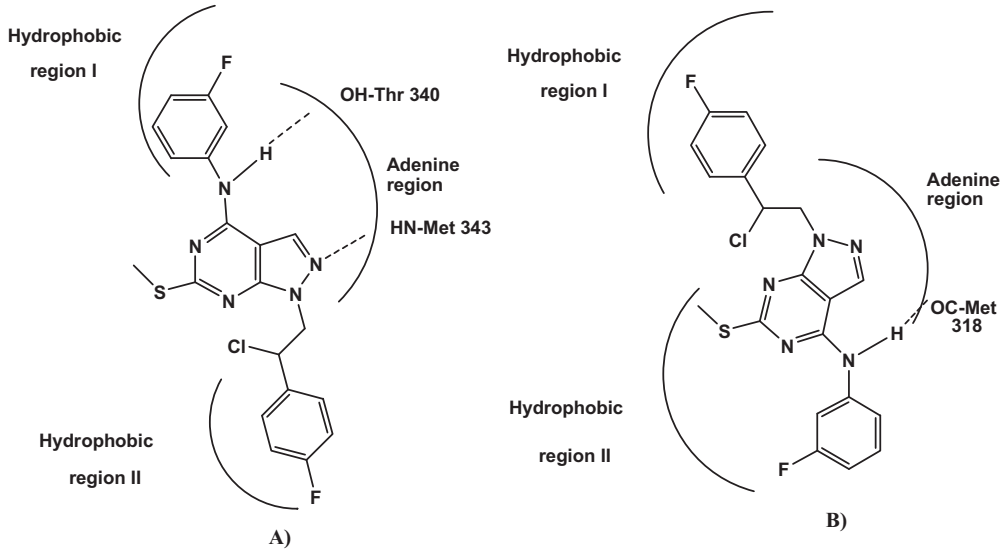


Fig. 11 **A** Binding of compound **29** into ATP-binding site of Src enzyme. **B** Binding of compound **29** into ATP-binding site of Ab1 enzyme

From the prepared derivatives, compound **28** was the most CDK inhibitor with IC50 = 5.1 μM with antiproliferative activity toward K-562 (chronic myelogeneous leukemia), and MCF-7 (breast adenocarcinoma) cell lines with IC_{50} = 24.6 and 24.3 μM, respectively.

In 2008, new derivatives of 4-aminosubstitutedpyrazolo [3,4-*d*]pyrimidines were prepared and exhibited inhibitory activity against Src and proto-oncogene tyrosine protein kinase Ab1 kinases [79]. From this series, compound **29** was docked within adenine triphosphate (ATP)-binding sites of the two target enzymes (Fig. 11). This study recorded that in both enzymes compound **29** located pyrazolopyrimidine nucleus into the adenine region of the ATP-binding site, introducing the side chains at C-4 and N-1 toward two hydrophobic regions and the alkylthio substituent toward the external region of the binding pocket. Furthermore, this target compound performed two hydrogen bonding interactions with Src enzyme and one hydrogen bonding interaction with Abl as shown below (Fig. 11).

Ducray et al. [80] reported the preparation and in vitro evaluation of a new group containing anilinopyrazolo[3,4-*d*]pyrimidine derivatives **30a–c** (Fig. 12) as receptor tyrosine protein kinase erb-2 (erbB2) and EGFR kinase inhibitors. Encouraging results with compound **30c** provided potent, orally active erbB2 kinase inhibitor in rats and dogs with IC_{50} = 0.001 μM toward erbB2. Furthermore, novel derivatives of pyrazolo[3,4-*d*]pyrimdine-3,6-diamines (Fig. 12) were synthesized as potent and selective non-receptor tyrosine kinase, activated Cdc42Hs-asociated Kinase1 (ACK1) inhibitors. Compounds **31a** and **31b** showed promising ACK1 suppression with IC_{50} = 0.02 μM and 0.04 μM. A brief description SAR is illustrated in Fig. 12 [81].

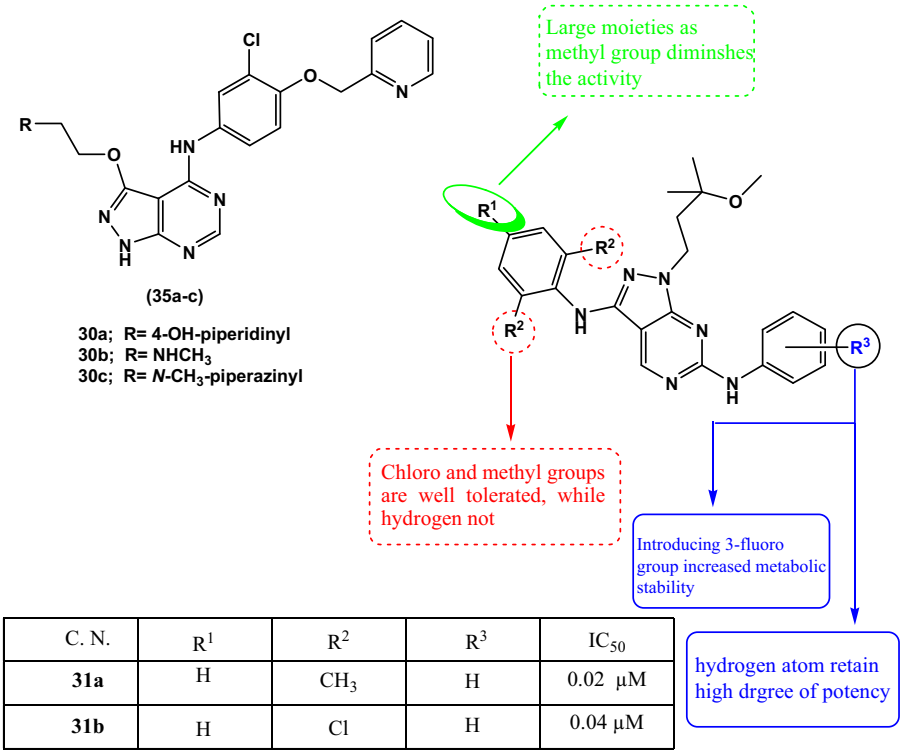
Moreover, compound **32** (Fig. 13) was identified to inhibit EGFR enzyme at low-micromolar concentration with antiproliferative effect against cancer cells [82]. The in silico docking study of compound **32** demonstrated that the amino H and N-5 of pyrimidine ring make hydrogen bonds with backbone atoms of M769. The interaction of the ligand with T766 is mediated by a water molecule, and the 3-methylphenyl moiety substituted at N(1) is buried within the binding pocket (Fig. 13).

Recently in 2016, a new series of pyrazolo[3,4-*d*]pyrimidines hybridized with (4-substitutedbenzylidene)acetohydrazide derivatives (**33a–g**) and (Fig. 14) were synthesized and evaluated for their inhibitory activity toward epidermal growth factor receptor tyrosine kinase (EGFR-TK) [83]. Among these targets **33a–g**, **33g** was the most potent EGFR inhibitor (IC_{50} = 4.18 μM) followed by compound **33c** (IC_{50} = 4.72 μM). Pyrazolo[3,4-*d*]pyrimidine combined with pyrazole moiety (**35**) revealed antiproliferative activity with IC_{50} = 5.00–32.52 μM on breast (MCF-7), colon (HCT-116), and liver (HEPG2) cancer cell lines [84]. Furthermore, this studied candidate inhibited fibroblast growth factor receptor (FGFR) with IC_{50} = 5.18 μM.

The [4-(1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-ylamino)phenyl]methanone derivative (**35**) was synthesized by heating 4-(1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-ylamino)benzohydrazide (**34**) with acetylacetone in acetic acid for 10 h under reflux conditions, as shown in Scheme 3.

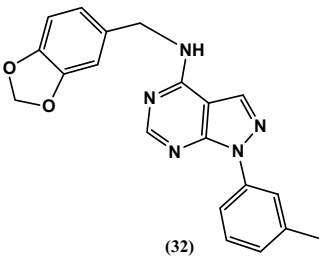
Pyrido[2,3-*d*]pyrimidine derivatives

Two decades ago, PD 089828 (**36**) was synthesized as a novel 6-aryl-pyrido[2,3-*d*]pyrimidine derivative (Fig. 15), which was discovered as inhibitor for many PKs as human



C. N.	R^1	R^2	R^3	IC_{50}
31a	H	CH_3	H	0.02 μM
31b	H	Cl	H	0.04 μM

Fig. 12 Chemical structures of some pyrazolo[3,4-*d*] pyrimidines (**30a–c**) and (**31a,b**)



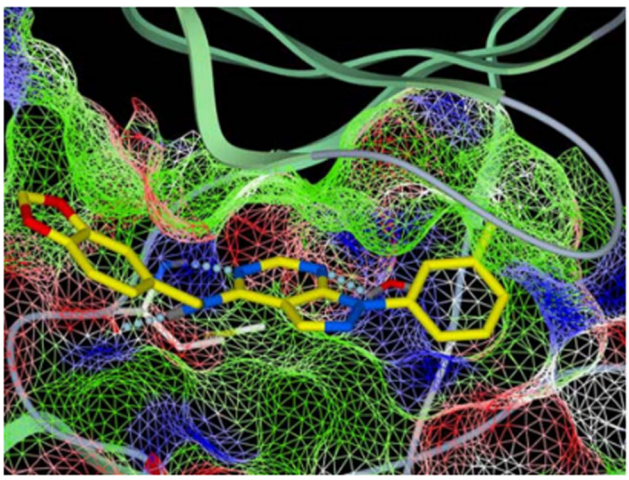


Fig. 13 Chemical structures of pyrazolo[3,4-*d*]pyrimidine derivative (**32**)and its binding mode within EGFR

full-length fibroblast growth factor receptor-1 (FGFR-1), platelet-derived growth factor (PDGF) receptor b subunit (PDGFR-b), Src nonreceptor tyrosine kinase (c-Src), and epidermal growth factor receptor (EGFR) [85]. In addition, another group of pyrido[2,3-*d*]pyrimidines (**37a–d**) (Fig. 15) had been prepared and assessed for their potential antitumor agents. These compounds showed ATP-competitive inhibition of c-Src kinase with IC_{50} values 10 nM and from 6 to 100-folds selectivity for c-Src tyrosine kinase relative to the basic fibroblast growth factor receptor (bFGFr) tyrosine kinase, platelet-derived growth factor receptor (PDGFr) tyrosine kinase, and epidermal growth factor receptor (EGFr) tyrosine kinase [86, 87]. Moreover, the pyridopyrimidine derivative (PD 180970, **38**) (Fig. 15) was prepared by Kraker et al. [87] and subjected to biological evaluation, which revealed that they inhibit Gab2 tyrosine phosphorylation in K-562 cells.

A group of coworkers [88] synthesized a novel series of pyrido[2,3-*d*]pyrimidine derivatives **39a–l** (Fig. 16) as tyrosine kinase inhibitors. From this series, PD 089828 (**39b**) exhibited highly inhibitory activity against PDGFr, FGFr, and c-Src tyrosine kinase with IC_{50} values of 1.25, 0.14, and 0.22 μM, respectively. A SAR study was performed to reveal the effect of phenyl substitution at the 6-position on the potency of these three kinases. This study ascertained the importance of the presence of phenyl moieties in the 6-position substituted with either halogen or methyl groups at 2- and/or 6-position of phenyl ring on the inhibitory activity against PDGFr, FGFr, and c-Src tyrosine kinase as in the target compounds (**39c**, **39d**, and **39f**) which showed inhibitory activity than the unsubstituted parent compound **39a**. Moreover, this study recorded that the introduction of ethyl

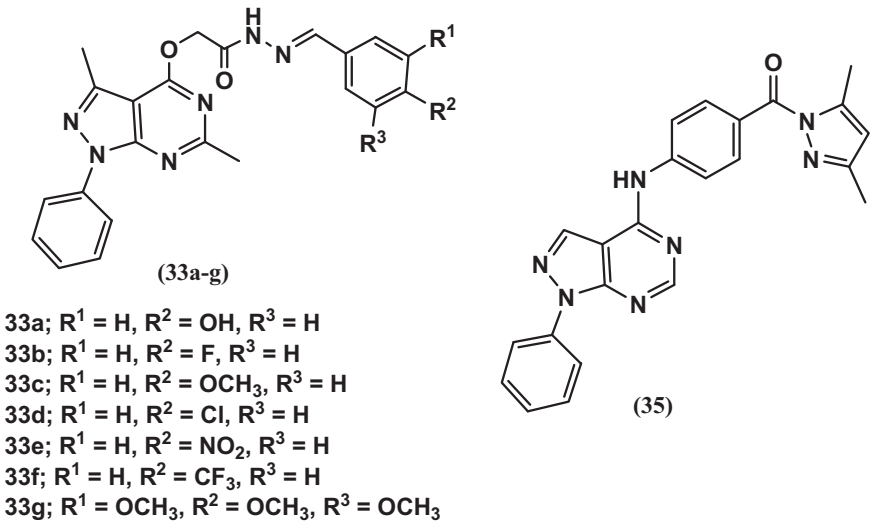
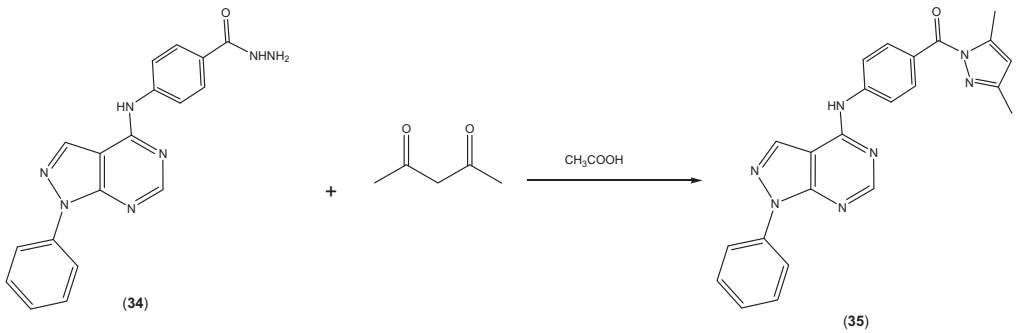


Fig. 14 Chemical structures of some pyrazolo[3,4-*d*]pyrimidine derivatives (**33a–g**) and (**35**) as EGFR and FGFR kinase inhibitors



Scheme 3 Synthesis of pyrazolo[3,4-*d*]pyrimidine derivative **(35)**

(**39i**), or methoxy (**39j**) in the 2-position of the phenyl ring resulted in a decreased the inhibitory activity against both PDGFr-TK and FGFr-TK but c-Src inhibitory activity is not affected. In addition, this work explained that compounds which substituted at 4-position of the phenyl ring such as **39e**, **39k**, and **39l** exhibited marked decrease or loss in their inhibitory activity against all tested kinases. Furthermore, the 2,4,6-trimethyl derivative **39h** exhibited the same inhibitory activity as the 2,6-dimethyl derivative **39f**, even though it contained a methyl substituent in the 4-position. Furthermore, the 3,5-dimethyl derivative **39g** displayed selectivity for the FGFr-TK relative to the PDGFr-TK and the c-Src tyrosine kinase.

In an attempt to design potent kinase inhibitors, Reddy et al. [89] tested more than 150 cyanopyrido[2,3- *d*]pyrimidine derivatives. They found pyrido[2,3-*d*]pyrimidine-6-carbonitrile derivative (**40**) (Fig. 17) revealed the most potent activity and the most apoptosis inducer in tumor cells at a concentration of 30–100 nM. Moreover, this target compound inhibited many kinases such as CDK4/CYCLIN D1 and ARK5 kinases. Furthermore, Edupugantiet al. [90] reported the design and synthesis of a novel series of pyrido [2,3-*d*]pyrimidine-2,4-dione derivatives, which were evaluated for the eukaryotic elongation factor-2 kinase (eEF-2K) inhibitory activity. This study reported that compounds **43** ($IC_{50} = 420$ nM) and **44** ($IC_{50} = 930$ nM) (Fig. 17) were found to be the most active compounds among all the tested compounds.

The in silico docking studies of derivatives **43** within Eef-2k is shown in Fig. 18. The binding of inhibitor 6 involves hydrogen bonds to residues K170, I232, and G234. The hydrophobic cyclopropyl and ethyl groups are buried deep inside the adenine-binding pocket and underneath the Gly-rich-loop, respectively.

Synthesis of pyrido[2,3-*d*]pyrimidine-2,4-dione derivatives **43** and **44** were demonstrated in Scheme 4. The uracil derivatives **41a,b** was subjected to Vilsmeierreactionto give the intermediate derivative **42**, which then was treated with triethylamine and cyanoacetamide in ethanol, to afford the target compounds **43** and **44**.

A novel 4-aminopyrido[2,3-*d*]pyrimidine derivative **45** (Fig. 19) was recorded to inhibit tyrosine kinases in the B-

cell receptor and demonstrated antiproliferative activity toward 20 non-Hodgkin's lymphomas (NHLs) cell lines with GI_{50} ranging from 1.3 to 6.9 µM at 24 h, and 1.4 to 7.2 µM at 48 h [83]. Also, a novel series of oxopyrido[2,3-*d*]pyrimidines was prepared and it was found that they inhibit gefitinib-resistant EGFRL858R, T790M with 100-fold selectivity over wild type. From this group, compound **46** (Fig. 19) showed strong antiproliferative activity against H1975 nonsmall cell lung cancer cell line, the first line mutant HCC827 cell line, and showed also promising antitumor activity in an EGFRL858R,T790M driven H1975 xenograft model sparing the side effects associated with the inhibition of wild-type EGFR [84].

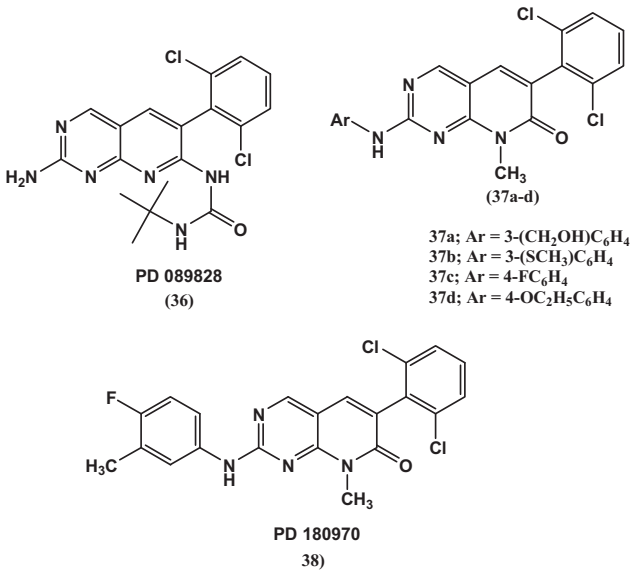


Fig. 15 Chemical structures of some pyrido[2,3-*d*]pyrimidine derivatives PD 089828 (**36**), **37a–d**, and PD 180970 (**38**)

Quinazoline derivatives

A new series of quinazoline derivatives was synthesized as EGFR kinase inhibitors and evaluated in cancer clinical trials. The anilinoquinazoline-containing compounds, Erlotinib (Tarceva™) (**47**) [91, 92] and gefitinib (Iressa™) (**48**) [93, 94], had been used for the treatment of patients with advanced nonsmall lung cancer. In addition, lapatinib (Tykerb™) (**49**) was used for the treatment of human epidermal growth factor receptor 2 (HER2) positive advanced or metastatic breast cancer [95–97] (Fig. 20).

Another series of 4-anilinoquinazoline derivatives was prepared and tested for their inhibitory activity toward EGFR tyrosine kinase. SAR performed on this series recorded that substitution on the three position of aniline moiety with small lipophilic electron withdrawing group led to an increase in the potency of quinazoline derivative (**50**) (Fig. 21), which showed EGFR inhibitory activity with $IC_{50} = 0.029$ nM [98]. Moreover, compound **51** (Fig. 21) was synthesized and exhibited inhibitory activity toward both c-Src and Abl kinases [99].

A new series of 5-aminopyrimidinylquinazolines **52a–e** (Fig. 22) had been designed as specific Aurora kinase inhibitors by Heron et al. [100]. The SAR study showed that the potency was dependent on the substitution on the phenyl ring of the benzamido group. The activity was increased by adding small hydrophobic groups such as 3-chloro (**52a**)

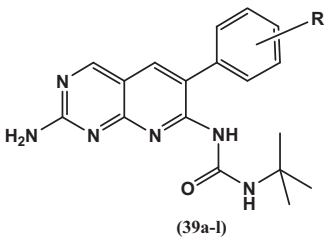
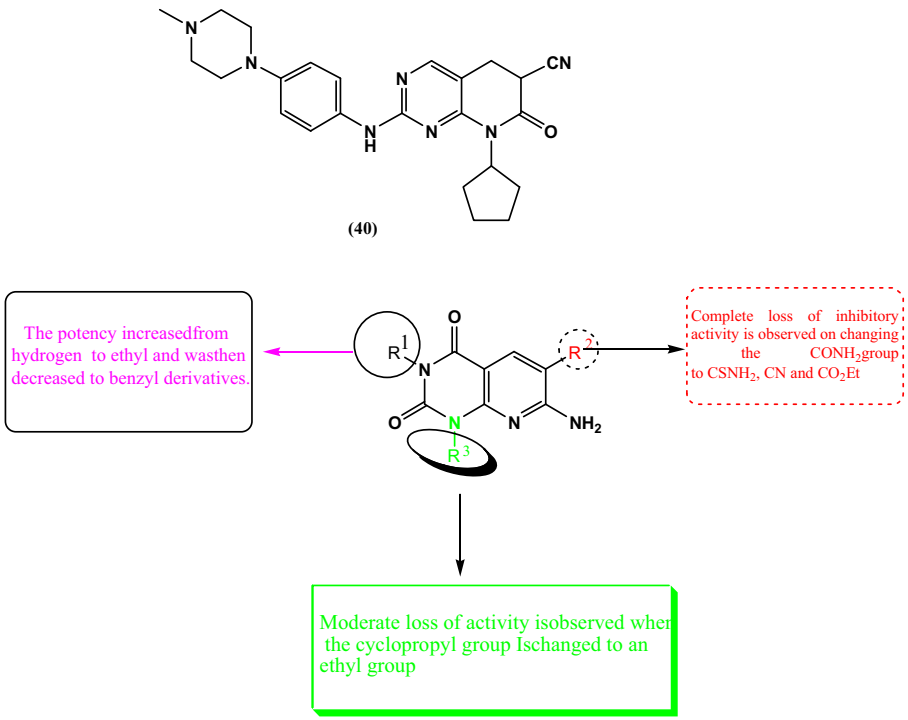


Fig. 16 Chemical structures of 6-phenylpyrido[2,3-*d*] pyrimidine derivatives (**39a–l**)

C.N	R	PDGFR (IC50)	FGFR (IC50)	C-SRC (IC50)
39a	H	13.24	8	19.33
39b	2,6-(Cl)2	1.25	0.14	0.22
39c	2,6-(Br)2	1.42	0.29	0.21
39d	2-Br-6-Cl	0.62	0.12	0.21
39e	4-CH3	1.05	1.40	0.41
39f	2,6-(CH3)2	0.34	0.40	0.11
39g	3,5-(CH3)2	52.90	1.13	50
39h	2, 4, 6-(CH3)3	1.47	0.27	0.36
39i	2-C2H5	4.48	11.22	10.43
39j	2-OCH3	4.48	11.22	10.43
39k	4-OCH3	2.89	3.97	50
39l	3,4-$(CH_3)_2$	50	20.25	50



C.N	R1	R2	R3	IC50 µM
43	Et	CONH2	Cyclopropyl	0.42
44	n-Pro	CONH2	Cyclopropyl	0.93

Fig. 17 Chemical structures of pyrido[2,3-*d*]pyrimidine-7-one derivative (**40**) and pyrido[2,3-*d*]pyrimidine-2,4-dione derivatives (**43** and **44**)

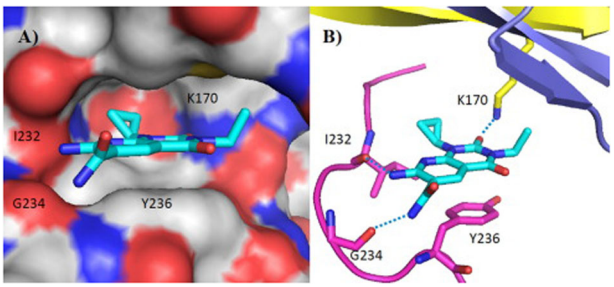


Fig. 18 Binding of compound **43** within eEF-2K active site

and the 3-chloro, 4-fluoro (**52b**) analogs. On the other side a drastic negative effect on potency was revealed on the introduction of larger groups such as 3-bromo-4-methylbenzamido derivative (**52c**). Furthermore, solubility could be improved by adding heterocyclic group instead of phenyl ring (**52d**) or an alkyl substituent (**52e**) but a drop in the potency was observed. SAR of these derivatives **52a-e** is explained in Fig. 22.

In addition, compound **53** (GW2016) (Fig. 23) was discovered to treat cancer cells selectively without affecting normal cells. This compound exerted its effect by inhibiting EGFR and ErbB-2 kinases and inducing apoptosis [101].

Furo[2,3-*d*]pyrimidine derivatives

Miyazaki et al. [102] recorded the synthesis and kinases inhibitory activity of a new series of 5,6-diaryl-furo-4-amino[2,3-*d*]pyrimidines. This work displayed that methoxyphenylfuro[2,3-*d*]pyrimidine (**54**) (Fig. 24) was the most active derivative with $IC_{50} < 3$ nM on both VEGFR2 and Tie-2 TK receptors. The activity of this compound was explained based on the X-ray crystal structure, which showed that the urea moiety formed two interactions with amino acids Asp1044 and Glu883. In addition, the amino group and nitrogen atom of the aminopyrimidine form interactions with Glu915 and Cys917.

In 2008, the same group modified the chemical structure of the previous furo[2,3-*d*]pyrimidine target compound **54**

Scheme 4 Synthesis of pyrido [2,3-*d*]pyrimidine derivatives **43** and **44**

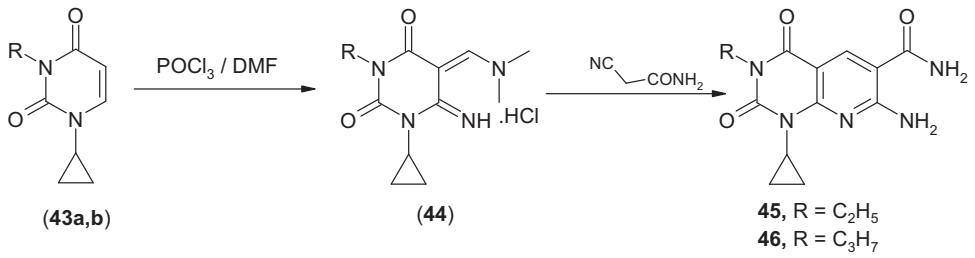
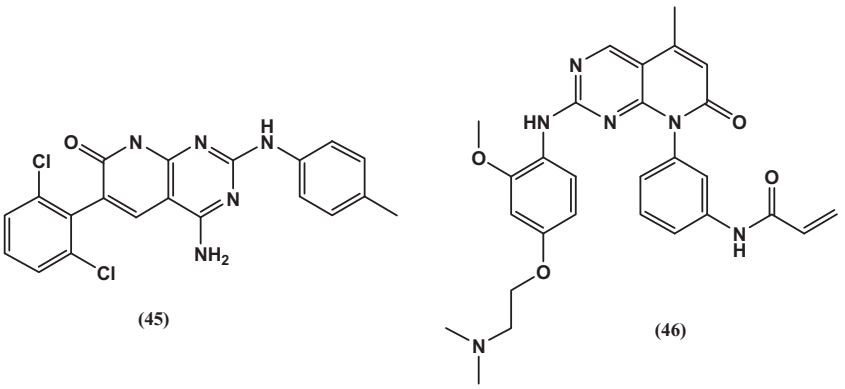
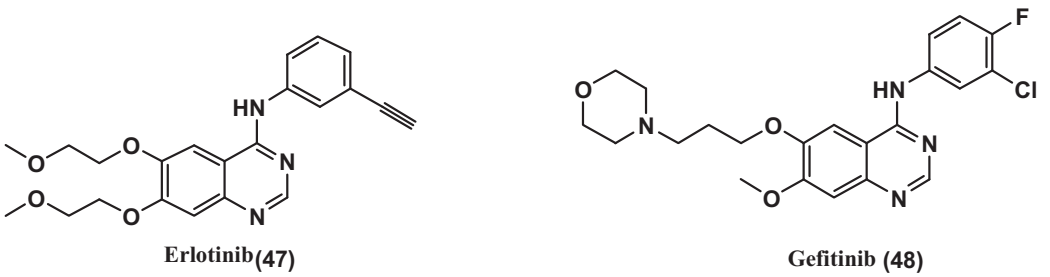


Fig. 19 Chemical structures of some pyrido[2,3-*d*]pyrimidine derivatives (**45, 46**)





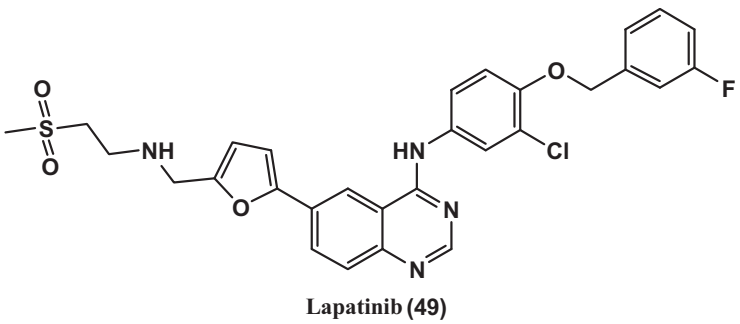
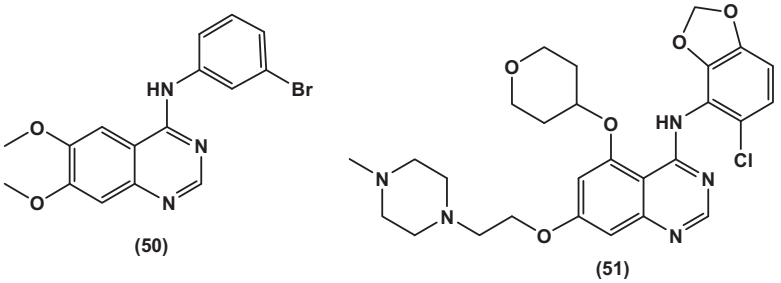


Fig. 20 Chemical structures of some anilinoquinazoline derivatives erlotinib (**47**), gefitinib (**48**) and lapatinib (**49**)

Fig. 21 Chemical structures of some 4-substituted-quinazoline derivatives (**50**) and (**51**)



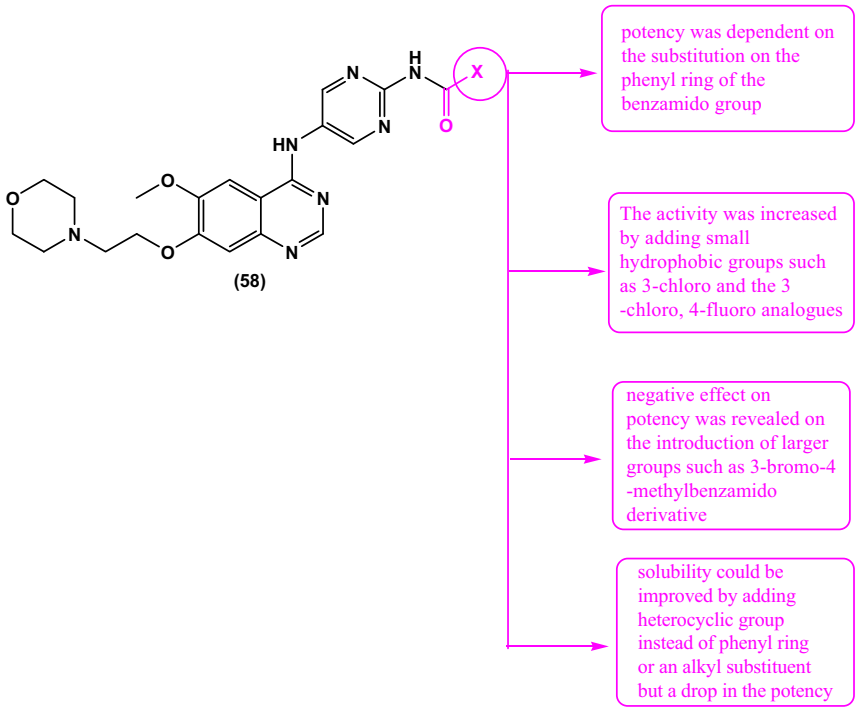


Fig. 22 Chemical structures of 5-aminopyrimidinylquinazolines derivatives (**52a–e**)

C.N	X	Aur A IC_{50} (?M)
52a	3-Cl-ph	0.1
52b	3-Cl-4-F-ph	0.15
52c	3-Br-4-CH3-ph	70
52d	4-pyridyl	690
52e	$CH_3CH_2CH_2CH2$	17

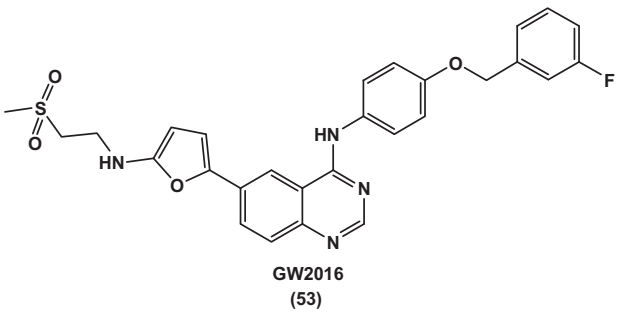


Fig. 23 Chemical structure of 4-quinazolinamine derivative (GW2016, **53**)

to change the activity of this compound away from Tie-2/VEGFR2 to target GSK-3 [103]. The structure modifications included the incorporation of the 3-pyridinyl moiety at the 6-position and different sulfonamides and amides at the *para* position of the 5-phenyl ring. From this series of the modified structure, compound **61** (Fig. 25) exhibited potent GSK-3b inhibitory activity with $IC_{50} = 30$ nM. The docking study of compound **61** displayed the aryl ring of the sulfonamide at 5-position appeared to clash with residues Met101, Leu112, and Leu130 of GSK-3. In addition, N3 nitrogen and NH_2 of aminopyrimidine are anchored with the carbonyl moiety and NH of Val135, respectively, via hydrogen bond interactions (Fig. 26). Moreover, the 3-pyridine moiety at 6-position is close to Lys85 of the conserved salt bridge (Lys85/Glu97).

The target furopyrimidine derivative (**61**) was prepared as illustrated in Scheme 5. Accordingly, sequential acetylation, bromination, and hydroxylation of 4-aminoacetophenone (**55**) resulted in the α-hydroxyketone (**56**) which upon treatment with malononitrile in the presence of diethylamine provided 2-amino-3-cyano-furan **57**. Reaction of **57** with triethylorthoformate, followed by amination and cyclization in the presence of sodium ethoxide yielded 4-amino-furo[2,3-*d*]pyrimidine **58**. Bromination of **58** at 6-position with NBS followed by Suzuki coupling with 3-pyridineboronic acid pinacol ester gave furopyrimidine **60** which upon removal of the acetyl group and reaction of the resulting amine with benzenesulfonyl chloride provided the target compound (**61**).

In addition, a group of 2,4-diaminofuro[2,3-*d*]pyrimidines were prepared as a novel class of in an attempt to

inhibit both dihydrofolate reductase and receptor tyrosine kinases [104]. Compound **62** (Fig. 27) serves as a template for rationally designed VEGFR2 and PDGFR-b inhibitory activity combined with DHFR inhibitory activity in one molecule. Moreover, the candidate compound (**63**) (Fig. 27) exhibited anticancer and anti-angiogenic activity in mouse HT-29 xenograft model via inhibition of both VEGFR2 and Tie-2 enzymes [105].

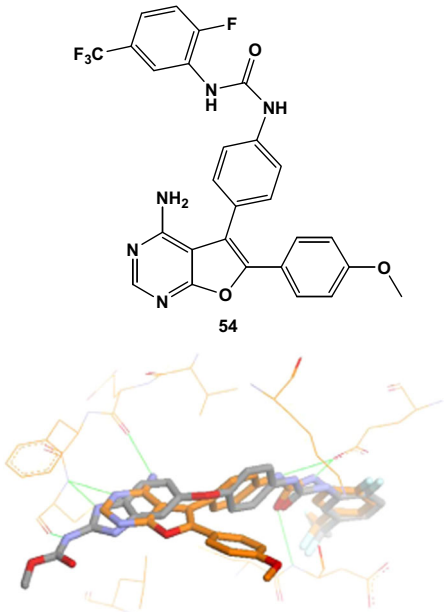


Fig. 24 The chemical structure of new furo[2,3-*d*]pyrimidine derivative (**54**) and its binding within VEGFR2

Furthermore, 3-pyridylfuro[2,3-*d*]pyrimidine derivative **64** (Fig. 28) was synthesized and evaluated for its inhibitory activity against a panel of many kinases [106]. This study

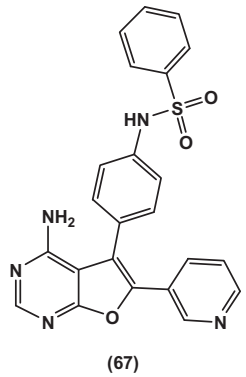


Fig. 25 Chemical structure of (benzenesulfonylaminophenylpyridyl) furo[2,3-*d*]pyrimidine **61**

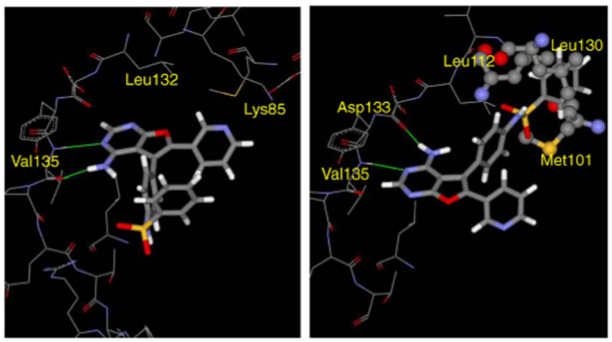
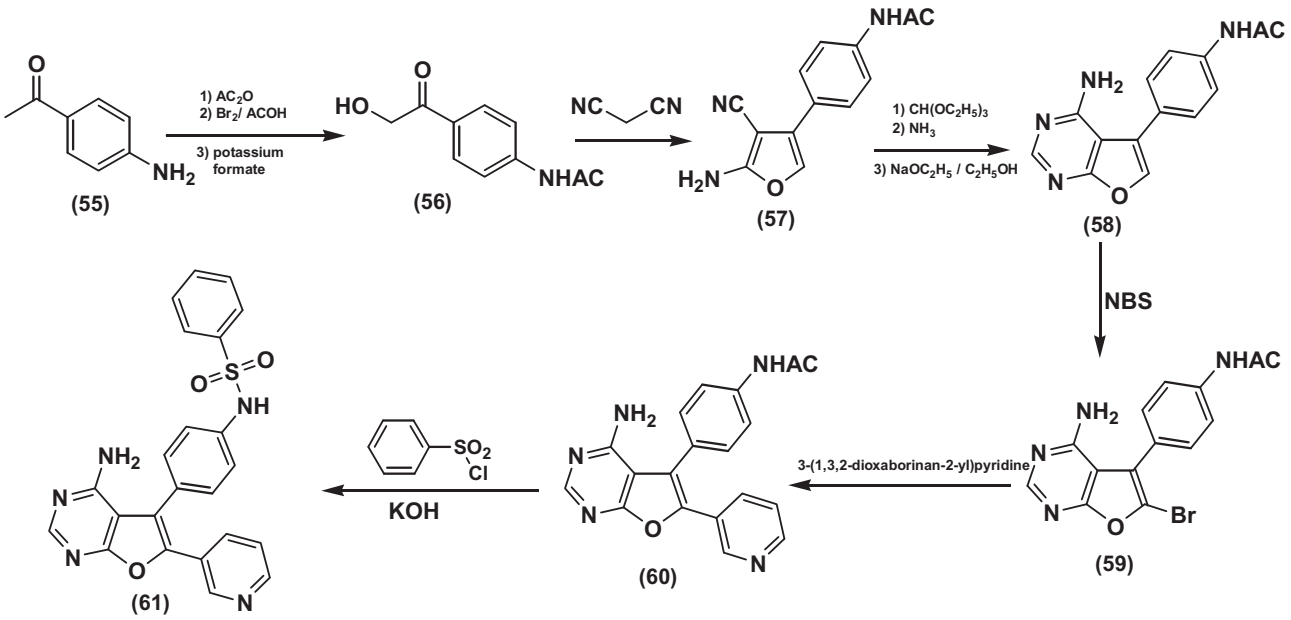


Fig. 26 Binding mode of compound **61** within GSK-3



Scheme 5 Synthesis of furo[2,3-*d*]pyrimidine derivative (**61**)

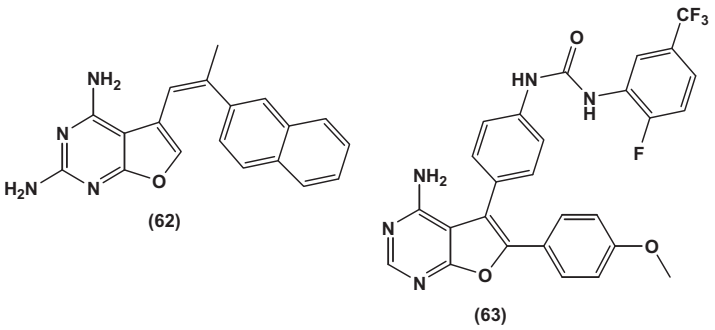


Fig. 27 Chemical structure of some furo[2,3-*d*]pyrimidine compounds (**62** and **63**) with dual inhibitors of receptor tyrosine kinases and dihydrofolate reductase (DHFR)

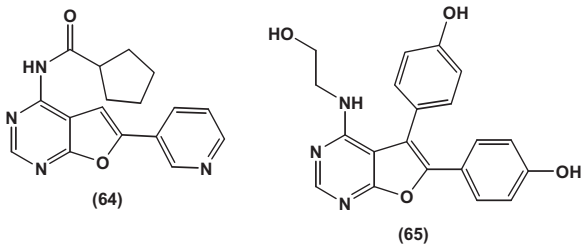


Fig. 28 Chemical structure of some furo[2,3-*d*]pyrimidine candidates (**64** and **6**5)

demonstrated that compound **64** exhibited selective and potent inhibitory activity against GSK-3b over other tested kinases. Moreover, the furo[2,3-*d*]pyrimidine derivative **65** (Fig. 28) was found to possess high inhibitory activity against aurora kinase A with $IC_{50} = 159$ nM [107].

Conclusion

Pyrimidine ring and its fused derivatives including pyrazolo [3,4-*d*]pyrimidine, pyrido[2,3-*d*]pyrimidine, quinazoline, and furo[2,3-*d*]pyrimidine derivatives have proved as great target molecules in medicinal chemistry and drug development. These scaffolds exerted their effect through inhibiting PKs which are considered as essential enzymes to regulate cell growth, differentiation, migration, and metabolism. This review has highlighted the most promising compounds among these scaffolds based on primary literature. It is anticipated that information given in this review would give rise to design of better molecules with better anticancer activity and increased specificity, and finally will lead to the development of novel synthetic strategies.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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