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Original article

Design, synthesis, and structure–activity relationships of novel 6,7-disubstituted-4-phenoxyquinoline derivatives as potential antitumor agents

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ABSTRACT

Two series of quinoline derivatives bearing the pyridine/pyrimidine scaffold were synthesized, and evaluated for their c-Met kinase inhibitory activity and antiproliferative activity against 5 cancer cell lines (HT-29, H460, MKN-45, A549, and U87MG) were evaluated *in vitro*. Most compounds showed moderate to excellent potency, and compared to foretinib, the most promising analog **18b** (c-Met half-maximal inhibitory concentration [IC_{50}] = 1.39 nM) showed a 7.3-fold increase in activity against HT-29 cell line *in vitro*. Structure–activity relationship studies indicated that regulation of the electron density on the pyridine/pyrimidine ring to a proper degree was a key factor in improving the antitumor activity.

1. Introduction

Cancer is a widespread, complex, and lethal disease. In 2008, 7.6 million people died of cancer (around 13% of all deaths), and this number is projected to increase with an estimated 13.1 million in 2030 [1]. Despite the efforts to discover and develop small molecule anticancer drugs in the last decade [2–5], development of new antitumor agents with improved tumor selectivity, efficiency, and safety remains desirable.

Recently, a number of new quinoline derivatives with excellent antitumor activity have been reported [6–18]. Among them, 6,7-disubstituted-4-phenoxyquinoline derivatives, which could inhibit c-Met kinase, have attracted our attention. Many of these derivatives are already being marketed or are under clinical/preclinical studies, such as cabozantinib, foretinib, MG10, Amgen, and AM7 (**1**–**5**, Fig. 1). The main modification of these quinoline derivatives was focused on the 5-atom linker between moiety A and moiety B, which was characterized by the illustrated "**5 atoms regulation**" [19]. In our previous study, we introduced 1,4-dihydrocinnoline and quinoline scaffolds as part of the 5-atom linker on the basis of "**5 atoms regulation**", and the resulting derivatives *N*-(3-fluoro-4-(6,7-disubstitutedquinolin-4-yloxy)phenyl)-4-oxo-1-(substitutedphenyl)-1,4-dihydrocinnoline-3-carboxamides (**6**, Fig. 1) and *N*-(3-fluoro-4-(6,7-disubstitutedquinolin-4-yloxy)phenyl)-2-substitutedphenylquinoline-4-carboxamides (**7**, Fig. 1) showed excellent potency [19,20].

Pyridine- and pyrimidine-based compounds are amongst the most commonly occurring heterocycles in anticancer drugs, such as imatinib, sorafenib, crizotinib, and abiraterone [5]. In this study, pyridine/pyrimidine as a part of the 5-atom linker was attached to the 6,7-disubstituted-4-phenoxyquinoline moiety via an amide bond and then 2 series of antitumor agents were designed (Fig. 2). According to our previous study, the 3-carbon tether at the 7 position of quinoline was reserved, while the morpholinyl group was replaced by other water-soluble substituents, including piperidinyl, pyrrolidinyl, and 4-methyl piperazinyl groups, to observe the effects of the different cyclic tertiary amino groups on activity of the new compounds. Furthermore, various substituents were introduced at the phenyl ring (moiety B) to investigate their effects on activity. Herein, 2 series of 6,7-disubstituted-4-phenoxyquinoline derivatives were designed and synthesized to study the structure–activity relationships (SARs) and find promising antitumor agents.

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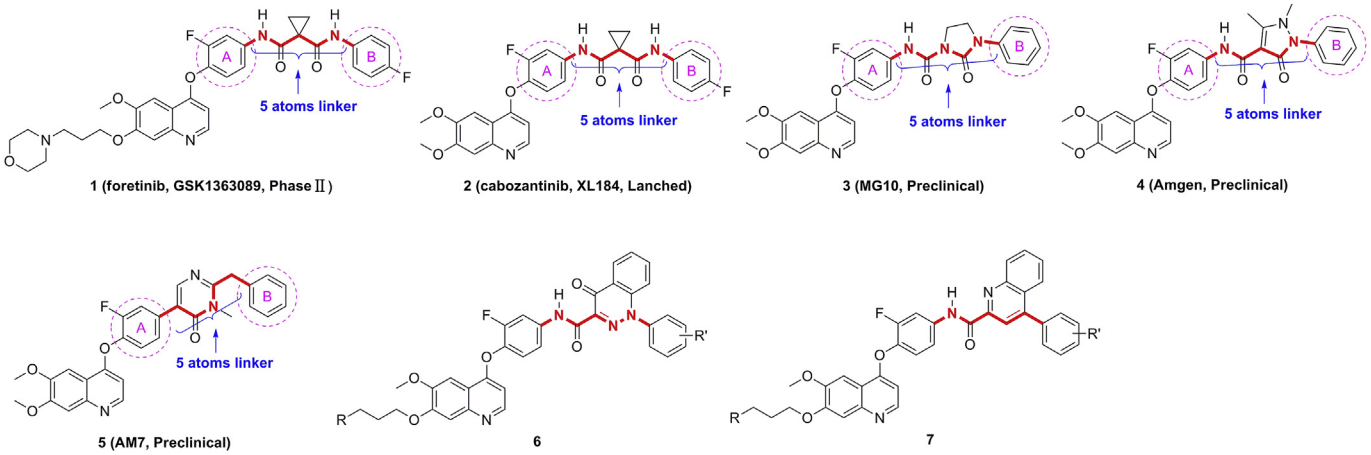


Fig. 1. Structures of small-molecule c-Met inhibitors based on the 6,7-disubstituted-4-phenoxyquinoline scaffold.

2. Chemistry

2.1. Synthesis of 6,7-disubstituted-4-phenoxyquinolines

The synthesis of the key intermediates of 6,7-disubstituted-4-phenoxyquinolines **15a**–**d** was achieved in 8 steps from the commercially available 1-(4-hydroxy-3-methoxyphenyl)ethanone as shown in Scheme 1, which has been illustrated in detail in our previous study [19,20].

2.2. Synthesis of the target compounds of pyridine-based quinolines

The target compounds **18a**–**ad** were prepared as illustrated in Scheme 2. Using sodium bromide (NaBr) as catalyst, chlorination of the commercially available 2-picolinic acid with thionyl chloride resulted in a high yield of the intermediate **16** [21,22]. Acylation of amides **15a**–**d** with acyl chloride **16** in the presence of *N*,*N*-diisopropylethylamine (DIPEA) proceeded smoothly to yield **17a**–**d**, which were subjected to palladium-catalyzed Suzuki–Miyaura cross-coupling reactions with substituted phenylboronic acids in hot 1,4-dioxane:H_2O (3:1, 85 °C) [23,24] and then yielded the target compounds **18a**–**ad**.

2.3. Synthesis of the target compounds of pyrimidine-based quinolines

The synthesis of the target compounds **25a**–**n** is described in Scheme 3. The commercially available substituted acetophenones were condensed with *N*,*N*-dimethyl formamide dimethyl acetal (DMF-DMA) at 80 °C to afford intermediates **20a**–**d** as yellow solids. Cyclization of **20a**–**d** with formamidine acetate in refluxing ethanol (EtOH) under basic conditions yielded 4-phenyl pyrimidines **21a**–**d**, which were subjected to free radical reaction with formamide catalyzed with 98% sulfuric acid (H_2SO_4)/ferrous sulfate ($FeSO_4 \cdot 7H_2O$)/30% hydrogen peroxide (H_2O_2) [25–27] to give the corresponding products **22a**–**d** in low to moderate yield (32–48%). Simple procedures such as hydrolysis and acyl chlorination were used to convert 4-phenylpyrimidine-2-carboxamides

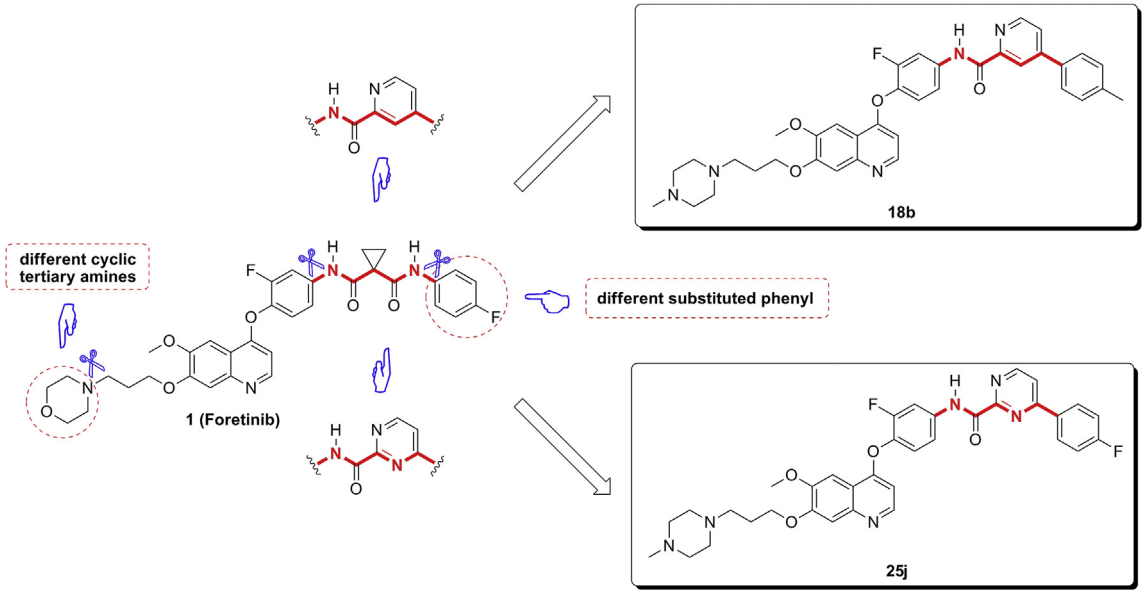
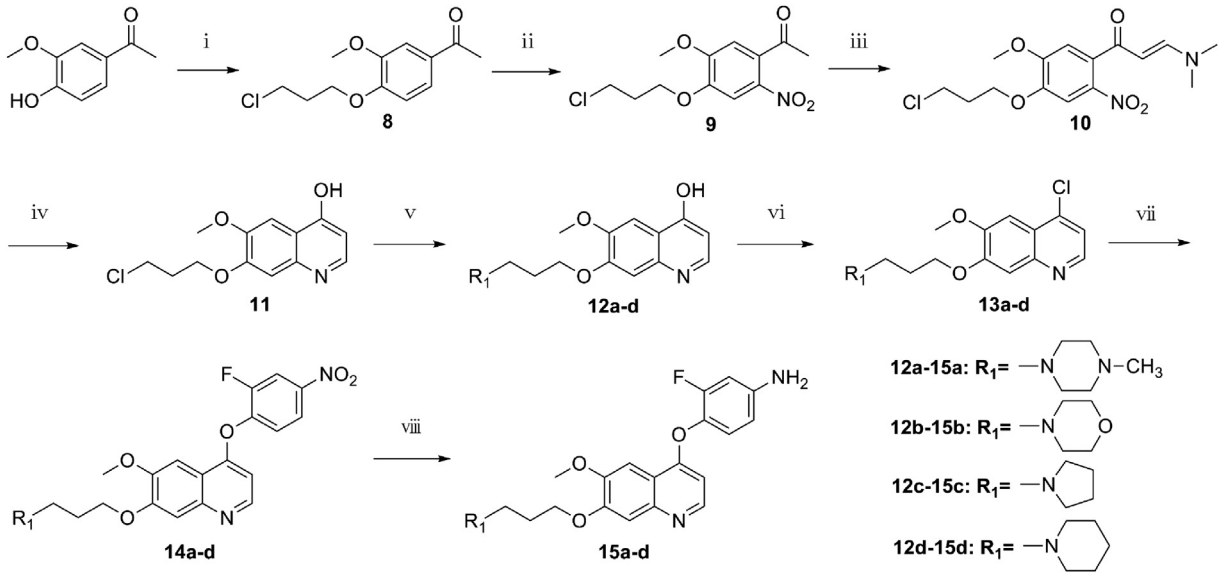


Fig. 2. Design strategy for pyridine- and pyrimidine-based quinoline derivatives.



Scheme 1. Reagents and conditions: (i) $Br(CH_2)_3Cl$, acetone, 0 °C, 30 min, rt, 12 h; (ii) 98%HNO_3, CH_2Cl_2, 0 °C, 4 h; (iii) DMF-DMA, toluene, 110 °C, 10 h; (iv) Fe powder, AcOH, rt, 30 min, 80 °C, 2 h; (v) secondary amines, CH_3CN, 85 °C, 10 h; (vi) $POCl_3$, 85 °C, 6 h; (vii) 2-fluoro-4-nitrophenol, PhCl, 140 °C, 30 h; (viii) Fe powder, NH_4Cl(cat.), EtOH/H_2O, reflux, 5 h.

22a–**d** to the corresponding acyl chlorides **24a**–**d**; the reactions proceeded with 20% H_2SO_4 and thionyl chloride, respectively. Reaction of amides **15a**–**d** with acyl chlorides **24a**–**d** promoted by DIPEA in dichloromethane at room temperature yielded the target compounds **25a**–**n**.

3. Results and discussion

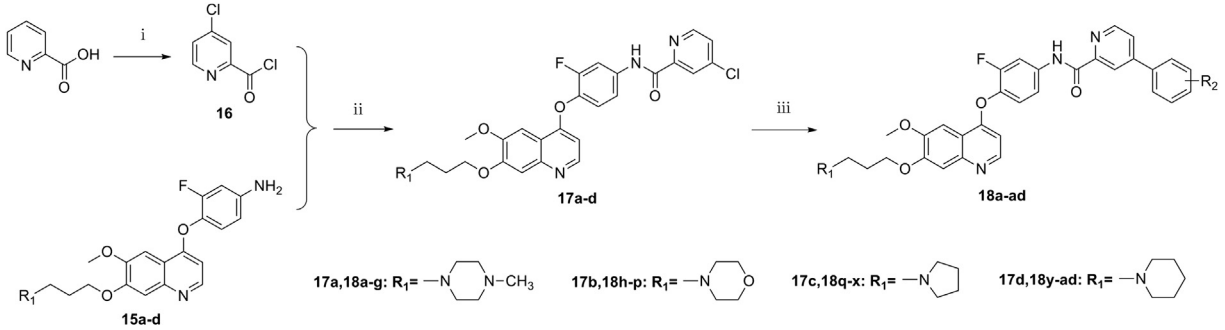
3.1. In vitro cytotoxic activities and SAR

The cytotoxic activities of the target compounds **18a**–**ad** and **25a**–**n** have been evaluated in HT-29 (human colon cancer), H460 (human lung cancer), MKN-45 (human gastric cancer), A549 (human lung adenocarcinoma), and U87MG (human glioblastoma) cell lines using the MTT assay. Foretinib was used as the positive control, and the results expressed as half-maximal inhibitory concentration (IC_{50}) values and are presented in Table 1, as mean values of experiments performed in triplicate.

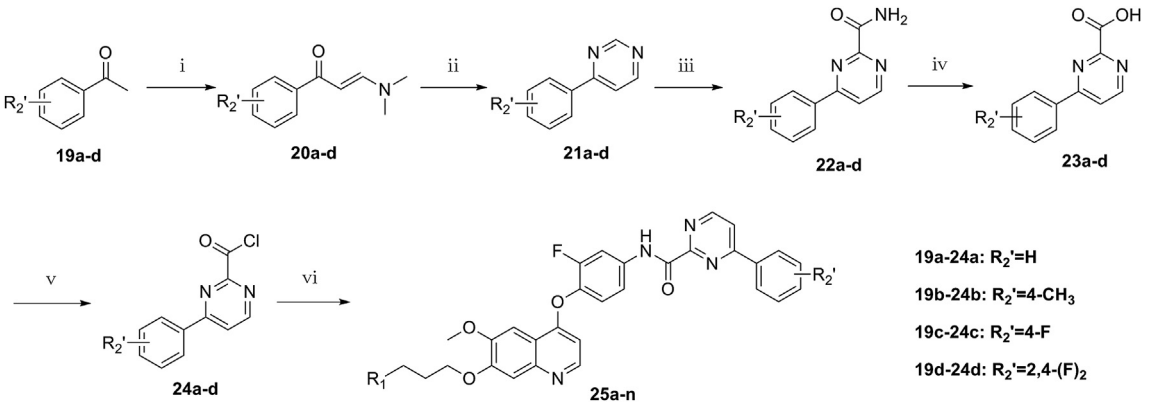
All the target compounds showed moderate to excellent cytotoxic activity against the different cancer cells with potencies in the single-digit μM range, and 21 of these compounds were more potent than foretinib against one or more cell lines, which suggested that replacement of *N*-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide framework of foretinib with 4-substitutedphenylpyridine-2-carboxamide or 4-substitutedphenylpyrimidine-2-carboxamide moiety maintained the potent cytotoxic activity (Table 1). The IC_{50} values of the most promising compound **18b** were 0.026 μM, 0.037 μM, and 0.81 μM against HT29, H460, and U87MG cell lines, respectively; these values indicated that this compound was 7.3, 5.8, and 1.2 times more active than foretinib (IC_{50} values: 0.19 μM, 0.21 μM, and 0.98 μM, respectively).

The cell lines data revealed a clear preference for activity when the R_1 group was 4-methyl piperazinyl group, which indicated that a more water-soluble cyclic tertiary amino group at the 7 position of quinoline contributed to the potency of the target compounds. For example, the IC_{50} value of compound **18a**, 0.082 μM, was clearly lower than that of **18i**, **18q**, and **18y**, 0.33 μM, 0.12 μM, and 0.27 μM, respectively, against HT29 cells.

Further investigations were performed to study the effect of different substituents on the phenyl ring (moiety B) on the cytotoxic activity. Introduction of mono-electron-withdrawing groups (mono-EWGs) on the phenyl ring showed totally different influences on the activity of the two series of compounds. Introduction of mono-EWGs to group R_2 reduced the antitumor activity,



Scheme 2. Reagents and conditions: (i) $SOCl_2$, NaBr, PhCl, 50 °C, 1 h, reflux, 20 h; (ii) 4-chloropicolinoyl chloride, DIPEA, CH_2Cl_2, 0 °C, 1 h, rt, 7 h; (iii) substituted phenylboronic acid, $PdCl_2(PPh_3)_2$, KI, $NaCO_3$, N_2, 1,4-dioxane/H_2O, rt, 30 min, 85 °C, 20–30 h.



Scheme 3. Reagents and conditions: (i) DMF-DMA, 80 °C, 8–12 h; (ii) formamidine acetate, EtONa, EtOH, 70 °C, 1 h, reflux, 15–20 h; (iii) acetamide, 98%H_2SO_4, $FeSO_4 \cdot 7H_2O$, 30% H_2O_2, 0–10 °C, 1 h, 10–15 °C, 30 min; (iv) 20% H_2SO_4, 100 °C, 5–10 h; (v) $SOCl_2$, reflux, 6 h; (vi) appropriate aniline, carbonyl chloride, DIPEA, 0 °C, 1 h, rt, 7–10 h.

while introduction of mono-EWGs to group R_2' improved the activity. For example, compound **18a** (IC_{50} = 0.082 μM), with no substituent on the phenyl ring, showed strong cytotoxicity against HT29 cells. The introduction of mono-EWGs to R_2 (**18d**, R_2 = 4-fluoro, IC_{50} = 1.46 μM) reduced the activity by 18.3-fold, which could be further confirmed by introduction of these groups in compounds **18l**, **18t**, and **18aa**. On the contrary, the activity of **25g** (R_2' = 4 – fluoro, IC_{50} = 0.12 μM) against HT29 cells after introduction of mono-EWGs to R_2' was 2.2 times that of **25e** (R_2' = H, IC_{50} = 0.66 μM), and the same trend was observed in compounds **25c** and **25n**. However, incorporation of double electron-withdrawing groups (double-EWGs) or strong electron-donating groups (EDGs) reduced the inhibitory activity in the 2 series of compounds. For example, the activities of compounds **18o** and **25d** reduced by 4.1-fold and 3.7-fold against MKN45 cells, respectively. The pharmacological data suggested that a proper degree of electron density on pyridine/pyrimidine ring was probably necessary to improve the antitumor activity. The pyridine ring, which is a part of the 5-atom linker, requires weak EDGs (such as methyl) to increase the lower electron density on it. EWGs (such as fluoro) are required to reduce the higher electron density on the pyrimidine ring.

Incorporation of bulky groups such as methoxy or trifluoromethyl group (**18f**, **18g**, **18n**, **18o**, and **18v**) on the phenyl ring (moiety B) reduced the antitumor activity. Moreover, the potency decreased with the number of substituents (**18h**, **18p**, **18x**, **25d**, and **25h**). The pharmacological data suggested that the hydrophobic pocket probably was not sufficiently large to accommodate moiety B with bulky groups, while the fluoro and methyl groups were well tolerated.

3.2. In vitro enzymatic assays

As shown in Table 2, the seven tested compounds all exhibited excellent c-Met enzymatic potency, suggesting that the inhibition of c-Met may be a mechanism for the antitumor effect of these derivatives. Compound **18b** showed the most potent activity with an IC_{50} value of 1.39 nM, which was comparable to that of the positive control foretinib (IC_{50} = 1.14 nM), and this compound should be studied further.

3.3. Enzymatic selectivity assays

In order to examine the selectivity of compound **18b** on c-Met over other kinases, it was screened against other 5 tyrosine kinases (Table 3). Compared with its high potency against c-Met (IC_{50} = 1.39 nM), **18b** also exhibited high inhibitory effects against Flt-3 (IC_{50} = 1.08 nM) and PDGFR-β (IC_{50} = 1.42 nM). Moreover, compound **18b** showed inhibitory effects against EGFR, c-Kit and VEGFR-2 although the potency was 65.1-, 323.5-, and 382.7-fold lower than that of c-Met. These data suggested that compound **18b** is a promising multitarget kinase inhibitor.

4. Conclusions

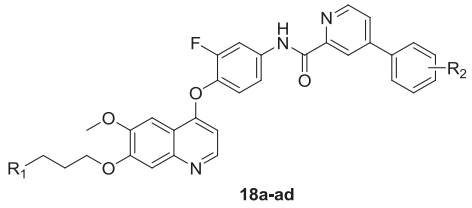
In summary, we designed and synthesized 44 quinoline derivatives on the basis of the pyridine/pyrimidine scaffold. Five human cell lines were used to evaluate the potency of the synthesized compounds, and 21 of these derivatives were more potent than foretinib. Compound **18b** (c-Met IC_{50} = 1.39 nM, a multitarget tyrosine kinase inhibitor) showed the strongest cytotoxic activities against HT-29, H460, and U87MG cell lines; this compound was 7.3, 5.8, and 1.2 times more active than foretinib against the 3 cell lines, respectively. The analysis of SARs indicated that a more water-soluble cyclic tertiary amine (R_1 = 4-methyl piperazinyl) contributed to the potency. A proper degree of the electron density on pyridine/pyrimidine ring was necessary, which could be achieved by substituting substituents (fluoro or methyl) with different electrical properties on the phenyl ring (moiety B). In addition, the hydrophobic pocket of c-Met was probably not sufficiently large to accommodate moiety B with bulky groups, while the fluoro and methyl groups were well tolerated. Further studies on SARs and mechanism of action of these compounds are in progress, and their results will be reported in the future.

5. Experimental

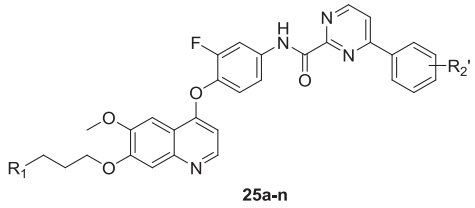
5.1. Chemistry

Unless otherwise noted, all materials were obtained from commercial suppliers and were used without further purification. Reactions' time and purity of the products were monitored by TLC on FLUKA silica gel aluminum cards (0.2 mm thickness) with fluorescent indicator 254 nm. Column chromatography was run on silica gel (200–300 mesh) from Qingdao Ocean Chemicals (Qingdao, Shandong, China). All melting points were obtained on a Büchi Melting Point B-540 apparatus (Büchi Labortechnik, Flawil, Switzerland) and were uncorrected. Mass spectra (MS) were taken in ESI mode on Agilent 1100 LC-MS (Agilent, Palo Alto, CA, USA). ^1H NMR and ^{13}C NMR spectra were recorded on Bruker ARX-300, 300 MHz or Bruker ARX-600, 600 MHz spectrometer (Bruker Bioscience, Billerica, MA, USA) with TMS as an internal standard.

Table 1
Structures and cytotoxic activities of compounds **18a**–**ad** and **25a**–**n** against HT-29, H460, MKN-45, A549, and U87MG cancer cell lines *in vitro*.



18a-ad



25a-n

Compd.	R_1	R_2/R'_2	IC_{50} (μM) ± SD[a]				
			HT-29	H460	MKN-45	A549	U87MG
18a	4-Methyl piperazinyl	H	**0.082 ± 0.01**	**0.091 ± 0.02**	0.15 ± 0.01	0.34 ± 0.02	**1.01 ± 0.15**
18b	4-Methyl piperazinyl	4-Methyl	**0.026 ± 0.003**	**0.037 ± 0.01**	0.073 ± 0.01	**0.10 ± 0.02**	**0.81 ± 0.19**
18c	4-Methyl piperazinyl	2-Methyl	0.18 ± 0.02	**0.15 ± 0.02**	0.24 ± 0.04	1.33 ± 0.23	2.03 ± 0.31
18d	4-Methyl piperazinyl	4-Fluoro	1.46 ± 0.27	0.43 ± 0.05	0.51 ± 0.04	ND	ND
18e	4-Methyl piperazinyl	2-Fluoro	0.22 ± 0.01	**0.14 ± 0.02**	0.15 ± 0.002	ND	ND
18f	4-Methyl piperazinyl	4-Trifluoromethyl	0.20 ± 0.05	**0.16 ± 0.03**	0.33 ± 0.01	ND	ND
18g	4-Methyl piperazinyl	4-Methoxyl	0.39 ± 0.06	0.37 ± 0.03	0.25 ± 0.02	ND	ND
18h	4-Methyl piperazinyl	2,4-Dimethoxyl	0.42 ± 0.02	0.43 ± 0.03	0.33 ± 0.03	ND	ND
18i	Morpholinyl	H	0.33 ± 0.02	0.35 ± 0.01	0.28 ± 0.02	3.45 ± 0.28	1.28 ± 0.13
18j	Morpholinyl	4-Methyl	0.29 ± 0.03	0.57 ± 0.05	0.44 ± 0.06	3.45 ± 0.32	6.79 ± 0.18
18k	Morpholinyl	2-Methyl	1.05 ± 0.16	2.13 ± 0.23	1.14 ± 0.12	ND	ND
18l	Morpholinyl	4-Fluoro	1.00 ± 0.12	1.87 ± 0.14	0.87 ± 0.01	ND	ND
18m	Morpholinyl	2-Fluoro	0.40 ± 0.02	0.68 ± 0.03	1.31 ± 0.12	3.99 ± 0.13	3.03 ± 0.27
18n	Morpholinyl	4-Trifluoromethyl	5.07 ± 0.24	52.72 ± 0.24	78.75 ± 036	ND	ND
18o	Morpholinyl	4-Methoxyl	1.34 ± 0.12	3.12 ± 0.25	1.15 ± 0.11	ND	ND
18p	Morpholinyl	2,4-Dimethoxyl	1.53 ± 0.24	12.69 ± 0.26	6.68 ± 035	ND	ND
18q	Pyrrolidinyl	H	**0.12 ± 0.02**	**0.13 ± 0.03**	0.21 ± 0.01	1.58 ± 0.17	**1.01 ± 0.12**
18r	Pyrrolidinyl	4-Methyl	0.35 ± 0.04	**0.16 ± 0.02**	0.44 ± 0.05	1.06 ± 0.15	**0.56 ± 0.06**
18s	Pyrrolidinyl	2-Methyl	1.15 ± 0.003	0.42 ± 0.03	0.44 ± 0.02	ND	ND
18t	Pyrrolidinyl	4-Fluoro	0.43 ± 0.01	0.37 ± 0.02	0.35 ± 0.05	1.80 ± 0.21	1.78 ± 0.18
18u	Pyrrolidinyl	2-Fluoro	0.23 ± 0.02	**0.14 ± 0.01**	0.23 ± 0.01	0.43 ± 0.02	**0.61 ± 0.05**
18v	Pyrrolidinyl	4-Trifluoromethyl	0.72 ± 0.02	0.25 ± 0.01	0.26 ± 0.04	ND	ND
18w	Pyrrolidinyl	4-Methoxyl	0.35 ± 0.05	**0.20 ± 0.04**	0.15 ± 0.03	ND	ND
18x	Pyrrolidinyl	2,4-Dimethoxyl	0.63 ± 0.02	0.52 ± 0.01	0.74 ± 0.05	ND	ND
18y	Piperidinyl	H	0.27 ± 0.01	**0.12 ± 0.02**	0.27 ± 0.15	1.80 ± 0.15	**0.79 ± 0.04**
18z	Piperidinyl	4-Methyl	0.34 ± 0.02	**0.16 ± 0.04**	1.67 ± 0.26	ND	ND
18aa	Piperidinyl	4-Fluoro	1.37 ± 0.24	0.25 ± 0.01	1.24 ± 0.27	10.09 ± 0.24	12.51 ± 0.16
18ab	Piperidinyl	2-Fluoro	0.32 ± 0.01	**0.13 ± 0.03**	0.18 ± 0.03	ND	ND
18ac	Piperidinyl	4-Trifluoromethyl	0.23 ± 0.01	0.36 ± 0.02	0.87 ± 0.01	1.64 ± 0.15	1.63 ± 0.11
18ad	Piperidinyl	4-Methoxyl	0.69 ± 0.03	**0.20 ± 0.01**	0.57 ± 0.04	ND	ND
25a	Morpholinyl	H	**0.15 ± 0.02**	0.24 ± 0.05	0.26 ± 0.01	0.51 ± 0.02	1.35 ± 0.13
25b	Morpholinyl	4-Methyl	0.24 ± 0.17	0.30 ± 0.15	0.31 ± 0.11	2.24 ± 0.21	2.40 ± 0.23
25c	Morpholinyl	4-Fluoro	**0.11 ± 0.01**	0.22 ± 0.02	0.36 ± 0.02	ND	ND
25d	Morpholinyl	2,4-Difluoro	2.19 ± 0.12	1.03 ± 0.11	0.96 ± 0.05	ND	ND
25e	Piperidinyl	H	0.26 ± 0.01	0.33 ± 0.02	1.03 ± 0.12	ND	ND
25f	Piperidinyl	4-Methyl	0.62 ± 0.02	0.23 ± 0.05	0.58 ± 0.06	0.90 ± 0.05	1.14 ± 0.22
25g	Piperidinyl	4-Fluoro	**0.12 ± 0.02**	0.24 ± 0.01	0.93 ± 0.03	ND	ND
25h	Piperidinyl	2,4-Difluoro	0.40 ± 0.01	0.55 ± 0.02	1.12 ± 0.11	0.47 ± 0.03	**0.78 ± 0.02**
25i	4-Methyl piperazinyl	4-Methyl	0.21 ± 0.01	0.16 ± 0.02	0.34 ± 0.03	ND	ND
25j	4-Methyl piperazinyl	4-Fluoro	**0.042 ± 0.01**	**0.063 ± 0.02**	0.09 ± 0.01	0.68 ± 0.03	**0.91 ± 0.02**
25k	4-Methyl piperazinyl	2,4-Difluoro	0.48 ± 0.03	0.45 ± 0.02	0.44 ± 0.01	0.66 ± 0.05	**0.78 ± 0.06**
25l	Pyrrolidinyl	H	0.39 ± 0.02	1.12 ± 0.15	1.36 ± 0.13	ND	ND
25m	Pyrrolidinyl	4-Methyl	0.67 ± 0.17	0.44 ± 0.05	0.24 ± 0.03	ND	ND
25n	Pyrrolidinyl	4-Fluoro	**0.16 ± 0.05**	0.30 ± 0.02	0.49 ± 0.03	0.99 ± 0.06	1.13 ± 0.17
Foretinib[b]			0.19 ± 0.01	0.21 ± 0.03	0.032 ± 0.005	0.11 ± 0.01	1.08 ± 0.12

Bold values show the IC_{50} values of the target compounds lower than the values of the positive control. ND: Not determined.
[a] IC_{50}: concentration of the compound (μM) producing 50% cell growth inhibition after 72 h of drug exposure, as determined by the MTT assay. Each experiment was carried out in triplicate.
[b] Used as the positive control.

The IR spectra were recorded by means of the KBr pellet technique on a Bruker FTS 135 spectrometer.

5.2. Preparation of 3-fluoro-4-(6,7-disubstituted quinolin-4-yloxy) anilines (*15a*–*d*)

The preparation of the key intermediates **15a**–**d** has been illustrated in detail in our previous work [15,16], and so the synthesis method would not be listed here.

5.2.1. 3-Fluoro-4-(6-methoxy-7-(3-(4-methylpiperdine-1-yl) propoxy)quinolin-4-yl-oxy)aniline (*15a*)

White solid; yield: 77%; m.p. 193–194 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.46 (d, J = 5.3 Hz, 1H), 7.58 (s, 1H), 7.41 (s, 1H), 7.03 (t, J = 8.7 Hz, 1H), 6.56 (dd, J = 11.8, 2.6 Hz, 1H), 6.50 (dd, J = 9.0, 2.9 Hz, 1H), 6.39 (dd, J = 5.3, 0.8 Hz, 1H), 4.25 (t, J = 6.7 Hz, 2H), 4.03 (s, 3H), 3.82 (s, 2H), 2.94 (d, J = 11.5 Hz, 2H), 2.57 (m, 2H), 2.15 (m, 2H), 1.98 (t, J = 10.9 Hz, 2H), 1.63 (d, J = 10.4 Hz, 2H), 1.28 (m, 3H), 0.93 (d, J = 6.0 Hz, 3H); MS (ESI) m/z (%): 441.4 $[M + H]^+$, 463.3 $[M + Na]^+$.

Table 2
c-Met kinase activity of selected compounds **18a**, **18b**, **18q**, **18y**, **25a**, **25j**, **25n**, and foretinib *in vitro*.

Compd.	IC_{50} on c-Met (nM)
18a	4.48
18b	1.39
18q	12.64
18y	9.37
25a	6.23
25j	7.96
25n	16.36
Foretinib	1.14

*5.2.2. 3-Fluoro-4-(6-methoxy-7-(3-morpholinopropoxy)quinolin-4-yloxy)aniline (**15b**)*

White solid; yield: 82%; m.p. 217–218 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.47 (d, J = 5.2 Hz, 1H), 7.58 (s, 1H), 7.44 (s, 1H), 7.04 (t, J = 8.7 Hz, 1H), 6.57 (dd, J = 11.9, 2.6 Hz, 1H), 6.50 (m, 1H), 6.41 (d, J = 5.3 Hz, 1H), 4.27 (t, J = 6.6 Hz, 2H), 4.04 (s, 3H), 3.82 (s, 2H), 3.74 (m, 4H), 2.60 (t, J = 7.1 Hz, 2H), 2.51 (d, J = 4.2 Hz, 4H), 2.13 (m, 2H); MS (ESI) m/z (%): 428.3 $[M + H]^+$.

*5.2.3. 3-Fluoro-4-(6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy) quinolin-4-yloxy)aniline (**15c**)*

Light yellow solid; yield: 72%; m.p. 208–209 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.49 (d, J = 5.2 Hz, 1H), 7.55 (s, 1H), 7.44 (s, 1H), 7.08 (t, J = 9.0 Hz, 1H), 6.57 (d, J = 14.1 Hz, 1H), 6.46 (m, J = 12.8, 7.1 Hz, 2H), 4.28 (t, J = 5.7 Hz, 2H), 3.96 (s, 3H), 3.59 (s, 2H), 3.04 (m, 9H), 2.28 (m, 2H), 1.96 (d, J = 28.0 Hz, 4H); MS (ESI) m/z (%): 412.2 $[M + H]^+$.

*5.2.4. 3-Fluoro-4-(6-methoxy-7-(3-(piperdine-1-yl)propoxy) quinolin-4-yloxy)aniline (**15d**)*

Gray solid; yield: 86%; m.p. 196–197 °C; IR (KBr, cm^{-1}): 3482.2, 3387.0, 2946.5, 2835.1, 2788.1, 1621.1, 1587.8, 1512.8, 1483.4, 1252.9, 1215.4, 853.5; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.46 (d, J = 5.3 Hz, 1H), 7.58 (s, 1H), 7.41 (s, 1H), 7.03 (t, J = 8.7 Hz, 1H), 6.56 (dd, J = 11.8, 2.6 Hz, 1H), 6.50 (m, 1H), 6.39 (dd, J = 5.3, 1.1 Hz, 1H), 4.24 (t, J = 6.8 Hz, 2H), 4.04 (d, J = 3.8 Hz, 3H), 3.81 (s, 2H), 2.54 (m, 2H), 2.43 (s, 4H), 2.14 (m, 2H), 1.60 (m, 4H), 1.45 (d, J = 5.2 Hz, 2H); MS (ESI) m/z (%): 426.4 $[M + H]^+$, 448.4 $[M + Na]^+$.

5.3. Preparation of pyridine-based quinoline derivatives

*5.3.1. Preparation of 4-chloropicolinoyl chloride (**16**)*

Thionyl chloride (30 mL) was added drop-wise to a stirred mixture of 2-picolinic acid (12.3 g, 0.1 mol) and anhydrous sodium bromide (1.0 g, 0.01 mol) in phenyl chloride (20 mL) while maintaining the temperature at 50 °C. Upon completion of the addition, the reaction mixture was heated at reflux for 20 h. The solvent was concentrated in vacuum to give 4-chloropicolinoyl chloride as yellow oil (19.4 g), and the mixture was used for the next step immediately without further purification.

Table 3
Inhibition of tyrosine kinases by compound **18b**.

Kinase	Enzyme IC_{50} (nM)
Flt-3	1.08
PDGFR-β	1.42
EGFR	90.05
c-Kit	449.7
VEGFR-2	531.9

*5.3.2. General procedure for the preparation of N-(3-fluoro-4-(6,7-disubstiteted quinolin-4-yloxy)phenyl)-4-chloropicolinamides (**17a–d**)*

A solution of an appropriate aniline **15a–d** (0.05 mol) and diisopropylethylamine (10.5 mL, 0.06 mol) in dichloromethane (400 mL) was added drop-wise to a solution of 4-chloropicolinoyl chloride (19.4 g, obtained in the last step) in dichloromethane (100 mL) in an ice bath. Upon completion of the addition, the reaction mixture was removed from the ice bath and placed in room temperature for 7 h and monitored by thin-layer chromatography (TLC). The mixture was washed with 10% K_2CO_3 (150 mL × 3) followed by brine (150 mL × 1), and the organic phase was separated, dried, and evaporated to yield **17a–d** as light yellow solids.

*5.3.2.1. 4-Chloro-N-(3-fluoro-4-(6-methoxy-7-(3-(4-methylpiperazin-1-yl)propoxy)quinolin-4-yloxy)phenyl)picolinamide (**17a**).* Yield: 82%; m.p. 168–169 °C; MS (ESI) m/z (%): 580.4 $[M + H]^+$; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.02 (s, 1H), 8.51 (d, J = 5.1 Hz, 1H), 8.47 (d, J = 5.2 Hz, 1H), 8.29 (d, J = 1.9 Hz, 1H), 7.95 (dd, J = 14.7, 2.4 Hz, 1H), 7.55 (s, 1H), 7.50 (dd, J = 5.2, 1.9 Hz, 1H), 7.46 (d, J = 8.9 Hz, 1H), 7.41 (s, 1H), 7.27 (d, J = 8.9 Hz, 1H), 6.40 (d, J = 5.2 Hz, 1H), 4.24 (t, J = 6.5 Hz, 2H), 4.02 (s, 3H), 2.62–2.35 (m, 10H), 2.27 (s, 3H), 2.15–2.07 (m, 2H).

*5.3.2.2. 4-Chloro-N-(3-fluoro-4-(6-methoxy-7-(3-morpholino propoxy)quinolin-4-yloxy)phenyl)picolinamide (**17b**).* Yield: 84%; m.p. 176–178 °C; MS (ESI) m/z (%): 567.3 $[M + H]^+$, 589.7 $[M + Na]^+$; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.02 (s, 1H), 8.51 (d, J = 5.3 Hz, 1H), 8.47 (d, J = 5.2 Hz, 1H), 8.29 (d, J = 1.9 Hz, 1H), 7.95 (dd, J = 11.9, 2.4 Hz, 1H), 7.55 (s, 1H), 7.50 (dd, J = 5.3, 1.9 Hz, 1H), 7.46 (d, J = 8.6 Hz, 1H), 7.41 (s, 1H), 7.27 (d, J = 8.6 Hz, 1H), 6.42 (d, J = 5.2 Hz, 1H), 4.26 (t, J = 6.6 Hz, 2H), 4.02 (s, 3H), 3.69–3.62 (m, 4H), 2.55 (t, J = 7.2 Hz, 2H), 2.48–2.42 (m, 4H), 2.11 (p, J = 6.8, 2H).

*5.3.2.3. 4-Chloro-N-(3-fluoro-4-(6-methoxy-7-(3-(pyrrolidin-1-yl) propoxy)quinolin-4-yloxy)phenyl)picolinamide (**17c**).* Yield: 79%; m.p. 145–146 °C; MS (ESI) m/z (%): 551.2 $[M + H]^+$; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.02 (s, 1H), 8.51 (d, J = 5.2 Hz, 1H), 8.47 (d, J = 5.3 Hz, 1H), 8.29 (d, J = 1.9 Hz, 1H), 7.95 (dd, J = 12.0, 2.4 Hz, 1H), 7.55 (s, 1H), 7.50 (dd, J = 5.2, 2.0 Hz, 1H), 7.46 (d, J = 9.4 Hz, 1H), 7.41 (s, 1H), 7.27 (d, J = 8.7 Hz, 1H), 6.43 (d, J = 5.1 Hz, 1H), 4.25 (t, J = 6.7 Hz, 2H), 4.02 (s, 3H), 2.70–2.61 (m, 2H), 2.52 (br, 4H), 2.15 (p, J = 6.8, 2H), 1.77 (br, 4H).

*5.3.2.4. 4-Chloro-N-(3-fluoro-4-(6-methoxy-7-(3-(piperidin-1-yl) propoxy)quinolin-4-yloxy)phenyl)picolinamide (**17d**).* Yield: 82%; m.p. 153–154 °C; MS (ESI) m/z (%): 565.2 $[M + H]^+$, 587.4 $[M + Na]^+$; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.02 (s, 1H), 8.51 (d, J = 5.3 Hz, 1H), 8.47 (d, J = 5.3 Hz, 1H), 8.29 (d, J = 1.9 Hz, 1H), 7.95 (dd, J = 12.4, 2.4 Hz, 1H), 7.55 (s, 1H), 7.50 (dd, J = 5.3, 1.9 Hz, 1H), 7.46 (d, J = 8.4 Hz, 1H), 7.41 (s, 1H), 7.27 (d, J = 8.4 Hz, 1H), 6.43 (d, J = 5.0 Hz, 1H), 4.25 (t, J = 6.7 Hz, 2H), 4.02 (s, 3H), 2.54 (t, J = 7.2 Hz, 2H), 2.45–2.38 (m, 4H), 2.16–2.04 (m, 2H), 1.61–1.51 (m, 4H), 1.4–1.29 (m, 2H).

*5.3.3. General procedure for the preparation of the target compounds (**18a–ad**)*

To the mixture of an appropriate amount of *N*-(3-fluoro-4-(6,7-disubstituted quinolin-4-yloxy)phenyl)-4-chloropicolinamides **17a–d** (0.9 mmol), substituted phenylboronic acid (0.18 mmol), anhydrous sodium carbonate (0.29 g, 2.7 mmol), anhydrous potassium iodide (0.15 g, 0.9 mmol), 1,4-dioxane (30 mL), H_2O (10 mL), and bis(triphenylphosphine)palladium(II) dichloride (0.09 g, 0.135 mmol) were added under an atmosphere of nitrogen at room temperature. The reaction mixture then was stirred at 85 °C for 20–

30 h and monitored by TLC. The solvent was concentrated in vacuum and the residue was resolved with dichloromethane (100 mL), washed with water (30 mL × 3), brine (30 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuum to give a black solid. To the mixture of the black solid, activated charcoal (3 g), silica gel (1 g), dichloromethane (60 mL), and methanol (10 mL) were added, and the mixture was stirred at reflux for 0.5 h. The mixture was filtered immediately, and the filtrate was concentrated in vacuum to give a yellow solid. The crude product was purified by chromatography on silica gel using MeOH/CH_2Cl_2 to afford the target compounds **18a**–**ad** as white solids.

*5.3.3.1. N-(3-Fluoro-4-(6-methoxy-7-(3-(4-methylpiperazin-1-yl) propoxy)quinolin-4-yloxy)phenyl)-4-phenylpicolinamide (**18a**).* Yield: 64%; m.p. 127–128 °C; IR (KBr, cm^{-1}): 3411.5, 3333.3, 2940.4, 2793.0, 1687.9, 1596.8, 1527.6, 1479.0, 1431.1, 1349.3, 1305.6, 1250.1, 1209.6, 1170.8, 1013.4, 853.4, 761.7, 694.5, 616.8; MS (ESI) *m/z* (%): 622.3 $[M + H]^+$; ^1H NMR (300 MHz, $CDCl_3$) δ 10.20 (s, 1H), 8.65 (d, J = 5.0 Hz, 1H), 8.54 (d, J = 1.2 Hz, 1H), 8.48 (d, J = 5.2 Hz, 1H), 8.00 (dd, J = 12.1, 2.5 Hz, 1H), 7.76–7.68 (m, 3H), 7.57 (s, 1H), 7.54–7.45 (m, 4H), 7.42 (s, 1H), 7.28 (d, J = 8.6 Hz, 1H), 6.43 (d, J = 4.3 Hz, 1H), 4.25 (t, J = 6.7 Hz, 2H), 4.02 (s, 3H), 2.64–2.53 (m, 4H), 2.48 (br, 6H), 2.28 (s, 3H), 2.16–2.06 (m, 2H). Anal. calcd. for $C_{36}H_{36}FN_5O_4$ (%): C, 69.55; H, 5.84; N, 11.26. Found (%): C, 69.53; H, 5.86; N, 11.29.

*5.3.3.2. N-(3-Fluoro-4-(6-methoxy-7-(3-(4-methylpiperazin-1-yl) propoxy)quinolin-4-yloxy)phenyl)-4-p-tolylpicolinamide (**18b**).* Yield: 64%; m.p. 131–132 °C; IR (KBr, cm^{-1}): 3408.2, 3331.3, 2938.3, 2792.5, 1688.7, 1598.0, 1526.4, 1479.1, 1431.3, 1349.1, 1305.7, 1249.2, 1209.5, 1167.2, 1113,6, 1013.6, 854.0, 814.4, 725.3, 686.6; MS (ESI) *m/z* (%): 636.2 $[M + H]^+$; ^1H NMR (300 MHz, $CDCl_3$) δ 10.20 (s, 1H), 8.62 (d, J = 5.1 Hz, 1H), 8.52 (d, J = 1.1 Hz, 1H), 8.48 (d, J = 5.3 Hz, 1H), 8.00 (dd, J = 12.1, 2.4 Hz, 1H), 7.70 (dd, J = 5.2, 1.8 Hz, 1H), 7.63 (d, J = 8.2 Hz, 2H), 7.57 (s, 1H), 7.49 (d, J = 8.4 Hz, 1H), 7.42 (s, 1H), 7.32 (d, J = 8.0 Hz, 2H), 7.27 (d, J = 8.7 Hz, 1H), 6.43 (d, J = 5.2 Hz, 1H), 4.25 (t, J = 6.6 Hz, 2H), 4.02 (s, 3H), 2.65–2.53 (m, 4H), 2.48 (br, 6H), 2.42 (s, 3H), 2.28 (s, 3H), 2.16–2.06 (m, 2H); ^{13}C NMR (600 MHz, $CDCl_3$) δ 162.32, 160.06, 152.26, 150.32, 149.83, 149.70, 148.83, 148.51, 146.93, 140.05, 137.22, 136.55, 134.14, 130.06 (2C), 126.97 (2C), 124.18, 123.91, 120.09, 115.89, 115.44, 109.23, 109.07, 108.78, 102.21, 99.52, 67.40, 56.18, 55.15 (2C), 54.95, 53.14 (2C), 46.04, 26.34, 21.31. Anal. calcd. for $C_{37}H_{38}FN_5O_4$ (%): C, 69.90; H, 6.02; N, 11.02. Found (%): C, 69.87; H, 5.98; N, 11.06.

*5.3.3.3. N-(3-Fluoro-4-(6-methoxy-7-(3-(4-methylpiperazin-1-yl) propoxy)quinolin-4-yloxy)phenyl)-4-o-tolylpicolinamide (**18c**).* Yield: 61%; m.p. 135–136 °C; MS (ESI) *m/z* (%): 636.5 $[M + H]^+$, 644.4 $[M + Na]^+$; ^1H NMR (300 MHz, $CDCl_3$) δ 10.20 (s, 1H), 8.63 (d, J = 5.1 Hz, 1H), 8.52 (d, J = 1.2 Hz, 1H), 8.48 (d, J = 5.3 Hz, 1H), 8.00 (dd, J = 12.1, 2.4 Hz, 1H), 7.57 (s, 1H), 7.55–7.44 (m, 2H), 7.43 (s, 1H), 7.40–7.28 (m, 4H), 7.25 (d, J = 8.4 Hz, 1H), 6.43 (d, J = 4.8 Hz, 1H), 4.26 (t, J = 6.7 Hz, 2H), 4.03 (s, 3H), 2.62–2.51 (m, 4H), 2.47 (br, 6H), 2.39 (s, 3H), 2.27 (s, 3H), 2.1–2.08 (m, 2H). Anal. calcd. for $C_{37}H_{38}FN_5O_4$ (%): C, 69.90; H, 6.02; N, 11.02. Found (%): C, 69.89; H, 6.05; N, 10.96.

*5.3.3.4. N-(3-Fluoro-4-(6-methoxy-7-(3-(4-methylpiperazin-1-yl) propoxy)quinolin-4-yloxy)phenyl)-4-(4-fluorophenyl)picolinamide (**18d**).* Yield: 65%; m.p. 144–145 °C; MS (ESI) *m/z* (%): 640.6 $[M + H]^+$; ^1H NMR (300 MHz, $CDCl_3$) δ 10.18 (s, 1H), 8.65 (d, J = 5.1 Hz, 1H), 8.49 (d, J = 1.2 Hz, 1H), 8.48 (d, J = 5.3 Hz, 1H), 8.00 (dd, J = 12.2, 2.4 Hz, 1H), 7.74–7.66 (m, 3H), 7.57 (s, 1H), 7.49 (d, J = 9.0 Hz, 1H), 7.42 (s, 1H), 7.28 (d, J = 8.7 Hz, 1H), 7.19 (d, J = 8.5 Hz, 2H), 6.42 (d, J = 5.4 Hz, 1H), 4.25 (t, J = 6.9 Hz, 2H), 4.02 (s, 3H), 2.61–2.52 (m, 4H), 2.45 (br, 6H), 2.27 (s, 3H), 2.14–2.08 (m, 2H); ^{13}C NMR (600 MHz, $CDCl_3$) δ 163.14, 162.35, 160.06, 152.24, 150.36, 149.83, 149.68, 148.76, 148.54, 146.93, 137.28, 136.48, 134.14, 129.38 (2C), 124.24, 123.91, 120.08, 116.43 (2C), 115.88, 115.44, 109.26, 109.09, 108.76, 102.22, 99.52, 67.44, 56.18, 55.17 (2C), 54.99, 53.25 (2C), 46.08, 26.35. Anal. calcd. for $C_{36}H_{35}F_2N_5O_4$ (%): C, 67.59; H, 5.51; N, 10.95. Found (%): C, 67.55; H, 5.53; N, 10.97.

*5.3.3.5. N-(3-Fluoro-4-(6-methoxy-7-(3-(4-methylpiperazin-1-yl) propoxy)quinolin-4-yloxy)phenyl)-4-(2-fluorophenyl)picolinamide (**18e**).* Yield: 62%; m.p. 142–143 °C; MS (ESI) *m/z* (%): 640.4 $[M + H]^+$; ^1H NMR (300 MHz, $CDCl_3$) δ 10.18 (s, 1H), 8.65 (d, J = 5.1 Hz, 1H), 8.50 (d, J = 1.2 Hz, 1H), 8.48 (d, J = 5.3 Hz, 1H), 8.00 (dd, J = 12.2, 2.4 Hz, 1H), 7.73 (dd, J = 5.3, 1.9 Hz, 1H), 7.56 (s, 1H), 7.52–7.31 (m, 4H), 7.30–7.26 (m, 3H), 6.43 (s, 1H), 4.25 (t, J = 6.7 Hz, 2H), 4.02 (s, 3H), 2.62 (br, 10H), 2.39 (s, 3H), 2.19–2.07 (m, 2H). Anal. calcd. for $C_{36}H_{35}F_2N_5O_4$ (%): C, 67.59; H, 5.51; N, 10.95. Found (%): C, 67.56; H, 5.48; N, 10.98.

*5.3.3.6. N-(3-Fluoro-4-(6-methoxy-7-(3-(4-methylpiperazin-1-yl) propoxy)quinolin-4-yloxy)phenyl)-4-(4-(trifluoromethyl)phenyl) picolinamide (**18f**).* Yield: 62%; m.p. 149–150 °C; MS (ESI) *m/z* (%): 690.6 $[M + H]^+$; ^1H NMR (300 MHz, $CDCl_3$) δ 10.17 (s, 1H), 8.71 (d, J = 5.1 Hz, 1H), 8.55 (d, J = 1.1 Hz, 1H), 8.48 (d, J = 5.3 Hz, 1H), 8.00 (dd, J = 12.2, 2.4 Hz, 1H), 7.82 (d, J = 8.4 Hz, 2H), 7.78 (d, J = 8.4 Hz, 2H), 7.73 (dd, J = 5.1, 1.9 Hz, 1H), 7.57 (s, 1H), 7.50 (d, J = 8.5 Hz, 1H), 7.42 (s, 1H), 7.29 (d, J = 8.6 Hz, 1H), 6.42 (d, J = 5.3 Hz, 1H), 4.24 (t, J = 6.7 Hz, 2H), 4.03 (s, 3H), 2.65–2.52 (m, 4H), 2.47 (br, 6H), 2.28 (s, 3H), 2.15–2.06 (m, 2H). Anal. calcd. for $C_{37}H_{35}F_4N_5O_4$ (%): C, 64.43; H, 5.11; N, 10.15. Found (%): C, 64.39; H, 5.08; N, 10.17.

*5.3.3.7. N-(3-Fluoro-4-(6-methoxy-7-(3-(4-methylpiperazin-1-yl) propoxy)quinolin-4-yloxy)phenyl)-4-(4-methoxyphenyl)picolinamide (**18g**).* Yield: 61%; m.p. 147–148 °C; IR (KBr, cm^{-1}): 3419.1, 2934.0, 2834.1, 1681.2, 1597.9, 1514.5, 1479.6, 1432.0, 1349.7, 1252.6, 1210.9, 1177.2, 1023.7, 855.7, 830.6, 694.2, 573.5; MS (ESI) *m/z* (%): 674.7 $[M + Na]^+$; ^1H NMR (300 MHz, $CDCl_3$) δ 10.20 (s, 1H), 8.60 (d, J = 5.2 Hz, 1H), 8.50 (d, J = 1.1 Hz, 1H), 8.48 (d, J = 4.9 Hz, 1H), 8.00 (dd, J = 12.1, 2.5 Hz, 1H), 7.72–7.65 (m, 3H), 7.57 (s, 1H), 7.49 (d, J = 8.5 Hz, 1H), 7.42 (s, 1H), 7.26 (s, 1H), 7.03 (d, J = 8.8 Hz, 2H), 6.43 (d, J = 5.3 Hz, 1H), 4.25 (t, J = 6.7 Hz, 2H), 4.02 (s, 3H), 3.87 (s, 3H), 2.64–2.52 (m, 4H), 2.47 (br, 6H), 2.27 (s, 3H), 2.15–2.07 (m, 2H). Anal. calcd. for $C_{37}H_{38}FN_5O_5$ (%): C, 68.19; H, 5.88; N, 10.75. Found (%): C, 68.16; H, 5.84; N, 10.79.

*5.3.3.8. N-(3-Fluoro-4-(6-methoxy-7-(3-(4-methylpiperazin-1-yl) propoxy)quinolin-4-yloxy)phenyl)-4-(2,4-dimethoxyphenyl)picolinamide (**18h**).* Yield: 56%; m.p. 151–152 °C; MS (ESI) *m/z* (%): 682.4 $[M + H]^+$, 704.2 $[M + Na]^+$; ^1H NMR (300 MHz, $CDCl_3$) δ 10.21 (s, 1H), 8.56 (d, J = 4.6 Hz, 1H), 8.47 (d, J = 1.2 Hz, 1H), 8.46 (d, J = 5.3 Hz, 1H), 8.00 (dd, J = 12.1, 2.4 Hz, 1H), 7.68 (dd, J = 5.1, 1.9 Hz, 1H), 7.57 (s, 1H), 7.49 (d, J = 7.7 Hz, 1H), 7.42 (s, 1H), 7.37 (d, J = 8.3 Hz, 1H), 7.25 (d, J = 8.2 Hz, 1H), 6.64–6.55 (m, 2H), 6.42 (d, J = 4.8 Hz, 1H), 4.25 (t, J = 6.7 Hz, 2H), 4.02 (s, 3H), 3.86 (s, 3H), 3.84 (s, 3H), 2.61–2.53 (m, 4H), 2.46 (br, 6H), 2.27 (s, 3H), 2.16–2.06 (m, 2H). Anal. calcd. for $C_{38}H_{40}FN_5O_6$ (%): C, 66.95; H, 5.91; N, 10.27. Found (%): C, 66.94; H, 5.89; N, 10.25.

*5.3.3.9. N-(3-Fluoro-4-(6-methoxy-7-(3-morpholinopropoxy)quinolin-4-yloxy)phenyl)-4-phenylpicolinamide (**18i**).* Yield: 64%; m.p. 176–177 °C; MS (ESI) *m/z* (%): 609.5 $[M + H]^+$, 631.3 $[M + Na]^+$; ^1H NMR (300 MHz, $CDCl_3$) δ 10.20 (s, 1H), 8.65 (d, J = 4.9 Hz, 1H), 8.54 (d, J = 1.2 Hz, 1H), 8.48 (d, J = 5.2 Hz, 1H), 8.00 (dd, J = 11.2, 2.4 Hz, 1H), 7.71 (br, 3H), 7.57 (s, 1H), 7.50 (d, J = 6.9 Hz, 4H), 7.42 (s, 1H), 7.28 (d, J = 8.2 Hz, 1H), 6.43 (d, J = 5.0 Hz, 1H), 4.26 (t, J = 6.4 Hz, 2H), 4.02 (s, 3H), 3.70 (br, 4H), 2.56 (t, J = 6.8 Hz, 2H), 2.47 (br, 4H),

2.16–2.05 (m, 2H). Anal. calcd. for $C_{35}H_{33}FN_4O_5$ (%): C, 69.07; H, 5.46; N, 9.20. Found (%): C, 69.05; H, 5.45; N, 9.23.

*5.3.3.10. N-(3-Fluoro-4-(6-methoxy-7-(3-morpholinopropoxy)quinolin-4-yloxy)phenyl)-4-p-tolylpicolinamide (**18j**).* Yield: 59%; m.p. 178–179 °C; IR (KBr, cm^{-1}): 3427.3, 3329.4, 2954.5, 1691.8, 1597.7, 1511.2, 1479.4, 1432.4, 1348.5, 1304.7, 1250.7, 1210.0, 1170.5, 1116.2, 855.1, 817.8, 724.2, 578.7; MS (ESI) *m/z* (%): 623.6 $[M + H]^+$; ^1H NMR (300 MHz, $CDCl_3$) δ 10.21 (s, 1H), 8.62 (d, J = 5.2 Hz, 1H), 8.53–8.44 (br, 2H), 8.01 (dd, J = 12.1, 2.4 Hz, 1H), 7.69 (dd, J = 5.1, 1.9 Hz, 1H), 7.64 (d, J = 8.4 Hz, 2H), 7.58 (s, 1H), 7.54 (d, J = 8.5 Hz, 1H), 7.49 (s, 1H), 7.32 (d, J = 7.8 Hz, 2H), 7.27 (d, J = 8.6 Hz, 1H), 6.47 (d, J = 5.1 Hz, 1H), 4.28 (t, J = 6.8 Hz, 2H), 4.01 (s, 3H), 3.78 (br, 4H), 2.27–2.61 (m, 6H), 2.42 (s, 3H), 2.25–2.11 (m, 2H). Anal. calcd. for $C_{38}H_{35}FN_4O_5$ (%): C, 69.44; H, 5.67; N, 9.00. Found (%): C, 69.43; H, 5.66; N, 9.02.

*5.3.3.11. N-(3-Fluoro-4-(6-methoxy-7-(3-morpholinopropoxy)quinolin-4-yloxy)phenyl)-4-o-tolylpicolinamide (**18k**).* Yield: 57%; m.p. 181–182 °C; MS (ESI) *m/z* (%): 623.5 $[M + H]^+$, 645.3 $[M + Na]^+$; ^1H NMR (300 MHz, $CDCl_3$) δ 10.20 (s, 1H), 8.65 (d, J = 5.1 Hz, 1H), 8.52 (d, J = 1.2 Hz, 1H), 8.48 (d, J = 5.3 Hz, 1H), 8.00 (dd, J = 12.1, 2.4 Hz, 1H), 7.57 (s, 1H), 7.53–7.46 (m, 2H), 7.43 (s, 1H), 7.37–7.28 (m, 4H), 7.26 (d, J = 8.1 Hz, 1H), 6.43 (d, J = 4.9 Hz, 1H), 4.26 (t, J = 6.7 Hz, 2H), 4.03 (s, 3H), 3.74–3.69 (m, 4H), 2.57 (t, J = 7.0 Hz, 2H), 2.52–2.44 (m, 4H), 2.31 (s, 3H), 2.17–2.09 (m, 2H). Anal. calcd. for $C_{38}H_{35}FN_4O_5$ (%): C, 69.44; H, 5.67; N, 9.00. Found (%): C, 69.41; H, 5.65; N, 9.04.

*5.3.3.12. N-(3-Fluoro-4-(6-methoxy-7-(3-morpholinopropoxy)quinolin-4-yloxy)phenyl)-4-(4-fluorophenyl)picolinamide (**18l**).* Yield: 63%; m.p. 186–187 °C; IR (KBr, cm^{-1}): 3401.2, 3340.6, 2934.8, 1691.9, 1599.0, 1511.4, 1481.2, 1431.4, 1348.9, 1308.5, 1255.4, 1212.1, 1169.8, 1115.8, 853.6, 834.7, 558.3; MS (ESI) *m/z* (%): 627.4 $[M + H]^+$; ^1H NMR (300 MHz, $CDCl_3$) δ 10.18 (s, 1H), 8.64 (d, J = 4.7 Hz, 1H), 8.48 (d, J = 5.3 Hz, 2H), 7.99 (dd, J = 12.1, 2.3 Hz, 1H), 7.75–7.63 (m, 3H), 7.57 (s, 1H), 7.49 (d, J = 8.7 Hz, 1H), 7.42 (s, 1H), 7.27 (d, J = 8.6 Hz, 1H), 7.19 (d, J = 8.7 Hz, 2H), 6.42 (d, J = 4.7 Hz, 1H), 4.26 (t, J = 6.6 Hz, 2H), 4.02 (s, 3H), 3.75–3.65 (m, 4H), 2.55 (t, J = 7.1 Hz, 2H), 2.51–2.40 (m, 4H), 2.17–2.05 (m, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 163.02, 162.13, 160.05, 152.23, 149.85, 149.81, 149.38, 148.84, 148.65, 146.92, 137.28, 136.46, 133.25, 129.02 (2C), 124.26, 123.94, 120.17, 116.45 (2C), 115.93, 115.45, 109.26, 109.11, 108.77, 102.22, 99.52, 67.25, 67.05 (2C), 56.19, 55.40, 53.73 (2C), 26.00. Anal. calcd. for $C_{35}H_{32}F_2N_4O_5$ (%): C, 67.08; H, 5.15; N, 8.94. Found (%): C, 67.09; H, 5.16; N, 8.93.

^{13}C NMR (600 MHz, $CDCl_3$) δ 162.08, 160.06, 152.22, 149.80, 149.61, 148.83, 148.25, 146.88, 145.64, 137.27, 136.47, 131.36, 130.33, 126.72, 125.35, 124.96, 123.92, 122.25, 116.70, 116.56, 115.94, 115.44, 109.26, 109.11, 108.73, 102.22, 99.53, 67.24, 67.03 (2C), 56.18, 55.40, 53.71 (2C), 25.99.

*5.3.3.13. N-(3-Fluoro-4-(6-methoxy-7-(3-morpholinopropoxy)quinolin-4-yloxy)phenyl)-4-(2-fluorophenyl)picolinamide (**18m**).* Yield: 61%; m.p. 188–189 °C; IR (KBr, cm^{-1}): 3415.3, 3322.5, 2940.8, 2750.4, 1691.1, 1597.6, 1527.2, 1479.2, 1432.0, 1349.0, 1304.9, 1248.9, 1206.8, 1173.2, 1115.2, 854.0, 695.3, 583.2; MS (ESI) *m/z* (%): 649.4 $[M + Na]^+$; ^1H NMR (300 MHz, $CDCl_3$) δ 10.18 (s, 1H), 8.66 (dd, J = 5.1, 1.7 Hz, 1H), 8.48 (d, J = 1.6 Hz, 1H), 8.47 (d, J = 4.8 Hz, 1H), 8.00 (dd, J = 12.1, 2.5 Hz, 1H), 7.72 (dt, J = 5.1, 1.8 Hz, 1H), 7.58 (dd, J = 3.8, 1.7 Hz, 1H), 7.57 (s, 1H), 7.52 (dd, J = 4.8, 1.6 Hz, 1H), 7.48 (dd, J = 4.6, 3.3 Hz, 1H), 7.45 (dd, J = 4.7, 2.8 Hz, 1H), 7.42 (s, 1H), 7.30 (dd, J = 7.5, 1.2 Hz, 1H), 7.25 (d, J = 4.2 Hz, 1H), 7.21 (dd, J = 2.6, 1.1 Hz, 1H), 6.43 (dd, J = 5.3, 1.1 Hz, 1H), 4.26 (t, J = 6.7 Hz, 2H), 4.02 (s, 3H), 3.75–3.65 (m, 4H), 2.56 (t, J = 7.1 Hz, 2H), 2.50–2.40 (m, 4H), 2.11 (p, J = 6.8 Hz, 2H); ^{13}C NMR (600 MHz, $CDCl_3$) δ 162.08, 160.06, 152.22, 149.80, 149.61, 148.83, 148.25, 146.88, 145.64, 137.27, 136.47, 131.36, 130.33, 126.72, 125.35, 124.96, 123.92, 122.25, 116.70, 116.56, 115.94, 115.44, 109.26, 109.11, 108.73, 102.22, 99.53, 67.24, 67.03 (2C), 56.18, 55.40, 53.71 (2C), 25.99. Anal. calcd. for $C_{35}H_{32}F_2N_4O_5$ (%): C, 67.08; H, 5.15; N, 8.94. Found (%): C, 67.06; H, 5.13; N, 8.96.

*5.3.3.14. N-(3-Fluoro-4-(6-methoxy-7-(3-morpholinopropoxy)quinolin-4-yloxy)phenyl)-4-(4-(trifluoromethyl)phenyl)picolinamide (**18n**).* Yield: 62%; m.p. 191–192 °C; IR (KBr, cm^{-1}): 3428.5, 2935.7, 1688.7, 1601.0, 1506.8, 1484.7, 1433.0, 1350.5, 1326.0, 1260.8, 1214.3, 1171.0, 1117.0, 1071.5, 1015.5, 837.0, 739.3, 694.3, 532.9; MS (ESI) *m/z* (%): 677.2 $[M + H]^+$; ^1H NMR (300 MHz, $CDCl_3$) δ 10.17 (s, 1H), 8.70 (d, J = 4.9 Hz, 1H), 8.54 (d, J = 1.2 Hz, 1H), 8.48 (d, J = 5.1 Hz, 1H), 8.00 (dd, J = 12.1, 2.4, 1H), 7.87–7.75 (m, 4H), 7.72 (dd, J = 5.1, 1.8 Hz, 1H), 7.57 (s, 1H), 7.50 (d, J = 5.9 Hz, 1H), 7.42 (s, 1H), 7.28 (d, J = 8.5 Hz, 1H), 6.42 (d, J = 5.0 Hz, 1H), 4.26 (t, J = 6.5 Hz, 2H), 4.02 (s, 3H), 3.75–3.64 (m, 4H), 2.56 (t, J = 7.2 Hz, 2H), 2.51–2.38 (m, 4H), 2.17–2.03 (m, 2H). Anal. calcd. for $C_{36}H_{32}F_4N_4O_5$ (%): C, 63.90; H, 4.77; N, 8.28. Found (%): C, 63.88; H, 4.76; N, 8.30.

*5.3.3.15. N-(3-Fluoro-4-(6-methoxy-7-(3-morpholinopropoxy)quinolin-4-yloxy)phenyl)-4-(4-methoxyphenyl)picolinamide (**18o**).* Yield: 62%; m.p. 189–190 °C; MS (ESI) *m/z* (%): 639.4 $[M + H]^+$, 661.6 $[M + Na]^+$; ^1H NMR (300 MHz, $CDCl_3$) δ 10.20 (s, 1H), 8.59 (d, J = 5.0 Hz, 1H), 8.54–8.43 (m, 2H), 8.00 (dd, J = 12.1, 2.3 Hz, 1H), 7.71–7.63 (m, 3H), 7.57 (s, 1H), 7.49 (d, J = 8.7 Hz, 1H), 7.43 (s, 1H), 7.27 (d, J = 8.4 Hz, 1H), 7.03 (d, J = 8.6 Hz, 2H), 6.43 (d, J = 4.8 Hz, 1H), 4.26 (t, J = 6.4 Hz, 2H), 4.02 (s, 3H), 3.87 (s, 3H), 3.71 (br, 4H), 2.56 (d, J = 7.3 Hz, 2H), 2.49 (br, 4H), 2.18–2.07 (m, 2H). Anal. calcd. for $C_{36}H_{35}FN_4O_6$ (%): C, 67.70; H, 5.52; N, 8.77. Found (%): C, 67.68; H, 5.50; N, 8.78.

*5.3.3.16. N-(3-Fluoro-4-(6-methoxy-7-(3-morpholinopropoxy)quinolin-4-yloxy)phenyl)-4-(2,4-dimethoxyphenyl)picolinamide (**18p**).* Yield: 56%; m.p. 196–197 °C; IR (KBr, cm^{-1}): 3420.3, 3321.9, 2960.2, 2796.5, 1683.9, 1598.4, 1577.9, 1510.4, 1479.9, 1430.7, 1349.9, 1303.6, 1252.8, 1210.2, 1169.4, 1118.2, 1058.3, 1026.3, 854.4, 738.1, 571.5; MS (ESI) *m/z* (%): 669.7 $[M + H]^+$; ^1H NMR (300 MHz, $CDCl_3$) δ 10.22 (s, 1H), 8.56 (d, J = 4.6 Hz, 1H), 8.52 (d, J = 1.2 Hz, 1H), 8.46 (d, J = 5.3 Hz, 1H), 8.01 (dd, J = 11.9, 2.5 Hz, 1H), 7.69 (dd, J = 5.3, 1.9 Hz, 1H), 7.58 (s, 1H), 7.49 (d, J = 7.8 Hz, 1H), 7.42 (s, 1H), 7.37 (d, J = 8.4 Hz, 1H), 7.25 (d, J = 8.3 Hz, 1H), 6.65–6.56 (m, 2H), 6.42 (d, J = 4.6 Hz, 1H), 4.26 (t, J = 6.7 Hz, 2H), 4.02 (s, 3H), 3.76–3.63 (m, 4H), 2.56 (t, J = 7.2 Hz, 2H), 2.50–2.37 (m, 4H), 2.15–2.03 (m, 2H). Anal. calcd. for $C_{37}H_{37}FN_4O_7$ (%): C, 66.46; H, 5.58; N, 8.38. Found (%): C, 66.45; H, 5.56; N, 8.39.

*5.3.3.17. N-(3-Fluoro-4-(6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy)quinolin-4-yloxy)phenyl)-4-phenylpicolinamide (**18q**).* Yield: 65%; m.p. 121–122 °C; IR (KBr, cm^{-1}): 3402.1, 3334.4, 2930.2, 1685.0, 1597.0, 1508.8, 1478.6, 1430.5, 1349.2, 1305.7, 1249.8, 1209.9, 1170.3, 854.5, 762.3, 616.2; MS (ESI) *m/z* (%): 615.6 $[M + Na]^+$; ^1H NMR (300 MHz, $CDCl_3$) δ 10.22 (s, 1H), 8.65 (d, J = 5.1 Hz, 1H), 8.53 (d, J = 1.2 Hz, 1H), 8.48 (d, J = 5.3 Hz, 1H), 8.02 (dd, J = 12.2, 2.4 Hz, 1H), 7.72 (d, J = 5.6 Hz, 3H), 7.58 (s, 1H), 7.54–7.45 (m, 5H), 7.28 (d, J = 8.7 Hz, 1H), 6.49 (d, J = 5.1 Hz, 1H), 4.27 (t, J = 7.1 Hz, 2H), 4.01 (s, 3H), 3.54–3.13 (m, 4H), 2.56 (t, J = 7.2 Hz, 2H), 2.16 (br, 6H); ^{13}C NMR (600 MHz, $CDCl_3$) δ 162.12, 160.71, 152.02, 149.92, 149.53, 148.27, 145.68, 136.97, 136.80, 131.41, 131.36, 130.32 (2C), 126.76 (2C), 125.34, 124.96, 123.84, 122.26, 116.71, 116.56, 116.01, 109.29, 109.14, 108.12, 102.41, 99.87, 65.92, 56.14, 53.74 (2C), 52.9, 25.4, 23.48 (2C). Anal. calcd. for $C_{35}H_{33}FN_4O_4$ (%): C, 70.93; H, 5.61; N, 9.45. Found (%): C, 70.91; H, 5.59; N, 9.47.

*5.3.3.18. N-(3-Fluoro-4-(6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy) quinolin-4-yloxy)phenyl)-4-p-tolylpicolinamide (**18r**).* Yield: 62%; m.p. 124–125 °C; MS (ESI) *m/z* (%): 607.5 $[M + H]^+$, 629.2 $[M + Na]^+$; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.21 (s, 1H), 8.64 (d, J = 5.2 Hz, 1H), 8.52 (d, J = 1.2 Hz, 1H), 8.48 (d, J = 5.1 Hz, 1H), 8.00 (dd, J = 12.2, 2.4 Hz, 1H), 7.70 (d, J = 5.4 Hz, 1H), 7.64 (d, J = 8.3 Hz, 2H), 7.57 (s, 1H), 7.51 (d, J = 8.1 Hz, 1H), 7.42 (s, 1H), 7.32 (d, J = 7.8 Hz, 2H), 7.27 (d, J = 8.4 Hz, 1H), 6.42 (d, J = 5.3 Hz, 1H), 4.27 (t, J = 6.8 Hz, 2H), 4.01 (s, 3H), 3.42–3.27 (m, 4H), 2.56 (t, J = 7.2 Hz, 2H), 2.16 (br, 6H). Anal. calcd. for $C_{36}H_{35}FN_4O_4$ (%): C, 71.27; H, 5.81; N, 9.23. Found (%): C, 71.26; H, 5.82; N, 9.24.

*5.3.3.19. N-(3-Fluoro-4-(6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy) quinolin-4-yloxy)phenyl)-4-o-tolylpicolinamide (**18s**).* Yield: 64%; m.p. 127–128 °C; MS (ESI) *m/z* (%): 607.7 $[M + H]^+$; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.20 (s, 1H), 8.64 (d, J = 5.1 Hz, 1H), 8.52 (d, J = 1.2 Hz, 1H), 8.48 (d, J = 5.3 Hz, 1H), 8.00 (dd, J = 11.9, 2.5 Hz, 1H), 7.57 (s, 1H), 7.54–7.45 (m, 2H), 7.42 (s, 1H), 7.39–7.29 (m, 4H), 7.26 (d, J = 8.4 Hz, 1H), 6.43 (d, J = 5.1 Hz, 1H), 4.27 (t, J = 6.7 Hz, 2H), 4.01 (s, 3H), 3.45–3.29 (m, 4H), 2.57 (t, J = 7.1 Hz, 2H), 2.15 (br, 6H). Anal. calcd. for $C_{36}H_{35}FN_4O_4$ (%): C, 71.27; H, 5.81; N, 9.23. Found (%): C, 71.25; H, 5.79; N, 9.24.

*5.3.3.20. N-(3-Fluoro-4-(6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy) quinolin-4-yloxy)phenyl)-4-(4-fluorophenyl)picolinamide (**18t**).* Yield: 63%; m.p. 131–132 °C; MS (ESI) *m/z* (%): 611.2 $[M + H]^+$; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.20 (s, 1H), 8.64 (d, J = 5.1 Hz, 1H), 8.49 (br, 2H), 8.01 (dd, J = 12.2, 2.4 Hz, 1H), 7.75–7.64 (m, 3H), 7.59 (s, 1H), 7.50 (d, J = 8.0 Hz, 2H), 7.28 (d, J = 8.8 Hz, 1H), 7.19 (d, J = 8.5 Hz, 2H), 6.48 (d, J = 6.6 Hz, 1H), 4.27 (t, J = 6.7 Hz, 2H), 4.01 (s, 3H), 3.45–3.29 (m, 4H), 2.55 (t, J = 7.2 Hz, 2H), 2.16 (br, 6H). Anal. calcd. for $C_{35}H_{32}F_2N_4O_4$ (%): C, 68.84; H, 5.28; N, 9.17. Found (%): C, 68.82; H, 5.26; N, 9.20.

*5.3.3.21. N-(3-Fluoro-4-(6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy) quinolin-4-yloxy)phenyl)-4-(2-fluorophenyl)picolinamide (**18u**).* Yield: 59%; m.p. 129–130 °C; MS (ESI) *m/z* (%): 611.5 $[M + H]^+$; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.19 (s, 1H), 8.66 (d, J = 5.1 Hz, 1H), 8.47 (s, 2H), 8.01 (dd, J = 12.6, 2.4 Hz, 1H), 7.73 (s, 1H), 7.58 (s, 1H), 7.52–7.36 (m, 4H), 7.35–7.25 (m, 2H), 7.18 (d, J = 8.4 Hz, 1H), 6.46 (d, J = 6.4 Hz, 1H), 4.27 (t, J = 6.7 Hz, 2H), 4.00 (s, 3H), 3.46–3.28 (m, 4H), 2.55 (t, J = 7.2 Hz, 2H), 2.15 (br, 6H); ^{13}C NMR (600 MHz, $CDCl_3$) δ 162.10, 160.12, 153.71, 151.64, 149.62, 148.94, 148.26, 146.57, 145.67, 137.25, 136.51, 131.40, 130.34, 130.06, 126.85, 125.40, 124.97, 123.89, 122.25, 116.71, 116.56, 115.94, 109.27, 109.12, 109.05, 102.43, 99.79, 66.10, 56.10, 53.83 (2C), 53.09, 26.05, 23.45 (2C). Anal. calcd. for $C_{35}H_{32}F_2N_4O_4$ (%): C, 68.84; H, 5.28; N, 9.17. Found (%): C, 68.83; H, 5.26; N, 9.21.

*5.3.3.22. N-(3-Fluoro-4-(6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy) quinolin-4-yloxy)phenyl)-4-(4-(trifluoromethyl)phenyl)picolinamide (**18v**).* Yield: 60%; m.p. 140–141 °C; IR (KBr, cm^{-1}): 3421.3, 2936.4, 2605.1, 1691.7, 1598.0, 1532.6, 1508.6, 1480.3, 1432.2, 1350.9, 1328.9, 1253.2, 1212.0, 1170.9, 1117.5, 1071.3, 1014.8, 856.4, 734.1, 572.0; MS (ESI) *m/z* (%): 661.5 $[M + H]^+$; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.19 (s, 1H), 8.70 (d, J = 4.7 Hz, 1H), 8.53 (s, 2H), 8.02 (dd, J = 12.8, 2.5 Hz, 1H), 7.81 (s, 2H), 7.77 (d, J = 8.2 Hz, 2H), 7.73 (s, 1H), 7.59 (s, 1H), 7.51 (d, J = 7.8 Hz, 2H), 7.29 (d, J = 8.4 Hz, 1H), 6.50 (s, 1H), 4.29 (t, J = 6.4 Hz, 2H), 4.01 (s, 3H), 3.47–3.27 (m,4H), 2.56 (br, 2H), 2.16 (br, 6H). Anal. calcd. for $C_{36}H_{32}F_4N_4O_4$ (%): C, 65.45; H, 4.88; N, 11.50. Found (%): C, 65.43; H, 4.86; N, 11.52.

*5.3.3.23. N-(3-Fluoro-4-(6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy) quinolin-4-yloxy)phenyl)-4-(4-methoxyphenyl)picolinamide (**18w**).* Yield: 58%; m.p. 138–139 °C; MS (ESI) *m/z* (%): 645.4 $[M + Na]^+$; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.22 (s, 1H), 8.59 (d, J = 5.2 Hz, 1H), 8.50 (s, 2H), 8.02 (dd, J = 12.0, 2.7 Hz, 1H), 7.69 (d, J = 8.7 Hz, 2H), 7.66 (s, 1H), 7.58 (s, 1H), 7.50 (d, J = 7.7 Hz, 2H), 7.28 (d, J = 8.6 Hz, 1H), 7.03 (d, J = 8.8 Hz, 2H), 6.46 (d, J = 5.3 Hz, 1H), 4.27 (t, J = 6.4 Hz, 2H), 4.01 (s, 3H), 3.86 (s, 3H), 3.48–3.28 (m, 4H), 2.56 (t, J = 7.2 Hz, 2H), 2.23–2.08 (m, 4H), 2.07–1.98 (m, 2H). Anal. calcd. for $C_{36}H_{35}FN_4O_5$ (%): C, 69.44; H, 5.67; N, 9.00. Found (%): C, 69.42; H, 5.66; N, 9.01.

*5.3.3.24. N-(3-Fluoro-4-(6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy) quinolin-4-yloxy)phenyl)-4-(2,4-dimethoxyphenyl)picolinamide (**18x**).* Yield: 56%; m.p. 143–144 °C; MS (ESI) *m/z* (%): 653.8 $[M + H]^+$, 665.5 $[M + Na]^+$; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.23 (s, 1H), 8.56 (d, J = 5.0 Hz, 1H), 8.52 (br, 1H), 8.45 (d, J = 5.3 Hz, 1H), 8.02 (dd, J = 12.4, 2.6 Hz, 1H), 7.69 (d, J = 3.5 Hz, 1H), 7.58 (s, 1H), 7.49 (d, J = 8.6 Hz, 2H), 7.37 (d, J = 8.3 Hz, 1H), 7.28 (d, J = 8.4 Hz, 1H), 6.66–6.53 (m, 2H), 6.46 (d, J = 4.6 Hz, 1H), 4.28 (t, J = 6.7 Hz, 2H), 4.01 (s, 3H), 3.86 (s, 3H), 3.84 (s, 3H), 3.48–3.27 (m, 4H), 2.55 (s, 2H), 2.15 (br, 4H), 2.01 (br, 2H). Anal. calcd. for $C_{37}H_{37}FN_4O_6$ (%): C, 68.08; H, 5.71; N, 8.58. Found (%): C, 68.07; H, 5.70; N, 8.59.

*5.3.3.25. N-(3-Fluoro-4-(6-methoxy-7-(3-(piperidin-1-yl)propoxy) quinolin-4-yloxy)phenyl)-4-phenylpicolinamide (**18y**).* Yield: 66%; m.p. 136–137 °C; IR (KBr, cm^{-1}): 3416.8, 3325.0, 2939.1, 2761.0, 1690.8, 1621.5, 1596.8, 1526.4, 1478.2, 1430.9, 1439.6, 1306.6, 1247.9, 1208.4, 1173.6, 853.6, 763.8, 696.4, 578.3; MS (ESI) *m/z* (%): 607.3 $[M + H]^+$, 629.2 $[M + Na]^+$; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.20 (s, 1H), 8.65 (d, J = 5.1 Hz, 1H), 8.54 (d, J = 1.2 Hz, 1H), 8.48 (d, J = 5.3 Hz, 1H), 8.00 (dd, J = 11.8, 2.3 Hz, 1H), 7.72 (s, 3H), 7.57 (s, 1H), 7.51 (d, J = 7.5 Hz, 4H), 7.42 (s, 1H), 7.28 (d, J = 9.0 Hz, 1H), 6.43 (d, J = 5.4 Hz, 1H), 4.24 (t, J = 6.7 Hz, 2H), 4.02 (s, 3H), 2.55 (t, J = 7.0 Hz, 2H), 2.45 (s, 4H), 2.14 (br, 2H), 1.60 (br, 4H), 1.43 (br, 2H). Anal. calcd. for $C_{36}H_{35}FN_4O_4$ (%): C, 71.27; H, 5.81; N, 9.23. Found (%): C, 71.26; H, 5.79; N, 9.25.

*5.3.3.26. N-(3-Fluoro-4-(6-methoxy-7-(3-(piperidin-1-yl)propoxy) quinolin-4-yloxy)phenyl)-4-p-tolylpicolinamide (**18z**).* Yield: 65%; m.p. 143–144 °C; IR (KBr, cm^{-1}): 3420.9, 2937.6, 1682.2, 1597.3, 1509.1, 1479.6, 1432.2, 1349.9, 1305.8, 1252.3, 1211.0, 1172.7, 854.1, 817.7, 694.5, 532.7; MS (ESI) *m/z* (%): 643.3 $[M + Na]^+$; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.20 (s, 1H), 8.62 (d, J = 5.2 Hz, 1H), 8.53 (d, J = 1.2 Hz, 1H), 8.48 (d, J = 5.2 Hz, 1H), 8.00 (dd, J = 12.2, 2.4 Hz, 1H), 7.70 (dd, J = 5.1, 1.8 Hz, 1H), 7.64 (d, J = 8.2 Hz, 2H), 7.57 (s, 1H), 7.51 (d, J = 8.3 Hz, 1H), 7.42 (s, 1H), 7.32 (d, J = 7.9 Hz, 2H), 7.27 (d, J = 8.6 Hz, 1H), 6.42 (d, J = 5.3 Hz, 1H), 4.23 (t, J = 6.8 Hz, 2H), 4.02 (s, 3H), 2.54 (t, J = 7.2 Hz, 2H), 2.42 (s, 3H), 2.41–2.34 (m, 4H), 2.14–2.09 (m, 2H), 1.60–1.55 (m, 4H), 1.45–1.39 (m, 2H); ^{13}C NMR (600 MHz, $CDCl_3$) δ 162.36, 160.06, 155.39, 153.73, 152.28, 149.84, 149.66, 148.78, 148.50, 146.93, 140.12, 137.22, 136.54, 130.12 (2C), 129.23, 126.89 (2C), 123.91, 123.72, 119.72, 115.88, 115.44, 109.21, 108.76, 102.20, 99.50, 67.62, 56.18, 55.82, 54.56 (2C), 26.35, 25.95 (2C), 24.46, 21.35. Anal. calcd. for $C_{37}H_{37}FN_4O_4$ (%): C, 71.59; H, 6.01; N, 9.03. Found (%): C, 71.57; H, 5.99; N, 9.02.

*5.3.3.27. N-(3-Fluoro-4-(6-methoxy-7-(3-(piperidin-1-yl)propoxy) quinolin-4-yloxy)phenyl)-4-(4-fluorophenyl)picolinamide (**18aa**).* Yield: 65%; m.p. 148–149 °C; MS (ESI) *m/z* (%): 625.1 $[M + H]^+$, 645.3 $[M + Na]^+$; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.19 (s, 1H), 8.64 (d, J = 5.1 Hz, 1H), 8.49 (br, 2H), 8.01 (dd, J = 11.1, 2.3 Hz, 1H), 7.75–7.65 (m, 3H), 7.58 (s, 1H), 7.50 (d, J = 8.2 Hz, 1H), 7.42 (s, 1H), 7.28 (d, J = 8.7 Hz, 1H), 7.19 (d, J = 8.6 Hz, 2H), 6.46 (d, J = 5.1 Hz, 1H), 4.27 (t, J = 6.7 Hz, 2H), 4.01 (s, 3H), 2.54 (t, J = 7.1 Hz, 2H), 2.43 (s, 4H), 2.11–2.01 (m, 2H), 1.62–1.57 (m, 4H), 1.41 (br, 2H). Anal. calcd. for $C_{36}H_{34}F_2N_4O_4$ (%): C, 69.22; H, 5.49; N, 8.97. Found (%): C, 66.23; H, 5.49; N, 9.01.

*5.3.3.28. N-(3-Fluoro-4-(6-methoxy-7-(3-(piperidin-1-yl)propoxy) quinolin-4-yloxy)phenyl)-4-(2-fluorophenyl)picolinamide (**18ab**).* Yield: 64%; m.p. 146–147 °C; MS (ESI) *m/z* (%): 625.3 $[M + H]^+$; ^1H NMR (300 MHz, $CDCl_3$) δ 10.18 (s, 1H), 8.67 (d, J = 5.1 Hz, 1H), 8.48 (br, 2H), 8.00 (dd, J = 10.2, 2.2 Hz, 1H), 7.73 (dd, J = 4.7, 1.8 Hz, 1H), 7.56 (s, 1H), 7.53–7.43 (m, 3H), 7.42 (s, 1H), 7.34–7.25 (m, 3H), 6.43 (d, J = 5.1 Hz, 1H), 4.23 (t, J = 7.0 Hz, 2H), 4.02 (s, 3H), 2.54 (t, J = 7.3 Hz, 2H), 2.43 (br, 4H), 2.16–2.10 (m, 2H), 1.63–1.55 (m, 4H), 1.47–1.40 (m, 2H). Anal. calcd. for $C_{36}H_{34}F_2N_4O_4$ (%): C, 69.22; H, 5.49; N, 8.97. Found (%): C, 66.21; H, 5.47; N, 8.99.

*5.3.3.29. N-(3-Fluoro-4-(6-methoxy-7-(3-(piperidin-1-yl)propoxy) quinolin-4-yloxy)phenyl)-4-(4-(trifluoromethyl)phenyl)picolinamide (**18ac**).* Yield: 63%; m.p. 149–150 °C; MS (ESI) *m/z* (%): 695.4 $[M + Na]^+$; ^1H NMR (300 MHz, $CDCl_3$) δ 10.17 (s, 1H), 8.71 (d, J = 5.8 Hz, 1H), 8.55 (s, 1H), 8.48 (d, J = 5.3 Hz, 1H), 7.99 (dd, J = 11.9, 2.5 Hz, 1H), 7.84 (d, J = 8.4 Hz, 2H), 7.78 (d, J = 8.3 Hz, 2H), 7.73 (dd, J = 5.0, 1.9 Hz, 1H), 7.56 (s, 1H), 7.50 (d, J = 11.1 Hz, 1H), 7.42 (s, 1H), 7.29 (d, J = 8.6 Hz, 1H), 6.43 (d, J = 6.3 Hz, 1H), 4.24 (t, J = 6.7 Hz, 2H), 4.02 (s, 3H), 2.55 (t, J = 7.7 Hz, 2H), 2.44 (br, 4H), 2.17–2.04 (m, 2H), 1.60 (br, 4H), 1.45 (br, 2H). Anal. calcd. for $C_{37}H_{34}F_4N_4O_4$ (%): C, 65.87; H, 5.08; N, 8.30. Found (%): C, 65.84; H, 5.07; N, 8.32.

*5.3.3.30. N-(3-Fluoro-4-(6-methoxy-7-(3-(piperidin-1-yl)propoxy) quinolin-4-yloxy)phenyl)-4-(4-methoxyphenyl)picolinamide (**18ad**).* Yield: 60%; m.p. 143–144 °C; MS (ESI) *m/z* (%): 637.3 $[M + H]^+$, 659.2 $[M + Na]^+$; ^1H NMR (300 MHz, $CDCl_3$) δ 10.20 (s, 1H), 8.59 (d, J = 5.1 Hz, 1H), 8.49 (d, J = 1.2 Hz, 1H), 8.47 (d, J = 5.2 Hz, 1H), 7.99 (dd, J = 12.1, 2.4 Hz, 1H), 7.68 (t, J = 7.5 Hz, 3H), 7.56 (s, 1H), 7.49 (d, J = 8.2 Hz, 1H), 7.41 (s, 1H), 7.27 (d, J = 8.5 Hz, 1H), 7.02 (d, J = 8.7 Hz, 2H), 6.42 (d, J = 5.1 Hz, 1H), 4.23 (t, J = 6.6 Hz, 2H), 4.02 (s, 3H), 3.86 (s, 3H), 2.54 (t, J = 7.3 Hz, 2H), 2.40 (br, 4H), 2.15–2.08 (m, 2H), 1.65–1.54 (m, 4H), 1.48–1.40 (m, 2H); ^{13}C NMR (600 MHz, $CDCl_3$) δ 162.37, 161.06, 160.06, 155.41, 153.75, 152.30, 149.86, 149.67, 148.78, 148.49, 146.93, 137.23, 136.52, 129.25, 128.38 (2C), 123.90, 123.74, 119.68, 115.88, 115.43, 114.74 (2C), 109.14, 108.75, 102.20, 99.51, 67.65, 56.18, 55.79, 55.46, 54.57 (2C), 26.35, 25.97 (2C), 24.44. Anal. calcd. for $C_{37}H_{37}FN_4O_5$ (%): C, 69.80; H, 5.86; N, 8.80. Found (%): C, 69.78; H, 5.84; N, 8.83.

5.4. Preparation of pyrimidine-based quinoline derivatives

*5.4.1. General procedure for the preparation of (E)-3-(dimethylamino)-1-substititedphenylprop-2-en-1-ones (**20a**–**d**)*

A mixture of an appropriate substituted acetophenone (0.1 mol) and DMF-DMA (39.8 mL, 0.3 mol) was heated at 80 °C for 8–12 h and monitored by TLC. Upon cooling to room temperature of the reaction mixture, Et_2O (40 mL) and petroleum ether (120 mL) were added and stirred for 0.5 h, and then the precipitate was collected by filtration and dried to give the corresponding (*E*)-3-(dimethylamino)-1-substititedphenylprop-2-en-1-one as yellow solids.

*5.4.1.1. (E)-3-(Dimethylamino)-1-phenylprop-2-en-1-one (**20a**).* Yield: 89%; m.p. 90–91 °C; MS (ESI) *m/z* (%): 176.3 $[M + H]^+$, 198.6 $[M + Na]^+$; ^1H NMR (300 MHz, DMSO) δ 7.89–7.41 (m, 5H), 7.75 (d, J = 12.4 Hz, 1H), 5.71 (d, J = 12.5 Hz, 1H), 3.05 (br, 6H).

*5.4.1.2. (E)-3-(Dimethylamino)-1-p-tolylprop-2-en-1-one (**20b**).* Yield: 82%; m.p. 94–96 °C; MS (ESI) *m/z* (%): 190.4 $[M + H]^+$; ^1H NMR (300 MHz, DMSO) δ 7.94 (d, J = 8.1 Hz, 2H), 7.75 (d, J = 12.4 Hz, 1H), 7.39 (d, J = 8.0 Hz, 2H), 5.71 (d, J = 12.5 Hz, 1H), 3.03 (br, 6H), 2.35 (s, 3H).

*5.4.1.3. (E)-3-(Dimethylamino)-1-(4-fluorophenyl)prop-2-en-1-one (**20c**).* Yield: 84%; m.p. 102–103 °C; MS (ESI) *m/z* (%): 216.6 $[M + Na]^+$; ^1H NMR (300 MHz, DMSO) δ 7.98–7.91 (m, 2H), 7.75 (d, J = 12.5 Hz, 1H), 7.18–7.09 (m, 2H), 5.67 (d, J = 12.4 Hz, 1H), 3.04 (br, 6H).

*5.4.1.4. (E)- 3-(Dimethylamino)-1-(2,4-difluorophenyl)prop-2-en-1-one (**20d**).* Yield: 81%; m.p. 109–110 °C; MS (ESI) *m/z* (%): 212.1 $[M + H]^+$; ^1H NMR (300 MHz, DMSO) δ 8.01–7.92 (m, 1H), 7.75 (d, J = 12.6 Hz, 1H), 6.94–6.81 (m, 2H), 5.63 (d, J = 12.5 Hz, 1H), 3.06 (br, 6H).

*5.4.2. General procedure for the preparation of 4-substititedphenylpyrimidines (**21a**–**d**)*

To the mixture of formamidine acetate (9.9 g, 0.096 mol), sodium ethoxide (10.9 g, 0.16 mol) and anhydrous EtOH (300 mL), an appropriate (*E*)-3-(dimethylamino)-1-substititedphenylprop-2-en-1-one (0.08 mol) was added slowly at 70 °C. Upon the completion of addition, the reaction mixture then was stirred at reflux for 15–20 h and monitored by TLC. The solvent was concentrated in vacuum and the residue was resolved with dichloromethane (300 mL), washed with water (30 mL × 3), brine (60 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuum to give the corresponding 4-substititedphenylpyrimidines as light yellow solids.

*5.4.2.1. 4-Phenylpyrimidine (**21a**).* Yield: 66%; m.p. 60–61 °C; MS (ESI) *m/z* (%): 157.5 $[M + H]^+$; ^1H NMR (300 MHz, $CDCl_3$) δ 9.29 (s, 1H), 8.79 (d, J = 5.4 Hz, 1H), 8.11 (d, J = 8.6 Hz, 2H), 7.74 (d, J = 5.6 Hz, 1H), 7.54 (m, 3H).

*5.4.2.2. 4-p-Tolylpyrimidine (**21b**).* Yield: 63%; m.p. 63–65 °C; MS (ESI) *m/z* (%): 193.5 $[M + Na]^+$; ^1H NMR (300 MHz, $CDCl_3$) δ 9.27 (s, 1H), 8.78 (d, J = 5.6 Hz, 1H), 8.12 (d, J = 8.8 Hz, 2H), 7.75 (d, J = 5.6 Hz, 1H), 7.36 (d, J = 8.6 Hz, 2H), 2.35 (s, 3H).

*5.4.2.3. 4-(4-Fluorophenyl)pyrimidine (**21c**).* Yield: 66%; m.p. 82–83 °C; MS (ESI) *m/z* (%): 175.1 $[M + H]^+$, 197.3 $[M + Na]^+$; ^1H NMR (300 MHz, $CDCl_3$) δ 9.28 (s, 1H), 8.76 (d, J = 5.6 Hz, 1H), 8.22 (d, J = 8.6 Hz, 2H), 7.74 (d, J = 5.6 Hz, 1H), 7.24 (d, J = 8.6 Hz, 2H).

*5.4.2.4. 4-(2,4-Difluorophenyl)pyrimidine (**21d**).* Yield: 65%; m.p. 88–90 °C; MS (ESI) *m/z* (%): 215.4 $[M + Na]^+$; ^1H NMR (300 MHz, $CDCl_3$) δ 9.29 (s, 1H), 8.78 (d, J = 5.4 Hz, 1H), 8.31–8.24 (m, 1H), 7.78 (d, J = 5.6 Hz, 1H), 7.59–7.51 (m, 2H).

*5.4.3. General procedure for the preparation of 4-substititedphenylpyrimidine-2-carboxamides (**22a**–**d**)*

To the mixture of an appropriate 4-substititedphenylpyrimidine (0.06 mol) and acetamide (500 mL), concentrated sulfuric acid (20 mL) was added drop-wise at the temperature of 0–10 °C. Upon the completion of addition, 30% H_2O_2 (50 mL) and saturated $FeSO_4 \cdot 7H_2O$ (aq. 100 mL) were added drop-wise at the same time at the temperature of 0–10 °C. The reaction mixture the was stirred at 10–15 °C for 0.5 h and then poured into water (2000 mL), basified with potassium hydroxide to pH 9, and extracted with dichloromethane (200 mL × 3). The combined extracts were washed with brine (200 mL × 2), dried over anhydrous Na_2SO_4, and concentrated in vacuum to give the corresponding 4-substititedphenylpyrimidine-2-carboxamides as white solids in a moderate yield.

*5.4.3.1. 4-Phenylpyrimidine-2-carboxamide (**22a**).* Yield: 47%; m.p. 152–153 °C; MS (ESI) *m/z* (%): 200.4 $[M + H]^+$, 222.5 $[M + Na]^+$; ^1H NMR (300 MHz, $CDCl_3$) δ 9.28 (d, J = 1.3 Hz, 1H), 8.38 (d, J = 1.2 Hz, 1H), 8.24 (d, J = 8.4 Hz, 2H), 7.84 (s, 2H), 7.61–7.46 (m, 3H).

*5.4.3.2. 4-p-Tolylpyrimidine-2-carboxamide (**22b**).* Yield: 37%; m.p. 155–156 °C; MS (ESI) *m/z* (%): 214.3 $[M + H]^+$, 236.2 $[M + Na]^+$; ^1H

NMR (300 MHz, $CDCl_3$) δ 9.27 (d, J = 1.3 Hz, 1H), 8.35 (d, J = 1.3 Hz, 1H), 8.10 (d, J = 8.2 Hz, 2H), 7.82 (s, 2H), 7.28 (d, J = 8.2 Hz, 2H), 2.35 (s, 3H).

*5.4.3.3. 4-(4-Fluorophenyl)pyrimidine-2-carboxamide (**22c**).* Yield: 45%; m.p. 161–162 °C; MS (ESI) m/z (%): 218.7 $[M + H]^+$, 240.5 $[M + Na]^+$; ^1H NMR (300 MHz, $CDCl_3$) δ 9.29 (d, J = 1.3 Hz, 1H), 8.38 (d, J = 1.3 Hz, 1H), 8.22 (d, J = 8.2 Hz, 2H), 7.81 (s, 2H), 7.16 (d, J = 8.4 Hz, 2H).

*5.4.3.4. 4-(2,4-Difluorophenyl)pyrimidine-2-carboxamide (**22d**).* Yield: 32%; m.p. 168–169 °C; MS (ESI) m/z (%): 236.6 $[M + H]^+$, 258.5 $[M + Na]^+$; ^1H NMR (300 MHz, $CDCl_3$) δ 9.27 (d, J = 1.2 Hz, 1H), 8.36 (d, J = 1.3 Hz, 1H), 8.30–8.24 (m, 1H), 7.82 (s, 2H), 7.18–7.04 (m, 2H).

*5.4.4. General procedure for the preparation of 4-substitited phenylpyrimidine-2-carboxylic acids (**23a**–**d**)*

A mixture of an appropriate 4-substititedphenylpyrimidine-2-carboxamide (0.025 mol) and 20% H_2SO_4 (100 mL) was heated at 100 °C for 5–10 h and monitored by TLC. The reaction mixture was poured onto ice/water with vigorously stirring and then the precipitate was collected by filtration and dried to give the corresponding 4-substititedphenylpyrimidine-2-carboxylic acids as light yellow solids.

*5.4.4.1. 4-Phenylpyrimidine-2-carboxylic acid (**23a**).* Yield: 87%; m.p. 155–157 °C; MS (ESI) m/z (%): 199.5 $[M - H]^-$; ^1H NMR (300 MHz, DMSO) δ 9.36 (d, J = 1.2 Hz, 1H), 8.44 (d, J = 1.3 Hz, 1H), 8.24 (dd, J = 7.3, 2.5 Hz, 2H), 7.63–7.48 (m, 3H).

*5.4.4.2. 4-p-Tolylpyrimidine-2-carboxylic acid (**23b**).* Yield: 81%; m.p. 159–161 °C; MS (ESI) m/z (%): 212.9 $[M - H]^-$; ^1H NMR (300 MHz, DMSO) δ 9.31 (d, J = 1.3 Hz, 1H), 8.40 (d, J = 1.3 Hz, 1H), 8.14 (d, J = 8.2 Hz, 2H), 7.34 (d, J = 8.0 Hz, 2H), 2.35 (s, 3H).

*5.4.4.3. 4-(4-Fluorophenyl)pyrimidine-2-carboxylic acid (**23c**).* Yield: 76%; m.p. 162–163 °C; MS (ESI) m/z (%): 217.6 $[M - H]^-$; ^1H NMR (300 MHz, DMSO) δ 9.32 (d, J = 1.3 Hz, 1H), 8.42 (d, J = 1.3 Hz, 1H), 8.26 (d, J = 8.1 Hz, 2H), 7.22 (d, J = 8.6 Hz, 2H).

*5.4.4.4. 4-(2,4-Difluorophenyl)pyrimidine-2-carboxylic acid (**23d**).* Yield: 77%; m.p. 166–167 °C; MS (ESI) m/z (%): 235.4 $[M - H]^-$; ^1H NMR (300 MHz, DMSO) δ 9.37 (d, J = 1.3 Hz, 1H), 8.48 (d, J = 1.3 Hz, 1H), 8.30–8.24 (m, 1H), 7.13–6.94 (m, 2H).

*5.4.5. General procedure for the preparation of 4-substititedphenylpyrimidine-2-carbonyl chlorides (**24a**–**d**)*

An appropriate 4-substititedphenylpyrimidine-2-carboxylic acid was added to thionyl chloride (0.02 mol) and refluxed for 6 h. The reaction mixture was evaporated to yield the corresponding 4-substititedphenylpyrimidine-2-carbonyl chlorides **24a**–**d**, which were used for the next step immediately without further purification.

*5.4.6. General procedure for the preparation of the target compounds **25a**–**n***

To a solution of an appropriate aniline **15a**–**d** (2 mmol) and diisopropylethylamine (2.4 mmol) in dichloromethane (40 mL), an appropriate carbonyl chloride **24a**–**d** (4 mmol) dissolved in dried dichloromethane (20 mL) was added drop-wise in an ice bath. Upon completion of the addition, the reaction mixture was removed to room temperature for 7–10 h and monitored by TLC. The mixture was washed with 10% K_2CO_3 (20 mL × 3) followed by brine (20 mL × 1), and the organic phase was separated, dried, and concentrated in vacuum. The crude product was purified by chromatography on silica gel using $MeOH/CH_2Cl_2$ to afford the target compounds **25a**–**n** as white solids.

*5.4.6.1. N-(3-Fluoro-4-(6-methoxy-7-(3-morpholinopropoxy)quinolin-4-yloxy)phenyl)-4-phenylpyrimidine-2-carboxamide (**25a**).* Yield: 61%; m.p. 183–184 °C; IR (KBr, cm^{-1}): 3321.8, 2941.5, 1694.2, 1587.0, 1528.1, 1480.1, 1432.0, 1350.2, 1248.3, 1209.3, 1174.4, 1114.8, 850.2, 582.6; MS (ESI) m/z (%): 610.2 $[M + H]^+$; ^1H NMR (300 MHz, $CDCl_3$) δ 10.02 (s, 1H), 9.30 (d, J = 1.3 Hz, 1H), 8.62 (d, J = 1.3 Hz, 1H), 8.48 (d, J = 5.2 Hz, 1H), 8.22 (dd, J = 6.5, 3.3 Hz, 2H), 7.97 (dd, J = 11.9, 2.5 Hz, 1H), 7.57 (s, 1H), 7.55 (d, J = 8.2 Hz, 2H), 7.54 (d, J = 1.3 Hz, 1H), 7.52–7.47 (m, 1H), 7.44 (s, 1H), 7.29 (d, J = 8.6 Hz, 1H), 6.43 (d, J = 5.2 Hz, 1H), 4.27 (t, J = 6.6 Hz, 2H), 4.02 (s, 3H), 3.72–3.67 (m, 4H), 2.56 (t, J = 7.1 Hz, 2H), 2.49–2.44 (m, 4H), 2.10 (p, J = 6.8 Hz, 2H); ^{13}C NMR (600 MHz, $CDCl_3$) δ 166.89, 160.82, 159.93, 157.85, 156.32, 155.42, 152.27, 149.86, 148.81, 146.96, 137.84, 135.76, 131.97, 129.26 (2C), 127.53 (2C), 124.05, 116.18, 115.44, 114.09, 109.55, 109.40, 108.79, 102.25, 99.48, 67.26, 67.05 (2C), 56.19, 55.40, 53.73 (2C), 26.01. Anal. calcd. for $C_{34}H_{32}FN_5O_5$ (%): C, 66.98; H, 5.29; N, 11.49. Found (%): C, 66.96; H, 5.28; N, 11.51.

*5.4.6.2. N-(3-Fluoro-4-(6-methoxy-7-(3-morpholinopropoxy)quinolin-4-yloxy)phenyl)-4-p-tolylpyrimidine-2-carboxamide (**25b**).* Yield: 56%; m.p. 188–189 °C; IR (KBr, cm^{-1}): 3425.5, 3343.3, 2953.5, 1696.8, 1588.6, 1533.7, 1480.7, 1432.6, 1347.9, 1208.2, 1115.7, 853.9, 740.8, 618.3; MS (ESI) m/z (%): 624.5 $[M + H]^+$, 646.2 $[M + Na]^+$; ^1H NMR (300 MHz, $CDCl_3$) δ 10.07 (s, 1H), 9.28 (d, J = 1.3 Hz, 1H), 8.59 (d, J = 1.3 Hz, 1H), 8.50 (d, J = 5.2 Hz, 1H), 8.13 (d, J = 8.2 Hz, 2H), 8.02 (dd, J = 12.1, 2.4 Hz, 1H), 7.59 (s, 1H), 7.52 (d, J = 10.6 Hz, 2H), 7.35 (d, J = 8.5 Hz, 2H), 7.29 (d, J = 8.8 Hz, 1H), 6.47 (d, J = 5.3 Hz, 1H), 4.29 (t, J = 6.6 Hz, 2H), 4.03 (s, 3H), 3.92–3.81 (m, 4H), 2.87 (br, 2H), 2.79 (br, 4H), 2.44 (s, 3H), 2.34–2.23 (m, 2H). Anal. calcd. for $C_{35}H_{34}FN_5O_5$ (%): C, 67.40; H, 5.49; N, 11.23. Found (%): C, 67.42; H, 5.70; N, 11.24.

*5.4.6.3. N-(3-Fluoro-4-(6-methoxy-7-(3-morpholinopropoxy)quinolin-4-yloxy)phenyl)-4-(4-fluorophenyl)pyrimidine-2-carboxamide (**25c**).* Yield: 58%; m.p. 201–202 °C; IR (KBr, cm^{-1}): 3326.2, 2940.4, 1693.4, 1587.9, 1509.7, 1480.7, 1430.9, 1352.1, 1211.4, 1170.8, 1114.7, 990.6, 844.1, 572.2; MS (ESI) m/z (%): 628.7 $[M + H]^+$, 650.4 $[M + Na]^+$; ^1H NMR (300 MHz, $CDCl_3$) δ 10.04 (s, 1H), 9.29 (d, J = 1.3 Hz, 1H), 8.58 (d, J = 1.3 Hz, 1H), 8.49 (d, J = 5.3 Hz, 1H), 8.25 (dd, J = 8.9, 5.3 Hz, 2H), 7.99 (dd, J = 11.8, 2.3 Hz, 1H), 7.56 (s, 1H), 7.50 (d, J = 8.9 Hz, 1H), 7.43 (s, 1H), 7.30 (d, J = 8.6 Hz, 1H), 7.26 (s, 1H), 7.20 (s, 1H), 6.42 (d, J = 5.0 Hz, 1H), 4.27 (t, J = 6.6 Hz, 2H), 4.03 (s, 3H), 3.76–3.66 (m, 4H), 2.58 (t, J = 7.0 Hz, 2H), 2.48 (br, 4H), 2.17–2.06 (m, 2H). Anal. calcd. for $C_{34}H_{31}F_2N_5O_5$ (%): C, 65.06; H, 4.98; N, 11.16. Found (%): C, 65.07; H, 5.01; N, 11.15.

*5.4.6.4. N-(3-Fluoro-4-(6-methoxy-7-(3-morpholinopropoxy)quinolin-4-yloxy)phenyl)-4-(2,4-difluorophenyl)pyrimidine-2-carboxamide (**25d**).* Yield: 53%; m.p. 208–209 °C; IR (KBr, cm^{-1}): 3423.3, 2939.4, 1685.2, 1587.1, 1510.5, 1431.9, 1347.8, 1300.8, 1248.6, 1214.9, 1116.6, 856.4, 572.1; MS (ESI) m/z (%): 646.6 $[M + H]^+$, 668.3 $[M + Na]^+$; ^1H NMR (300 MHz, $CDCl_3$) δ 9.97 (s, 1H), 9.33 (s, 1H), 8.68 (s, 1H), 8.48 (d, J = 5.0 Hz, 1H), 8.27 (dd, J = 8.7, 5.3 Hz, 1H), 7.96 (d, J = 11.6 Hz, 1H), 7.56 (s, 1H), 7.50 (d, J = 8.6 Hz, 1H), 7.43 (s, 1H), 7.28 (d, J = 8.5 Hz, 1H), 7.12–6.91 (m, 2H), 6.43 (d, J = 5.3 Hz, 1H), 4.27 (t, J = 6.6 Hz, 2H), 4.01 (s, 3H), 3.79–3.62 (m, 4H), 2.56 (t, J = 7.1 Hz, 2H), 2.51–2.42 (m, 4H), 2.17–2.04 (m, 2H); ^{13}C NMR (600 MHz, $CDCl_3$) δ 162.39, 160.55, 159.92, 157.67, 156.37, 152.27, 149.86, 148.80, 146.96, 137.96, 135.69, 132.39, 132.30, 124.06, 117.91, 117.83, 116.15, 115.44, 112.70, 112.56, 109.55, 109.39, 108.78, 105.16, 102.25, 99.48, 67.26, 67.04 (2C), 56.19, 55.40, 53.73 (2C), 26.01. Anal.

calcd. for $C_{34}H_{30}F_3N_5O_5$ (%): C, 63.25; H, 4.68; N, 10.85. Found (%): C, 63.24; H, 4.67; N, 10.86.

*5.4.6.5. N-(3-Fluoro-4-(6-methoxy-7-(3-(piperidin-1-yl)propoxy) quinolin-4-yloxy)phenyl)-4-phenylpyrimidine-2-carboxamide (**25e**).* Yield: 61%; m.p. 151–152 °C; MS (ESI) *m/z* (%): 608.6 $[M + H]^+$, 630.2 $[M + Na]^+$; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.03 (s, 1H), 9.28 (d, J = 1.3 Hz, 1H), 8.61 (d, J = 1.3 Hz, 1H), 8.48 (d, J = 5.2 Hz, 1H), 8.22 (dd, J = 8.2, 5.3 Hz, 2H), 7.96 (dd, J = 11.9, 2.5 Hz, 1H), 7.57 (s, 1H), 7.55 (d, J = 2.3 Hz, 2H), 7.54 (d, J = 1.2 Hz, 1H), 7.49 (d, J = 7.8 Hz, 1H), 7.44 (s, 1H), 7.29 (d, J = 8.6 Hz, 1H), 6.43 (d, J = 5.2 Hz, 1H), 4.25 (t, J = 6.7 Hz, 2H), 4.01 (s, 3H), 2.54 (t, J = 7.2 Hz, 2H), 2.42–2.33 (m, 4H), 2.15–2.05 (m, 2H), 1.62–1.52 (m, 4H), 1.46–1.38 (m, 2H). Anal. calcd. for $C_{35}H_{34}FN_5O_4$ (%): C, 69.18; H, 5.64; N, 11.52. Found (%): C, 69.17; H, 5.64; N, 11.66.

*5.4.6.6. N-(3-Fluoro-4-(6-methoxy-7-(3-(piperidin-1-yl)propoxy) quinolin-4-yloxy)phenyl)-4-p-tolylpyrimidine-2-carboxamide (**25f**).* Yield: 66%; m.p. 157–158 °C; IR (KBr, cm^{-1}): 3343.3, 2931.8, 1697.4, 1587.8, 1528.6, 1479.6, 1431.9, 1348.2, 1248.4, 1209.6, 854.8, 581.5; MS (ESI) *m/z* (%): 621.3 $[M + H]^+$, 643.4 $[M + Na]^+$; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.00 (s, 1H), 9.27 (d, J = 1.3 Hz, 1H), 8.59 (d, J = 1.3 Hz, 1H), 8.48 (s, 1H), 8.13 (d, J = 8.2 Hz, 2H), 7.96 (dd, J = 11.8, 2.2 Hz, 1H), 7.57 (s, 1H), 7.49 (d, J = 7.8 Hz, 1H), 7.44 (s, 1H), 7.35 (d, J = 8.0 Hz, 2H), 7.28 (d, J = 8.6 Hz, 1H), 6.43 (d, J = 5.9 Hz, 1H), 4.25 (t, J = 6.7 Hz, 2H), 4.01 (s, 3H), 2.54 (t, J = 7.2 Hz, 2H), 2.44 (s, 3H), 2.43–2.36 (m, 4H), 2.15–2.05 (m, 2H), 1.62–1.51 (m, 4H), 1.41–1.10 (m, 2H). Anal. calcd. for $C_{36}H_{36}FN_5O_4$ (%): C, 69.55; H, 5.84; N, 11.26. Found (%): C, 69.54; H, 5.82; N, 11.38.

*5.4.6.7. N-(3-Fluoro-4-(6-methoxy-7-(3-(piperidin-1-yl)propoxy) quinolin-4-yloxy)phenyl)-4-(4-fluorophenyl)pyrimidine-2-carboxamide (**25g**).* Yield: 58%; m.p. 161–162 °C; IR (KBr, cm^{-1}): 3327.8, 2935.4, 2769.5, 1693.7, 1587.7, 1509.5, 1480.0, 1431.5, 1351.5, 1306.8, 1251.3, 1211.4, 1173.0, 843.5, 756.2, 572.4; MS (ESI) *m/z* (%): 625.6 $[M + H]^+$, 647.2 $[M + Na]^+$; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.00 (s, 1H), 9.28 (d, J = 1.3 Hz, 1H), 8.57 (d, J = 1.3 Hz, 1H), 8.48 (d, J = 5.2 Hz, 1H), 8.13 (d, J = 8.3 Hz, 2H), 7.97 (dd, J = 11.9, 2.4 Hz, 1H), 7.56 (s, 1H), 7.49 (d, J = 8.7 Hz, 1H), 7.43 (s, 1H), 7.29 (d, J = 8.6 Hz, 1H), 7.25 (d, J = 1.9 Hz, 1H), 7.21 (d, J = 8.6 Hz, 1H), 6.42 (d, J = 4.5 Hz, 1H), 4.24 (t, J = 6.7 Hz, 2H), 4.02 (s, 3H), 2.52 (t, J = 6.9 Hz, 2H), 2.44–2.37 (m, 4H), 2.16–2.05 (m, 2H), 1.62–1.53 (m, 4H), 1.47–1.39 (m, 2H). Anal. calcd. for $C_{35}H_{33}F_2N_5O_4$ (%): C, 67.19; H, 5.32; N, 11.19. Found (%): C, 67.18; H, 5.30; N, 11.21.

*5.4.6.8. N-(3-Fluoro-4-(6-methoxy-7-(3-(piperidin-1-yl)propoxy) quinolin-4-yloxy)phenyl)-4-(2,4-difluorophenyl)pyrimidine-2-carboxamide (**25h**).* Yield: 56%; m.p. 166–167 °C; MS (ESI) *m/z* (%): 644.8 $[M + H]^+$, 666.7 $[M + Na]^+$; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.96 (s, 1H), 9.33 (d, J = 1.3 Hz, 1H), 8.68 (d, J = 1.3 Hz, 1H), 8.48 (d, J = 5.2 Hz, 1H), 8.25 (dd, J = 15.3, 6.4 Hz, 2H), 7.96 (dd, J = 11.9, 2.4 Hz, 1H), 7.56 (s, 1H), 7.49 (d, J = 8.9 Hz, 1H), 7.43 (s, 1H), 7.28 (d, J = 8.7 Hz, 1H), 7.10–6.94 (m, 2H), 6.42 (d, J = 5.3 Hz, 1H), 4.25 (t, J = 6.6 Hz, 2H), 4.01 (s, 3H), 2.51 (t, J = 7.2 Hz, 2H), 2.44–2.37 (m, 4H), 2.16–2.05 (m, 2H), 1.63–1.53 (m, 4H), 1.47–1.38 (m, 2H). Anal. calcd. for $C_{35}H_{32}F_3N_5O_4$ (%): C, 65.31; H, 5.01; N, 10.88. Found (%): C, 65. 30; H, 5.00; N, 10.89.

*5.4.6.9. N-(3-Fluoro-4-(6-methoxy-7-(3-(4-methylpiperazin-1-yl) propoxy)quinolin-4-yloxy)phenyl)-4-p-tolylpyrimidine-2-carboxamide (**25i**).* Yield: 63%; m.p. 167–168 °C; IR (KBr, cm^{-1}): 3326.1, 2938.0, 2795.0, 1690.0, 1588.8, 1528.8, 1479.8, 1432.2, 1349.2, 1248.6, 1209.9, 1173.0, 1013.4, 855.6, 574.7; MS (ESI) *m/z* (%): 637.3 $[M + H]^+$, 659.5 $[M + Na]^+$; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.02 (s, 1H), 9.27 (d, J = 1.3 Hz, 1H), 8.59 (d, J = 1.3 Hz, 1H), 8.48 (d, J = 5.3 Hz, 1H), 8.13 (d, J = 8.3 Hz, 2H), 7.97 (dd, J = 11.8, 2.4 Hz, 1H), 7.56 (s, 1H), 7.49 (d, J = 7.9 Hz, 1H), 7.43 (s, 1H), 7.35 (d, J = 7.9 Hz, 2H), 7.29 (d, J = 8.6 Hz, 1H), 6.43 (d, J = 4.6 Hz, 1H), 4.25 (t, J = 6.6 Hz, 2H), 4.02 (s, 3H), 2.57 (t, J = 7.1 Hz, 2H), 2.49 (d, J = 12.7 Hz, 8H), 2.44 (s, 3H), 2.28 (s, 3H), 2.10 (dt, J = 13.4, 6.6 Hz, 2H); ^{13}C NMR (600 MHz, $CDCl_3$) δ 166.82, 160.93, 159.95, 157.80, 156.48, 156.13, 152.32, 149.89, 148.76, 146.92, 142.66, 135.74, 132.98, 130.01 (2C), 127.46 (2C), 124.04, 116.16, 115.42, 113.72, 109.52, 109.40, 108.75, 102.24, 99.48, 67.36, 56.18, 55.03 (2C), 54.90, 53.00 (2C), 45.90, 26.30, 21.57. Anal. calcd. for $C_{36}H_{37}FN_6O_4$ (%): C, 67.91; H, 5.86; N, 13.22. Found (%): C, 67. 90; H, 5.84; N, 13.24.

*5.4.6.10. N-(3-Fluoro-4-(6-methoxy-7-(3-(4-methylpiperazin-1-yl) propoxy)quinolin-4-yloxy)phenyl)-4-(4-fluorophenyl)pyrimidine-2-carboxamide (**25j**).* Yield: 62%; m.p. 175–176 °C; IR (KBr, cm^{-1}): 3329.8, 2936.3, 2794.5, 1693.6, 1509.4, 1480.1, 1431.7, 1351.2, 1251.8, 1211.5, 1169.5, 1014.6, 992.1, 843.0, 572.5; MS (ESI) *m/z* (%): 641.6 $[M + H]^+$, 663.5 $[M + Na]^+$; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.00 (s, 1H), 9.29 (d, J = 1.3 Hz, 1H), 8.58 (d, J = 1.3 Hz, 1H), 8.48 (d, J = 5.2 Hz, 1H), 8.25 (dt, J = 8.9, 5.3 Hz, 2H), 7.96 (dd, J = 11.9, 2.5 Hz, 1H), 7.56 (s, 1H), 7.49 (d, J = 9.0 Hz, 1H), 7.43 (s, 1H), 7.29 (d, J = 8.6 Hz, 1H), 7.21 (d, J = 8.6 Hz, 2H), 6.43 (d, J = 5.3 Hz, 1H), 4.25 (t, J = 6.6 Hz, 2H), 4.02 (s, 3H), 2.57 (t, J = 7.1 Hz, 2H), 2.47 (d, J = 23.5 Hz, 8H), 2.27 (s, 3H), 2.16–2.04 (m, 2H); ^{13}C NMR (600 MHz, $CDCl_3$) δ 165.70, 164.42, 160.71, 159.90, 157.84, 156.40, 155.42, 152.34, 149.90, 148.76, 146.99, 135.63, 131.92, 129.74 (2C), 124.05, 116.41 (2C), 116.16, 115.42, 113.69, 109.56, 109.40, 108.79, 102.23, 99.46, 67.43, 56.18, 55.19 (2C), 54.97, 53.22 (2C), 46.09, 26.35. Anal. calcd. for $C_{35}H_{34}F_2N_6O_4$ (%): C, 65.61; H, 5.35; N, 13.12. Found (%): C, 65.59; H, 5.34; N, 13.13.

*5.4.6.11. N-(3-Fluoro-4-(6-methoxy-7-(3-(4-methylpiperazin-1-yl) propoxy)quinolin-4-yloxy)phenyl)-4-(2,4-difluorophenyl)pyrimidine-2-carboxamide (**25k**).* Yield: 59%; m.p. 179–180 °C; MS (ESI) *m/z* (%): 659.3 $[M + H]^+$, 681.6 $[M + Na]^+$; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.97 (s, 1H), 9.33 (d, J = 1.4 Hz, 1H), 8.68 (d, J = 1.5 Hz, 1H), 8.48 (d, J = 5.2 Hz, 1H), 8.28 (td, J = 8.8, 6.5 Hz, 1H), 7.96 (dd, J = 11.9, 2.5 Hz, 1H), 7.56 (s, 1H), 7.49 (d, J = 7.5 Hz, 1H), 7.43 (s, 1H), 7.28 (d, J = 8.6 Hz, 1H), 7.11–6.93 (m, 2H), 6.42 (d, J = 5.2 Hz, 1H), 4.25 (t, J = 6.7 Hz, 2H), 4.01 (s, 3H), 2.57 (t, J = 7.2 Hz, 2H), 2.47 (d, J = 23.4 Hz, 8H), 2.27 (s, 3H), 2.17–2.04 (m, 2H). Anal. calcd. for $C_{35}H_{33}F_3N_6O_4$ (%): C, 63.82; H, 5.05; N, 12.76. Found (%): C, 63.80; H, 5.04; N, 12.75.

*5.4.6.12. N-(3-Fluoro-4-(6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy) quinolin-4-yloxy)phenyl)-4-phenylpyrimidine-2-carboxamide (**25l**).* Yield: 61%; m.p. 128–129 °C; MS (ESI) *m/z* (%): 594.2 $[M + H]^+$, 616.7 $[M + Na]^+$; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.04 (s, 1H), 9.27 (d, J = 1.3 Hz, 1H), 8.59 (d, J = 1.3 Hz, 1H), 8.48 (d, J = 5.2 Hz, 1H), 8.22 (dd, J = 8.4, 5.3 Hz, 2H), 7.96 (dd, J = 11.9, 2.2 Hz, 1H), 7.57 (s, 1H), 7.55 (d, J = 2.3 Hz, 2H), 7.54 (d, J = 1.2 Hz, 1H), 7.49 (d, J = 7.8 Hz, 1H), 7.44 (s, 1H), 7.29 (d, J = 8.6 Hz, 1H), 6.43 (d, J = 5.2 Hz, 1H), 4.28 (t, J = 6.7 Hz, 2H), 4.02 (s, 3H), 3.45–3.21 (m, 4H), 2.56 (t, J = 7.2 Hz, 2H), 2.16 (br, 6H). Anal. calcd. for $C_{34}H_{32}FN_5O_4$ (%): C, 68.79; H, 5.43; N, 11.80. Found (%): C, 68.78; H, 5.44; N, 11.79.

*5.4.6.13. N-(3-Fluoro-4-(6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy) quinolin-4-yloxy)phenyl)-4-p-tolylpyrimidine-2-carboxamide (**25m**).* Yield: 53%; m.p. 133–134 °C; IR (KBr, cm^{-1}): 3424.0, 2961.1, 2809.2, 1684.4, 1586.6, 1527.4, 1480.0, 1431.7, 1350.5, 1252.6, 1212.9, 1173.5, 855.2, 749,7, 574.9; MS (ESI) *m/z* (%): 608.7 $[M + H]^+$, 630.5 $[M + Na]^+$; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.07 (s, 1H), 9.28 (d, J = 1.2 Hz, 1H), 8.59 (d, J = 1.3 Hz, 1H), 8.50 (d, J = 6.4 Hz, 1H), 8.12 (d, J = 8.2 Hz, 2H), 8.02 (dd, J = 11.8, 2.2 Hz, 1H), 7.58 (s, 1H), 7.51 (d,

J = 5.9 Hz, 2H), 7.35 (d, J = 8.0 Hz, 2H), 7.28 (d, J = 8.8 Hz, 1H), 6.49 (d, J = 4.5 Hz, 1H), 4.29 (t, J = 6.7 Hz, 2H), 4.02 (s, 3H), 3.43–3.22 (m, 4H), 2.54 (t, J = 7.2 Hz, 2H), 2.44 (s, 3H), 2.16 (br, 6H). Anal. calcd. for $C_{35}H_{34}FN_5O_4$ (%): C, 69.18; H, 5.64; N, 11.52. Found (%): C, 69.17; H, 5.63; N, 11.53.

*5.4.6.14. N-(3-Fluoro-4-(6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy) quinolin-4-yloxy)phenyl)-4-(4-fluorophenyl)pyrimidine-2-carboxamide (**25n**).* Yield: 59%; m.p. 138–139 °C; MS (ESI) *m/z* (%): 612.3 $[M + H]^+$, 634.6 $[M + Na]^+$; ^1H NMR (300 MHz, $CDCl_3$) δ 9.99 (s, 1H), 9.28 (s, 1H), 8.57 (s, 1H), 8.48 (d, J = 5.3 Hz, 1H), 8.24 (dd, J = 8.7, 5.3 Hz, 2H), 7.96 (dd, J = 11.9, 2.2 Hz, 1H), 7.56 (s, 1H), 7.49 (d, J = 8.9 Hz, 1H), 7.43 (s, 1H), 7.28 (d, J = 8.5 Hz, 1H), 7.21 (d, J = 8.8 Hz, 2H), 6.42 (d, J = 5.3 Hz, 1H), 4.27 (t, J = 6.6 Hz, 2H), 4.01 (s, 3H), 2.67 (t, J = 7.2 Hz, 2H), 2.54 (br, 4H), 2.20–2.08 (m, 2H), 1.77 (br, 4H). Anal. calcd. for $C_{34}H_{31}F_2N_5O_4$ (%): C, 66.77; H, 5.11; N, 11.45. Found (%): C, 66.76; H, 5.09; N, 11.46.

5.5. Pharmacology

5.5.1. MTT assay in vitro

The anti-proliferative activities of compounds **18a**–**ad** and **25a**–**n** were evaluated against HT-29, H460, MKN-45, A549 and U87MG cell lines using the standard MTT assay *in vitro*, with foretinib as the positive control. The cancer cell lines were cultured in minimum essential medium (MEM) supplemented with 10% fetal bovine serum (FBS). Approximate 4×10^3 cells, suspended in MEM medium, were plated onto each well of a 96-well plate and incubated in 5% CO_2 at 37 °C for 24 h. The compounds tested at the indicated final concentrations were added to the culture medium and the cell cultures were continued for 72 h. Fresh MTT was added to each well at a terminal concentration of 5 μg/mL, and incubated with cells at 37 °C for 4 h. The formazan crystals were dissolved in 100 mL of DMSO each well, and the absorbency at 492 nm (for absorbance of MTT formazan) and 630 nm (for the reference wavelength) was measured with an ELISA reader. All of the compounds were tested three times in each cell line. The results expressed as IC_{50} (inhibitory concentration 50%) were the averages of three determinations and calculated by using the Bacus Laboratories Incorporated Slide Scanner (Bliss) software.

5.5.2. Tyrosine kinases assay

The tyrosine kinases activities were evaluated using homogeneous time-resolved fluorescence (HTRF) assays, as previously reported protocol [28,29]. Briefly, 20 μg/mL poly (Glu, Tyr) 4:1 (Sigma) was preloaded as a substrate in 384-well plates. Then 50 μL of 10 mM ATP (Invitrogen) solution diluted in kinase reaction buffer (50 mM HEPES, pH 7.0, 1 M DTT, 1 M $MgCl_2$, 1 M $MnCl_2$, and 0.1% NaN_3) was added to each well. Various concentrations of compounds diluted in 10 μL of 1% DMSO (v/v) were used as the negative control. The kinase reaction was initiated by the addition of purified tyrosine kinase proteins diluted in 39 μL of kinase reaction buffer solution. The incubation time for the reactions was 30 min at 25 °C, and the reactions were stopped by the addition of 5 μL of Streptavidin-XL665 and 5 μL Tk Antibody Cryptate working solution to all of wells. The plates were read using Envision (PerkinElmer) at 320 nm and 615 nm. The inhibition rate (%) was calculated using the following equation: % inhibition = 100 − [(activity of enzyme with tested compounds − Min)/(Max − Min)] × 100 (Max: the observed enzyme activity measured in the presence of enzyme, substrates, and cofactors; Min: the observed enzyme activity in the presence of substrates, cofactors and in the absence of enzyme). IC_{50} values were calculated from the inhibition curves.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.ejmech.2013.08.019.

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