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Original article

Design, synthesis and antitumour activity of bisquinoline derivatives connected by 4-oxy-3-fluoroaniline moiety

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ABSTRACT

A series of novel bisquinoline derivatives connected by a 4-oxy-3-fluoroaniline moiety were synthesized and evaluated for their *in vitro* antitumour activities against a panel of five cancer cell lines (H460, HT-29, MKN-45, U87MG, and SMMC-7721). Most of compounds tested showed a potent activity and high selectivity towards the H460 and MKN-45 cell lines. Among the compounds tested, six (**15d**, **15e**, **15m**, **15n**, **16a**, and **16i**) were further examined for their c-Met kinase activity; the compounds showed high efficacy with IC_{50} values in the single-digit nM range. An analysis of structure–activity relationships indicated that an unsubstituted or a halogen-substituted phenyl ring on the 2-arylquinoline-4-carboxamide moiety was favourable for antitumour activity.

1. Introduction

The leading causes of death worldwide remain cardiovascular disease and cancer, although a recent report disclosed a tendency for an increase in cancer mortality [1,2]. Although cancer chemotherapy has entered a new era of molecularly targeted therapeutics, drug resistance and side effects remain serious problems [3,4]. Therefore, the search for safer and more efficient chemotherapeutic agents is very important [5].

Foretinib (**1**, Fig. 1), a novel oral multi-kinase inhibitor targeting c-Met, vascular endothelial growth factor receptor 2 (VEGFR-2), RON, KDR, and Flt-1, is currently undergoing phase II clinical trials for different types of cancer [6]. Due to its dual mechanism of action and broad-spectrum anticancer potency, researchers drew attention to the optimization of foretinib. In the past few years, a variety of 4-(2-fluorophenoxy) quinoline derivatives have been reported as potent c-Met kinase inhibitors [7–12]. During the course of studying these analogues (Fig. 1) [13–15], we found that modification of moiety A usually occurs at position 7 of quinoline, where the methoxy group is replaced by a water-soluble fragment, such as 3-morpholinopropoxy group. Furthermore, the modification of the linker is variable, but the reported linkers have two common characteristics, namely, a distance of six chemical bonds between moiety A and moiety B, which is known as '5 atoms regulation', and the linker contains both a hydrogen-bond donor or acceptor and at least one amide group. In contrast, there is little change to B moiety except for a phenyl ring or a substituted phenyl ring. These structural characteristics suggest that exploring a satisfactory linker is a practicable way of designing this series of quinoline derivatives.

To date, many studies have reported that compounds with a 2-arylquinoline-4-carboxamide framework display a multitude of biological activities, including antitumour, antiviral, and anti-inflammatory activities [16–18]. A novel candidate for the signal transducer and activator of transcription 3 (STAT3) inhibitor, STX-0119 (**I**, Fig. 2), displays a potent anti-proliferative effect with an IC_{50} of 5–10 μM on haematological cancer cells *in vitro*, as well as potent antitumour activity *in vivo* in SCC3-bearing nude mice through down-regulation of STAT3 target genes and induction of apoptosis in the tumours [16,19,20]. Interestingly, the 2-arylquinoline-4-carboxamide skeleton conformed to the two structural characteristics of the linkers mentioned above. Based on these observation, we designed a series of bisquinoline derivatives connected by a 4-oxy-3-fluoroaniline moiety (**II**, Fig. 2), in which the A moiety of foretinib was preserved, and the 2-phenylquinoline-4-carboxamide framework was attached to the C-4′ position of the A moiety as the linker and B moiety. In addition, the morpholinyl group was replaced by other water-soluble substituents, including piperidinyl, pyrrolidinyl, and 4-methyl piperidinyl groups. Furthermore, various substituents (R_3), especially mono-electron-withdrawing groups (mono-EWGs), such as halogen atoms (F and

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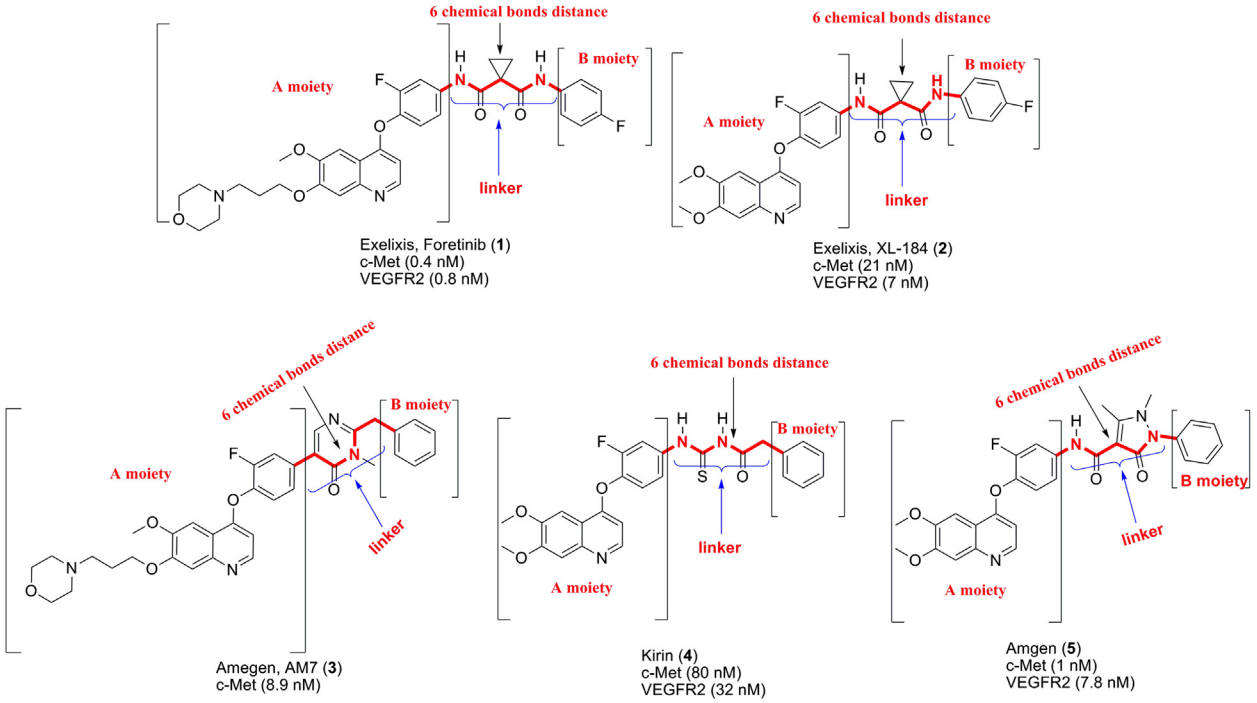


Fig. 1. Structures of foretinib and other 4-(2-fluorophenoxy)quinoline derivatives.

Cl), were introduced into the phenyl ring (B moiety) to investigate their effect on activity. In this study, we report newly synthesized target compounds and their *in vitro* antitumour activities against five human cancer cell lines and c-Met kinase.

2. Chemistry

The key intermediates **8a**–**d** were synthesized using the convenient eight-step procedure starting from 1-(4-hydroxy-3-methoxyphenyl)ethanone depicted in Scheme 1. Commercially available acetophenone was alkylated with 1-bromo-3-chloropropane in acetone under basic conditions to give intermediate **1** [21], which was converted to nitro-ketone **2** by using fuming nitric acid as a nitration reagent in dichloromethane at −20 °C for 6 h, with a 70% yield [22]. Then, condensation of **2** with dimethyl formamide dimethyl acetal (DMF–DMA) in refluxing toluene provided yellow solid **3** [23], which was reduced and cyclized using glacial acetic acid and iron powder to afford hydroxy-quinoline **4**, with a high yield and purity in a single step [24]. The reaction of **4** with excessive secondary amines (piperidine, 4-methyl piperidine, morpholine, and pyrrolidine) in acetonitrile at reflux provided intermediates **5a**–**d** [25], which were converted to chloro-quinolines **6a**–**d** by refluxing in the mixed solvent of phosphorus oxychloride and acetonitrile in sequence [26]. Next, the etherification reaction of **6a**–**d** with 2-fluoro-4-nitrophenol afforded purified **7a**–**d**, which were reduced using iron powder and catalytic amounts of ammonium chloride in ethanol to obtain amides **8a**–**d**.

Target compounds **15a**–**s** and **16a**–**n** were prepared as outlined in Scheme 2. The side chains **13a**–**h** and **14a**–**g** were synthesized from aniline and 4-fluoroaniline, which refluxed with chloralic hydras and hydroxylamine hydrochloride in the diluted aqueous solution of hydrogen chloride to afford indoline-2,3-dione **9** and 5-fluoro-indoline-2,3-dione **10**, respectively [27]. Subsequently, via Pfitzinger–Borsche reaction with variously

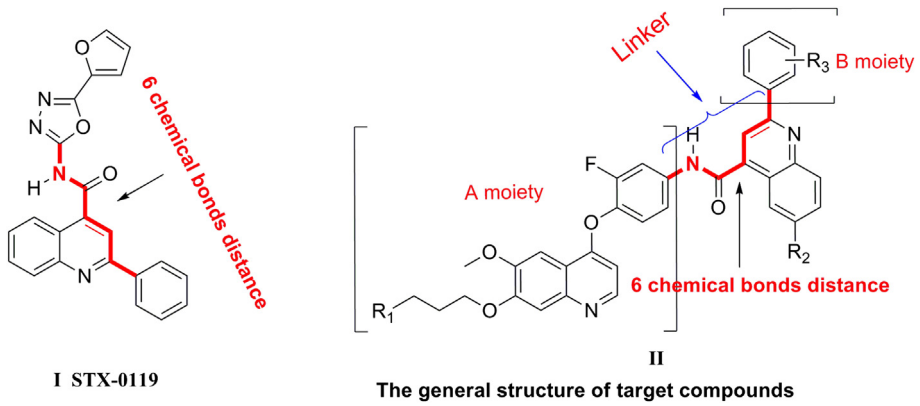
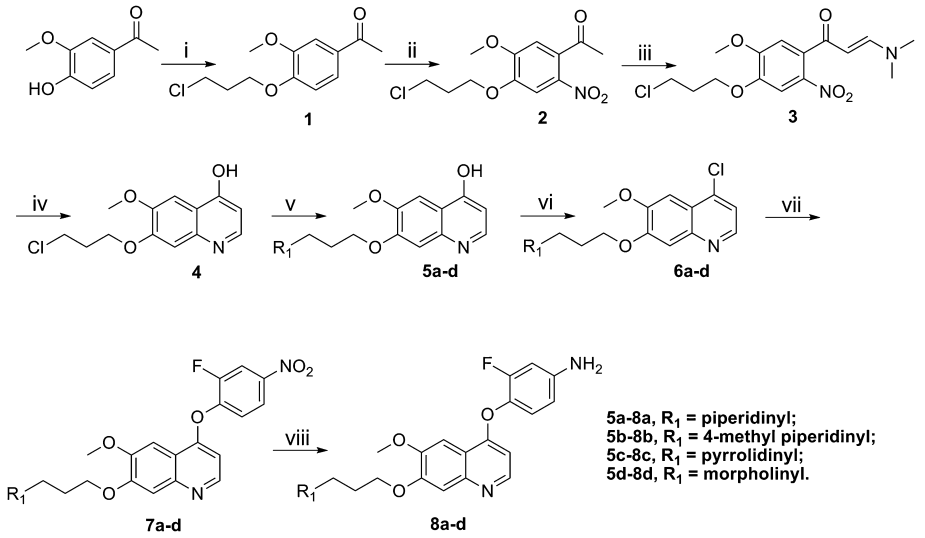


Fig. 2. Structure of STX-0119 and the target compounds.



Scheme 1. Reagents and conditions: (i) $Br(CH_2)_3Cl$, $(CH_3)_2CO$, K_2CO_3, r.t.; (ii) fuming HNO_3, CH_2Cl_2, −20 °C; (iii) DMF–DMA, PhMe, 110 °C; (iv) Fe, HOAc, 85 °C; (v) amine, CH_3CN, reflux; (vi) $POCl_3$, CH_3CN, 85 °C; (vii) 2-fluoro-4-nitrophenol, PhCl, reflux; (viii) Fe, NH_4Cl, EtOH, reflux.

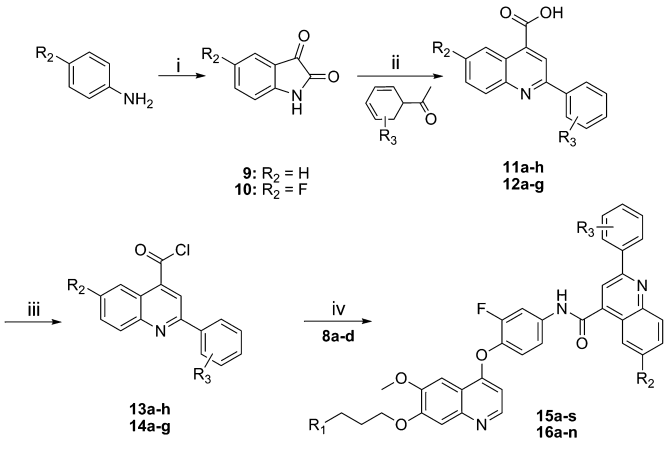
substituted acetophenone in the presence of potassium hydroxide as the base, compounds **9** and **10** were separately converted to acids **11a**–**h** and **12a**–**g**, which were further treated with dichlorosulfoxide to provide acyl chlorides **13a**–**h** and **14a**–**g** in sequence [28].

Finally, compounds **15a**–**s** and **16a**–**n** were successfully obtained via the reaction of the amides **8a**–**d** with **13a**–**h** or **14a**–**g** in the presence of triethylamine in dichloromethane at room temperature overnight, respectively [28].

3. Results and discussion

3.1. In vitro cytotoxicity and structure–activity relationships

The cytotoxic actions of the target compounds were evaluated against the cancer cells lines H460 (human lung cancer), HT-29



11a, 13a, R_2 = H, R_3 = H;
11b, 13b, R_2 = H, R_3 = 4-OCH_3; **12a, 14a,** R_2 = F, R_3 = H;
11c, 13c, R_2 = H, R_3 = 3-OCH_3; **12b, 14b,** R_2 = F, R_3 = 4-OCH_3;
11d, 13d, R_2 = H, R_3 = 3-Cl; **12c, 14c,** R_2 = F, R_3 = 3-OCH_3;
11e, 13e, R_2 = H, R_3 = 4-CF_3; **12d, 14d,** R_2 = F, R_3 = 3-Cl;
11f, 13f, R_2 = H, R_3 = 4-F; **12e, 14e,** R_2 = F, R_3 = 4-F;
11g, 13g, R_2 = H, R_3 = 4-CH_3; **12f, 14f,** R_2 = F, R_3 = 4-CH_3;
11h, 13h, R_2 = H, R_3 = 3,4-$(Cl)_2$; **12g, 14g,** R_2 = F, R_3 = 2,4-$(Cl)_2$;

Scheme 2. Reagents and conditions: (i) $Cl_3CCH(OH)_2$, Na_2SO_4, $HONH_2{\cdot}HCl$, HCl/H_2O, H_2SO_4, reflux; (ii) KOH/H_2O, reflux; (iii) PhMe, $SOCl_2$, reflux; (iv) CH_2Cl_2, Et_3N, r.t.

(human colon cancer), MKN-45 (human gastric cancer), U87MG (human glioblastoma), and SMMC-7721 (human liver cancer) by using an MTT assay. Using foretinib as the positive control, the results expressed as IC_{50} values are summarized in Tables 1 and 2. The IC_{50} values are the average of at least three independent experiments.

As illustrated in Table 1, all the target compounds showed moderate to excellent cytotoxic activity against the different cancer cells with potencies in the single-digit μM range, suggesting that replacement of the *N*-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide framework of foretinib with the 2-arylquinoline-4-carboxamide moiety maintained the potent cytotoxicity. On the other hand, the introduction of different R_1 groups only slightly altered cytotoxicity, indicating that the R_1 group contributed little to potency. For example, compounds **15e**, **15j**, and **15m** exhibited comparable antitumour activity with IC_{50} values ranging from 0.011 to 0.035 μM against MKN-45 cells. In addition, most of the compounds displayed higher selectivity against H460 and MKN-45 cells than against the other three cell lines. It was worth noting that compounds **15d**, **15e**, **15m**, and **15n** exhibited more potent antitumour activity against all tested cell lines than the positive control foretinib with IC_{50} values ranging from 0.011 to 0.98 μM.

Further analysis clearly revealed that different biological properties were observed when various R_3 groups were introduced into the phenyl ring (moiety B). Compound **15a**, with no substituent on the phenyl ring, displayed strong cytotoxicity with an IC_{50} of 0.11 μM against H460 cells. The introduction of mono-EWGs (**15d**, R_3 = 4-fluoro, IC_{50} = 0.021 μM; **15e**, R_3 = 3-chloro, IC_{50} = 0.011 μM) led to an obvious improvement in antitumour activity, which could be further confirmed by compounds **15g**, **15j**, and **15k**. However, the introduction of double-electron-withdrawing groups (double-EWGs) (**15f**, 3,4-dichloro, IC_{50} = 0.82 μM) or electron-donating groups (EDGs) (**15b**, 4-methoxy, IC_{50} = 0.29 μM; **15c**, 3-methoxy, IC_{50} = 0.21 μM) reduced activity by 7.4-, 2.2-, and 1.9-fold, respectively. We also demonstrated that no substitution and mono-EWGs had a positive effect on the cytotoxic activity, but double-EWGs and EDGs had a negative effect. Moreover, it is worth mentioning that the position of the R_3 group was also closely related to the cytotoxicity. Compounds with a substituent at position 3 of the phenyl

Table 1
Cytotoxicity of compounds **15a**–**15s** against H460, HT-29, MKN-45, U87MG and SMMC-7721 cell lines *in vitro*.

Compd.	R_1	R_2	R_3	IC_{50} (μmol/L) ± SD				
				H460	HT-29	MKN-45	U87MG	SMMC-7721
15a		H	H	0.11 ± 0.02	0.53 ± 0.06	0.015 ± 0.002	1.49 ± 0.30	0.29 ± 0.07
15b		H	4-OCH_3	0.29 ± 0.03	0.69 ± 0.10	0.21 ± 0.03	1.36 ± 0.25	0.21 ± 0.04
15c		H	3-OCH_3	0.21 ± 0.04	1.74 ± 0.32	0.36 ± 0.07	ND	0.38 ± 0.05
15d		H	4-F	0.021 ± 0.005	0.13 ± 0.03	0.028 ± 0.005	0.98 ± 0.15	0.074 ± 0.01
15e		H	3-Cl	0.011 ± 0.002	0.062 ± 0.01	0.011 ± 0.003	0.15 ± 0.03	0.03 ± 0.004
15f		H	3,4-$(Cl)_2$	0.82 ± 0.10	1.21 ± 0.15	0.73 ± 0.10	ND	0.77 ± 0.08
15g		H	H	0.19 ± 0.03	1.52 ± 0.35	0.091 ± 0.01	1.14 ± 0.20	0.33 ± 0.07
15h		H	4-OCH_3	0.75 ± 0.09	3.19 ± 0.50	0.16 ± 0.01	ND	1.18 ± 0.31
15i		H	3-OCH_3	0.56 ± 0.09	3.05 ± 0.62	0.11 ± 0.02	ND	1.13 ± 0.15
15j		H	3-Cl	0.08 ± 0.02	1.08 ± 0.15	0.035 ± 0.005	1.47 ± 0.22	0.32 ± 0.05
15k		H	4-CF_3	0.068 ± 0.01	0.23 ± 0.03	0.012 ± 0.002	1.01 ± 0.17	0.10 ± 0.02
15l		H	4-CH_3	1.10 ± 0.20	3.56 ± 0.50	0.83 ± 0.11	ND	1.52 ± 0.21
15m		H	3-Cl	0.065 ± 0.01	0.10 ± 0.01	0.030 ± 0.007	0.58 ± 0.08	0.08 ± 0.01
15n		H	H	0.068 ± 0.01	0.12 ± 0.02	0.019 ± 0.003	0.92 ± 0.15	0.16 ± 0.03
15o		H	4-OCH_3	0.11 ± 0.01	1.11 ± 0.15	0.32 ± 0.05	ND	0.45 ± 0.06
15p		H	4-CH_3	0.88 ± 0.10	3.15 ± 0.46	0.77 ± 0.08	ND	1.26 ± 0.23
15q		H	3,4-$(Cl)_2$	0.40 ± 0.04	1.96 ± 0.25	0.17 ± 0.02	ND	0.34 ± 0.05
15r		H	3-OCH_3	0.29 ± 0.05	1.02 ± 0.09	0.43 ± 0.10	ND	0.79 ± 0.05
15s		H	4-CH_3	0.24 ± 0.04	0.85 ± 0.12	0.30 ± 0.05	ND	0.52 ± 0.06
Foretinib				0.12 ± 0.01	0.18 ± 0.03	0.031 ± 0.005	1.04 ± 0.15	0.30 ± 0.04

ND: Not determined.

ring (**15i**, IC_{50} = 0.56 μM [H460]) displayed a higher potency than those with a substituent at position 4 of the ring (**15h**, IC_{50} = 0.75 μM [H460]).

The data presented in Table 2 indicate that the cytotoxicity for compounds **16a**–**n** is generally higher than that for the corresponding compounds **15a**–**s**, suggesting that the introduction of the 6-fluoro group to the 2-arylquinoline-4-carboxamide moiety is favourable for activity. In addition, it is interesting to note that derivatives **16a**–**n** have structure–activity relationships (SARs) similar to analogues **15a**–**s**. The difference in the cytotoxicity observed in the H460 cell line between compounds with different R_1 groups was minor (**16b**, R_1 = piperidinyl, IC_{50} = 1.00 μM, vs. **16j**, R_1 = 4-methyl piperidinyl, IC_{50} = 0.84 μM); the introduction of mono-EWGs to the phenyl ring had a positive effect on the activity (e.g. **16a**, R_3 = H, IC_{50} = 0.032 μM; **16f**, R_3 = 4-F, IC_{50} = 0.027 μM), while the addition of EDGs caused an adverse effect (**16b**, R_3 = 3-OCH_3, IC_{50} = 1.00 μM).

Table 2
Cytotoxicity of compounds **16a**–**16n** against H460, HT-29, MKN-45, and U87MG cell lines *in vitro*.

Compd.	R_1	R_2	R_3	IC_{50} (μmol/L) ± SD			
				H460	HT-29	MKN-45	U-87MG
16a		F	H	0.032 ± 0.005	0.12 ± 0.02	0.030 ± 0.004	0.69 ± 0.10
16b		F	3-OCH_3	1.00 ± 0.11	2.50 ± 0.30	0.69 ± 0.15	1.61 ± 0.25
16c		F	4-CH_3	0.26 ± 0.03	0.50 ± 0.08	0.17 ± 0.03	1.05 ± 0.27
16d		F	4-OCH_3	0.24 ± 0.04	0.60 ± 0.05	0.26 ± 0.05	1.10 ± 0.20
16e		F	2,4-$(Cl)_2$	0.31 ± 0.05	0.53 ± 0.10	0.25 ± 0.03	1.04 ± 0.15
16f		F	4-F	0.027 ± 0.003	0.25 ± 0.06	0.051 ± 0.01	2.15 ± 0.30
16g		F	3-Cl	0.068 ± 0.01	1.20 ± 0.30	0.060 ± 0.01	1.06 ± 0.11
16h		F	4-CH_3	0.44 ± 0.03	0.39 ± 0.05	0.32 ± 0.05	0.82 ± 0.11
16i		F	3-Cl	0.06 ± 0.001	0.092 ± 0.02	0.010 ± 0.001	0.11 ± 0.015
16j		F	3-OCH_3	0.84 ± 0.10	1.21 ± 0.15	0.73 ± 0.08	0.84 ± 0.11
16k		F	4-CH_3	0.48 ± 0.07	0.42 ± 0.08	0.26 ± 0.04	2.00 ± 0.45
16l		F	H	0.09 ± 0.002	0.16 ± 0.02	0.11 ± 0.01	0.96 ± 0.11
16m		F	3-Cl	0.072 ± 0.01	0.67 ± 0.11	0.067 ± 0.01	0.99 ± 0.20
16n		F	4-OCH_3	0.25 ± 0.03	0.61 ± 0.09	0.17 ± 0.03	0.93 ± 0.12
Foretinib				0.12 ± 0.01	0.18 ± 0.03	0.031 ± 0.005	1.04 ± 0.15

3.2. In vitro enzymatic assays

As shown in Table 3, the six tested compounds all exhibited excellent c-Met enzymatic potency with IC_{50} values in the single-digit nM range, suggesting that the inhibition of c-Met may be a mechanism for the antitumour effect of these derivatives. The potency of compound **15e** was the highest and comparable to that of the positive control foretinib (IC_{50} values, 1.32 nM vs. 1.16 nM, respectively), indicating that this compound deserves further investigation.

Table 3
c-Met kinase activity of selected compounds **15d**, **15e**, **15m**, **15n**, **16a** and **16i** *in vitro*.

Compd.	IC_{50} on c-met (nM)
15d	2.64
15e	1.32
15m	3.13
15n	2.72
16a	3.45
16i	1.65
Foretinib	1.16

4. Conclusions

In summary, we designed and prepared a series of novel bis-quinoline derivatives connected by a 4-oxy-3-fluoroaniline moiety. The synthesized compounds were evaluated for cytotoxic activity in five human cancer cell lines. Our preliminary investigation showed that most compounds had good to excellent activity with higher selectivity against H460 and MKN-45 cells than against HT-29, U87MG, and SMMC-7721 cells. In particular, compounds **15d**, **15e**, **15m**, **15n**, **16a**, and **16i** exhibited more potent activity against all five human cancer cell lines than foretinib, and their strong c-Met kinase inhibitory potency suggested that this series of compounds may act via inhibition of c-Met. The SAR analyses indicated that compounds with no substituent or mono-EWGs on the phenyl ring were more active than those with double-EWGs or EDGs. In addition, the introduction of a fluoro group at position 6 of the 2-aryl quinoline-4-carboxamide framework led to a slight

improvement in activity. Further studies on the structural optimization of these derivatives are currently underway in our laboratory.

5. Experimental

5.1. Chemistry

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). Proton (^{1}H) nuclear magnetic resonance spectroscopy was performed using Bruker ARX-300, 300 MHz spectrometers (Bruker Bioscience, Billerica, MA, USA) with TMS as an internal standard. Column chromatography was run on silica gel (200–300 mesh) from Qingdao Ocean Chemicals (Qingdao, Shandong, China). Unless otherwise noted, all materials were obtained from commercially available sources and were used without further purification.

5.2. 1-(4-(3-Chloropropoxy)-3-methoxyphenyl)ethanone (**1**)

A stirred solution of 1-(4-hydroxy-3-methoxyphenyl)ethanone (24.9 g, 0.15 mol) and anhydrous potassium carbonate (57.9 g, 0.21 mol) in acetone was added drop-wise with an acetone solution of 1-bromo-3-chloropropane (66.1 g, 4.2 mol, in 200 mL acetone) while maintaining the temperature below 25 °C. Upon completion of the addition, the reaction mixture was stirred at room temperature overnight. The solid was removed by filtration, and the filtrate was poured slowly into 1 L of ice water, which was stirred vigorously. A lot of precipitated white solid was filtered and dried in vacuo at 40 °C for 24 h to yield the target compound (69.5 g, yield: 92.5%). M.p. 71–73 °C; MS (ESI) *m*/*z* (%): 264.8 $[M + Na]^+$.

5.3. 1-(4-(3-Chloropropoxy)-5-methoxy-2-nitrophenyl)ethanone (**2**)

To a solution of 1-(4-(3-chloropropoxy)-3-methoxyphenyl)ethanone **1** (35 g, 0.14 mol) in dichloromethane (150 mL), fuming nitric acid (10 mL, 0.28 mol) was added drop-wise at a rate to maintain the reaction temperature below 0 °C. Upon the completion of addition, the mixture was stirred at 0 °C for another 4 h. The reaction mixture was poured slowly into the mixed solution of cold water (200 mL) and dichloromethane (100 mL). The organic layer was separated and washed with brine (600 mL × 5), dried with anhydrous sodium sulphate and evaporated. The residue was cooled and dried at room temperature to give a light yellow solid (360 g, yield: 86.7%). M.p. 60–61 °C; MS (ESI) *m*/*z* (%): 288.0 $[M + H]^+$, 310.0 $[M + Na]^+$.

5.4. (E)-1-(4-(3-Chloropropoxy)-5-methoxy-2-nitrophenyl)-3-(dimethylamino)prop-2-en-1-one (**3**)

1-(4-(3-Chloropropoxy)-5-methoxy-2-nitrophenyl)ethanone **2** (36 g, 0.125 mol) was added to toluene (100 mL) and heated to 110 °C. When the mixture became clear, *N*,*N*-dimethylformamide dimethyl acetal (90 mL, 6.25 mol) was poured into the solution and kept reacting for more 10 h. The resulting precipitate from the cooled reaction mixture was filtered to obtain the target compound as a yellow powder (31 g, yield: 72.4%). M.p. 117–119 °C; MS (ESI) *m*/*z* (%): 343.4 $[M + H]^+$, 355.3 $[M + Na]^+$.

5.5. 7-(3-Chloropropoxy)-6-methoxyquinolin-4-ol (**4**)

(*E*)-1-(4-(3-Chloropropoxy)-5-methoxy-2-nitrophenyl)-3-(dimethylamino) prop-2-en-1-one **3** (14.5 g, 0.05 mol) was dissolved in glacial acetic acid (110 mL), and stirred at room temperature. Iron powder was added slowly to keep the temperature below 60 °C. Upon the completion of addition, the reaction mixture was heated to 80 °C for 2 h, and then filtered immediately to remove iron powder. The precipitate was filtered and the filter cake was washed to be colourless with water, and dried at room temperature to obtain a white solid (10.5 g, yield: 78.4%). M.p. 232–233 °C; MS (ESI) *m*/*z* (%): 268.1 $[M + H]^+$, 290.2 $[M + Na]^+$, 557.3 $[2M + Na]^+$.

5.6. General procedure for preparation of 4-hydroxyquinolines (**5a**–**d**)

A stirring solution of 7-(3-chloropropoxy)-6-methoxyquinolin-4-ol (**4**) (10.15 g, 0.032 mol) in acetonitrile (80 mL) at 25 °C was added appropriately secondary amines (0.3 mol), and the resulting reaction mixture was heated to 85 °C for 10 h, then cooled to room temperature and filtered. The light yellow filter cake was kept, and the filtrate was concentrated in vacuum. Ethyl acetate (100 mL) was added to the residue and stirred fully. The turbid fluid was filtered and the cake was combined with the earlier one and recrystallized with ethanol and acetone (2:5) to give the corresponding 4-hydroxyquinolines **5a**–**d**.

5.6.1. 6-Methoxy-7-(3-(piperidin-1-yl)propoxy)quinolin-4-ol (**5a**)

White solid; Yield: 85.5%; M.p. 175–176 °C; MS (ESI) *m*/*z* (%): 317.4 $[M + H]^+$.

5.6.2. 6-Methoxy-7-(3-(4-methylpiperidin-1-yl)propoxy)quinolin-4-ol (**5b**)

Sallow solid; Yield: 93.4%; M.p. 182–183 °C; MS (ESI) *m*/*z* (%): 331.5 $[M + H]^+$.

5.6.3. 6-Methoxy-7-(3-(pyrrolidin-1-yl)propoxy)quinolin-4-ol (**5c**)

Light yellow solid; Yield: 85.5%; M.p. 171–173 °C; MS (ESI) *m*/*z* (%): 303.2 $[M + H]^+$.

5.6.4. 6-Methoxy-7-(3-morpholinopropoxy)quinolin-4-ol (**5d**)

White solid; Yield: 97.6%; M.p. 187–188 °C; MS (ESI) *m*/*z* (%): 319.1 $[M + H]^+$, 659.3 $[2M + Na]^+$.

5.7. General procedure for preparation of 4-chloroquinolines (**6a**–**d**)

To a solution of an appropriate 4-hydroxyquinoline (0.05 mol) in acetonitrile (80 mL) at 85 °C was dropped $POCl_3$ (80 mL), and the resulting mixture was kept at this temperature for 6 h. The solvent was concentrated in vacuum and the residue was poured into stirring ice-water (200 mL), basified with potassium hydroxide to pH 12, and extracted with CH_2Cl_2 (3 × 500 mL). The combined extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuum to give the corresponding 4-chloroquinolines **6a**–**d**.

5.7.1. 4-Chloro-6-methoxy-7-(3-(piperidin-1-yl)propoxy)quinoline (**6a**)

White solid; Yield: 85.4%; M.p. 155–156 °C; MS (ESI) *m*/*z* (%): 335.3 $[M + H]^+$.

5.7.2. 4-Chloro-6-methoxy-7-(3-(4-methylpiperidin-1-yl)propoxy) quinoline (**6b**)

White solid; Yield: 79.7%; M.p. 160–161 °C; MS (ESI) *m*/*z* (%): 349.4 $[M + H]^+$.

5.7.3. 4-Chloro-6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy) quinoline (**6c**)

Yellow solid; Yield: 78.2%; M.p. 158–159 °C; MS (ESI) *m*/*z* (%): 321.2 $[M + H]^+$.

*5.7.4. 4-Chloro-6-methoxy-7-(3-morpholinopropoxy)quinoline (**6d**)*

White solid; Yield: 82.4%; M.p. 162–63 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.57 (d, J = 4.8 Hz, 1H), 7.44 (s, 1H), 7.39 (s, 1H), 7.34 (d, J = 4.8 Hz, 1H), 4.27 (t, J = 6.7 Hz, 2H), 4.04 (s, 3H), 3.72 (m, 4H), 2.57 (t, J = 7.1 Hz, 2H), 2.48 (m, 4H), 2.12 (m, 2H); MS (ESI) m/z (%): 337.4 $[M + H]^+$, 359.4 $[M + Na]^+$.

*5.8. General procedure for preparation of nitro compounds (**7a**–**d**)*

A stirring mixture of an appropriate 4-chloroquinoline (0.2 mol) and 2-fluoro-4-nitrophenol (0.4 mol) in chlorobenzene (450 mL, 5v/w) was heated to 140 °C for 30 h. The resulting mixture was cooled, and filtered. The filter cake was washed with saturated K_2CO_3 solution, and recrystallized with ethanol to give the corresponding nitro compounds **7a**–**d**.

*5.8.1. 4-(2-Fluoro-4-nitrophenoxy)-6-methoxy-7-(3-(piperidin-1-yl)propoxy)quinoline (**7a**)*

Yellowish-white solid; Yield: 90.4%; M.p. 137–138 °C; MS (ESI) m/z (%): 456.4 $[M + H]^+$.

*5.8.2. 4-(2-Fluoro-4-nitrophenoxy)-6-methoxy-7-(3-(4-methylpiperidin-1-yl)propoxy)quinoline (**7b**)*

Yellow solid; Yield: 88.7%; M.p. 133–134 °C; MS (ESI) m/z (%): 470.6 $[M + H]^+$.

*5.8.3. 4-(2-Fluoro-4-nitrophenoxy)-6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy)quinoline (**7c**)*

Yellow solid; Yield: 86.3%; M.p. 140–141 °C; MS (ESI) m/z (%): 442.2 $[M + H]^+$.

*5.8.4. 4-(3-(4-(2-Fluoro-4-nitrophenoxy)-6-methoxyquinolin-7-yloxy)propyl)morpholine (**7d**)*

Light yellow solid; Yield: 82.5%; M.p. 135–136 °C; MS (ESI) m/z (%): 458.4 $[M + 1]^+$, 480.4 $[M + 23]^+$.

*5.9. General procedure for preparation of anilines (**8a**–**d**)*

To a refluxing solution of an appropriate nitro compound (0.1 mol) in EtOH (450 mL, 10v/w) was added saturation NH_4Cl solution (450 mL) and Fe Powder in batches. The mixture was kept at this temperature for more 5 h. After completion of the reaction as indicated by TLC, the mixture was filtered immediately, and the filtrate was cooled, filtered to obtain the corresponding anilines **8a**–**d**.

*5.9.1. 3-Fluoro-4-(6-methoxy-7-(3-(piperdine-1-yl)propoxy) quinolin-4-yloxy) aniline (**8a**)*

Grey solid; Yield: 85.5%; 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 m/z (ESI): 426.3 $[M + H]^+$.

*5.9.2. 3-Fluoro-4-(6-methoxy-7-(3-(4-methylpiperdine-1-yl) propoxy)quinolin-4-yl-oxy)aniline (**8b**)*

White solid; Yield: 77.4%; 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 (%): 440.3 $[M + H]^+$.

*5.9.3. 3-Fluoro-4-(6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy) quinolin-4-yloxy) aniline (**8c**)*

Light yellow solid; Yield: 72.3%; 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 (%): 412.5 $[M + H]^+$.

*5.9.4. 3-Fluoro-4-(6-methoxy-7-(3-morpholinopropoxy)quinolin-4-yloxy)aniline (**8d**)*

White solid; Yield: 81.8%; 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 m/z (ESI): 428.2 $[M + H]^+$, 450.1 $[M + Na]^+$.

*5.10. General procedure for preparation indoline-2, 3-dione (**9** and **10**)*

To a solution of chloralic hydras (45 g, 0.27 mol) in water (100 mL), anhydrous sodium sulphate (286 g), aniline or 4-fluoroaniline hydrochloride (0.25 mol), and hydrochloric acid hydroxyl amine solution (55 g in 250 mL water) were added in sequence. The reaction mixture was heated to 100 °C for 5–10 min, and then cooled to room temperature. The resulting precipitate was filtered and dried to obtain intermediates 2-(hydroxyimino)-*N*-phenylacetamide and *N*-(4-fluorophenl)-2-(hydroxyimino)acetamide, respectively.

2-(Hydroxyimino)-*N*-phenylacetamide or *N*-(4-fluorophenl)-2-(hydroxyimino)acetamide (0.41 mol) was added to a stirring solution of concentrated sulphuric acid (60 mL) slowly to keep the temperature at the range of 60–70 °C. Upon the completion of addition, the mixture was heated to 85 °C for another 10–15 min. The resulting cooling reaction solution was poured into appropriate trash ice and kept stirring for 2 h. The precipitate was filtered, washed with water and dried to afford orange solid **9** and **10**.

*5.10.1. Indoline-2,3-dione (**9**)*

Orange solid; Yield: 32.5%; M.p. 78–79 °C; MS (ESI) m/z (%): 170.0 $[M + Na]^+$.

*5.10.2. 5-Fluoroindoline-2,3-dione (**10**)*

Orange solid; Yield: 32.5%; M.p. 85–86 °C; IR (KBr) cm^{-1}: 3444.7, 3068.4, 2860.9, 1737.0, 1622.6, 1486.3, 1198.0, 846.6, 655.5; ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.03 (s, 1H), 7.46 (m, 1H), 7.41 (m, 1H), 6.93 (dd, J = 8.5, 3.9 Hz, 1H); MS (ESI) m/z (%): 188.1 $[M + Na]^+$.

*5.11. General procedure for preparation of 2-arylquinoline-4-carboxylic acid (**11a**–**h**)*

To a stirring mixtures of indoline-2,3-dione (3.1 g, 0.02 mol) in 33% potassium hydroxide solution (10 mL), various substituted acetophenone (1.1 equiv) in ethanol (30 mL) was dropped slowly. The resulting reaction mixture was heated to 80 °C for 24–72 h, and monitored by TLC. The solvent was concentrated in vacuum and the residue was dissolved by water (100 mL), which was extracted with diethyl ether (100 mL × 3), and the aqueous layer was acidified with glacial acetic acid to pH 5. The resulting precipitate was filtered, dried, and recrystallized with ethanol to yield a series of 2-arylquinoline-4-carboxylic acids **11a**–**h**.

*5.11.1. 2-Phenylquinoline-4-carboxylic acid (**11a**)*

Yellowish white solid; Yield: 46.5%; M.p. 137–138 °C; IR (KBr) cm^{-1}: 3429.3, 3032.2, 2924.3, 2471.5, 1926.9, 1705.2, 1600.9, 1550.2, 1257.3, 893.9, 760.4, 700.0, 646.4; ^1H NMR (300 MHz, DMSO-d_6) δ 13.94 (s, 1H), 8.67 (d, J = 8.2 Hz, 1H), 8.47 (s, 1H), 8.30 (d, J = 6.5 Hz, 2H), 8.18 (d, J = 8.3 Hz, 1H), 7.86 (t, J = 7.6 Hz, 1H), 7.71 (m, 1H), 7.58 (m, 3H); MS (ESI) m/z (%): 247.7 $[M-1]^-$.

*5.11.2. 2-(4-Methoxyphenyl)quinoline-4-carboxylic acid (**11b**)*

Yellowish white solid; Yield: 50.1%; M.p. 153–154 °C; MS (ESI) m/z (%): 277.7 $[M-1]^-$.

*5.11.3. 2-(3-Methoxyphenyl)quinoline-4-carboxylic acid (**11c**)*

Faint yellow solid; Yield: 43.0%; M.p. 151–152 °C; MS (ESI) m/z (%): 277.9 $[M-1]^-$.

*5.11.4. 2-(3-Chlorophenyl)quinoline-4-carboxylic acid (**11d**)*

Light yellow solid; Yield: 47.3%; M.p. 172–173 °C; MS (ESI) m/z (%): 281.8 $[M-1]^-$.

*5.11.5. 2-(4-Trifluoromethyl)phenylquinoline-4-carboxylic acid (**11e**)*

Yellow solid; Yield: 40.5%; M.p. 186–187 °C; MS (ESI) m/z (%): 315.7 $[M-1]^-$.

*5.11.6. 2-(4-Fluorophenyl)quinoline-4-carboxylic acid (**11f**)*

Light yellow solid; Yield: 50.2%; M.p. 145–146 °C; MS (ESI) m/z (%): 265.9 $[M-1]^-$.

*5.11.7. 2-p-Tolylquinoline-4-carboxylic acid (**11g**)*

White solid; Yield: 52.5%; M.p. 124–125 °C; MS (ESI) m/z (%): 262.0 $[M-1]^-$.

*5.11.8. 2-(3,4-Dichlorophenyl)quinoline-4-carboxylic acid (**11h**)*

Light yellow solid; Yield: 47.3%; M.p. 191–192 °C; MS (ESI) m/z (%): 315.8 $[M-1]^-$.

*5.11.9. 6-Fluoro-2-phenylquinoline-4-carboxylic acid (**12a**)*

Light yellow solid; Yield: 42.5%; M.p. 135–136 °C; IR (KBr) cm^{-1}: 3030.6, 2611.5, 1696.0, 1593.5, 1548.2, 1236.8, 930.9, 873.3, 689.3; ^1H NMR (300 MHz, DMSO-d_6) δ 14.13 (s, 1H), 8.55 (s, 1H), 8.48 (dd, J = 11.0, 2.9 Hz, 1H), 8.26 (m, 3H), 7.78 (td, J = 8.7, 2.9 Hz, 1H), 7.58 (m, 3H); MS (ESI) m/z (%): 265.7 $[M-1]^-$.

*5.11.10. 6-Fluoro-2-(4-methoxyphenyl)quinoline-4-carboxylic acid (**12b**)*

White solid; Yield: 48.5%; M.p. 128–129 °C; MS (ESI) m/z (%): 295.8 $[M-1]^-$.

*5.11.11. 6-Fluoro-2-(3-methoxyphenyl)quinoline-4-carboxylic acid (**12c**)*

White solid; Yield: 46.1%; M.p. 124–125 °C; IR (KBr) cm^{-1}: 3528.0, 3073.5, 2935.5, 2837.7, 2555.7, 2014.1, 1698.1, 1584.7,1222.1, 1044.0, 884.4, 699.9; ^1H NMR (300 MHz, DMSO-d_6) δ 8.49 (m, 2H), 8.21 (dd, J = 9.2, 5.8 Hz, 1H), 7.78 (m, 3H), 7.49 (t, J = 8.0 Hz, 1H), 7.10 (d, J = 7.3 Hz, 1H), 3.89 (s, 3H); MS (ESI) m/z (%): 295.7 $[M-1]^-$.

*5.11.12. 2-(3-Chlorophenyl)-6-fluoroquinoline-4-carboxylic acid (**12d**)*

Light yellow solid; Yield: 40.4%; M.p. 162–163 °C; IR (KBr) cm^{-1}: 3425.8, 3113.4, 2855.2, 2515.4, 1967.1, 1720.8, 1554.7, 1247.0, 881.8, 680.8; ^1H NMR (300 MHz, DMSO-d_6) δ 14.06 (s, 1H), 8.55 (s, 1H), 8.45 (m, 1H), 8.32 (s, 1H), 8.25 (m, 2H), 7.78 (m, 1H), 7.59 (s, 2H); MS (ESI) m/z (%): 299.7 $[M-1]^-$.

*5.11.13. 6-Fluoro-2-(4-fluorophenyl)quinoline-4-carboxylic acid (**12e**)*

Light yellow solid; Yield: 47.1%; M.p. 158–159 °C; MS (ESI) m/z (%): 283.7 $[M-1]^-$.

*5.11.14. 6-Fluoro-2-p-tolyquinoline-4-carboxylic acid (**12f**)*

White solid; Yield: 52.7%; M.p. 119–120 °C; IR (KBr) cm^{-1}: 3428.2, 2922.9, 2515.7, 1923.3, 1712.2, 1549.2, 1233.1, 831.3, 677.5; ^1H NMR (300 MHz, DMSO-d_6) δ 8.48 (s, 2H), 8.19 (t, J = 8.4 Hz, 3H), 7.74 (t, J = 7.5 Hz, 1H), 7.38 (d, J = 7.8 Hz, 2H), 2.40 (s, 3H); MS (ESI) m/z (%): 279.5 $[M-1]^-$.

*5.11.15. 2-(2,4-Dichlorophenyl)-6-fluoroquinoline-4-carboxylic acid (**12g**)*

Light yellow solid; Yield: 41.5%; M.p. 188–189 °C; MS (ESI) m/z (%): 334.1 $[M-1]^-$.

*5.12. General procedure for preparation of 2-arylquinoline-4-carbonyl chloride (**13a–h** and **14a–g**)*

Various substituted 2-arylquinoline-4-carboxylic acids **11a–h** and **12a–g** (0.01 mol) were added to thionyl chloride (15 mL), respectively, and refluxed for 5–7 h. The reaction mixture was evaporated to yield corresponding 2-arylquinoline-4-carbonyl chloride **13a–h** and **14a–g**.

*5.13. General procedure for preparation of the target compounds (**15a–s** and **16a–n**)*

To a mixture of an appropriate aniline **8a–d** (0.48 mmol), diisopropylethylamine (0.58 mmol) and dichloromethane (10 mL) in an ice bath, an appropriate carbonyl chloride **13a–h** or **14a–g** (0.52 mol) was dissolved in dried dichloromethane (10 mL) to add drop-wise. Upon the completion of addition, the reaction mixture was removed to room temperature for 10 h and monitored by TLC. The mixture was washed with 10% K_2CO_3 (20 mL × 3), brine (20 mL × 3) in sequence, and the organic phase was separated, dried, and evaporated. The crude product was purified by chromatography on silica gel using CH_2Cl_2/MeOH (40:1) to afford the target compounds **15a–s** and **16a–n**.

*5.13.1. N-(3-Fluoro-4-(6-methoxy-7-(3-(piperidin-1-yl)propoxy) quinolin-4-yloxy)phenyl)-2-phenylquinoline-4-carboxamide (**15a**)*

Yield: 62%; M.p.: 138–139 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 9.42 (s, 1H), 8.43 (d, J = 5.2 Hz, 1H), 8.13 (m, 5H), 7.96 (s, 1H), 7.74 (t, J = 7.4 Hz, 1H), 7.64 (d, J = 8.0 Hz, 1H), 7.54 (d, J = 6.1 Hz, 2H), 7.49 (d, J = 5.2 Hz, 3H), 7.36 (s, 1H), 7.30 (d, J = 7.2 Hz, 1H), 6.41 (d, J = 4.9 Hz, 1H), 4.13 (s, 2H), 4.03 (s, 3H), 2.65 (s, 2H), 2.55 (s, 4H), 2.16 (m, 2H), 1.65 (s, 4H), 1.45 (s, 2H); MS (ESI) m/z (%): 657.0 $[M+H]^+$; Anal. calcd. for $C_{40}H_{37}FN_4O_4$ (%): C, 73.15; H, 5.68; N, 8.53. Found (%): C, 73.26; H, 5.60; N, 8.44.

*5.13.2. N-(3-Fluoro-4-(6-methoxy-7-(3-(piperidin-1-yl)propoxy) quinolin-4-yloxy)phenyl)-2-(4-methoxyphenyl)quinoline-4-carboxamide (**15b**)*

Yield: 72%; M.p.: 145–146 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 8.83 (s, 1H), 8.43 (d, J = 5.3 Hz, 1H), 8.05 (m, 3H), 7.95 (d, J = 8.8 Hz, 2H), 7.74 (s, 1H), 7.68 (t, J = 7.6 Hz, 1H), 7.53 (d, J = 7.4 Hz, 2H), 7.44 (t, J = 7.6 Hz, 1H), 7.32 (s, 1H), 7.27 (t, J = 8.6 Hz, 1H), 6.94 (d, J = 8.8 Hz, 2H), 6.39 (d, J = 5.1 Hz, 1H), 4.14 (t, J = 6.6 Hz, 2H), 3.99 (s, 3H), 3.83 (s, 3H), 2.52 (m, 2H), 2.42 (s, 4H), 2.08 (m, 2H), 1.56 (m, 4H), 1.41 (d, J = 5.3 Hz, 2H); MS (ESI) m/z (%): 687.0 $[M+H]^+$; Anal. calcd. for $C_{41}H_{39}FN_4O_5$ (%): C, 71.70; H, 5.72; N, 8.16. Found (%): C, 71.78; H, 5.69; N, 8.20.

*5.13.3. N-(3-Fluoro-4-(6-methoxy-7-(3-(piperidin-1-yl)propoxy) quinolin-4-yloxy)phenyl)-2-(3-methoxyphenyl)quinoline-4-carboxamide (**15c**)*

Yield: 69%; M.p.: 147–148 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.71 (s, 1H), 8.41 (d, J = 5.3 Hz, 1H), 8.11 (m, 2H), 7.98 (m, 1H), 7.82 (s, 1H), 7.71 (m, 1H), 7.62 (m, 1H), 7.50 (q, J = 7.0 Hz, 4H), 7.34 (m, 2H), 7.26 (t, J = 8.7 Hz, 1H), 6.97 (dd, J = 7.9, 2.2 Hz, 1H), 6.38 (d, J = 5.0 Hz, 1H), 4.13 (t, J = 6.6 Hz, 2H), 3.99 (s, 3H), 3.85 (s, 3H), 2.49 (t, J = 4.5 Hz, 2H), 2.39 (s, 4H), 2.07 (m, 2H), 1.54 (m, 4H), 1.40 (d, J = 4.9 Hz, 2H); MS (ESI) m/z (%): 687.0 $[M + H]^+$; Anal. calcd. for $C_{41}H_{39}FN_4O_5$ (%): C, 71.70; H, 5.72; N, 8.16. Found (%): C, 71.75; H, 5.70; N, 8.19.

*5.13.4. N-(3-Fluoro-4-(6-methoxy-7-(3-(piperidin-1-yl)propoxy) quinolin-4-yloxy)phenyl)-2-(4-fluorophenyl)quinoline-4-carboxamide (**15d**)*

Yield: 74%; M.p.: 162–163 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.71 (d, J = 7.0 Hz, 1H), 8.49 (d, J = 4.6 Hz, 1H), 8.18 (m, 3H), 8.06 (d, J = 8.8 Hz, 2H), 7.91 (d, J = 11.2 Hz, 1H), 7.78 (m, 1H), 7.58 (m, 3H), 7.39 (s, 1H), 7.34 (d, J = 8.7 Hz, 1H), 7.19 (t, J = 7.4 Hz, 1H), 7.01 (d, J = 8.7 Hz, 1H), 6.45 (s, 1H), 4.21 (t, J = 6.3 Hz, 2H), 4.06 (s, 3H), 2.59 (s, 2H), 2.48 (s, 4H), 2.15 (m, 2H), 1.64 (s, 4H), 1.47 (d, J = 6.8 Hz, 2H); MS (ESI) m/z (%): 675.0 $[M + H]^+$; Anal. calcd. for $C_{40}H_{36}F_2N_4O_4$ (%): C, 71.20; H, 5.38; N, 8.30. Found (%): C, 71.28; H, 5.30; N, 8.26.

*5.13.5. 2-(3-Chlorophenyl)-N-3-fluoro-4-6-methoxy-7-(3-(piperdin-1-yl)propoxy)quinoline-4-carboxamide (**15e**)*

Yield: 63%; M.p.: 190–191 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.36 (s, 1H), 8.38 (d, J = 4.9 Hz, 1H), 8.23 (d, J = 8.4 Hz, 1H), 8.18 (s, 1H), 8.12 (d, J = 8.5 Hz, 1H), 8.01 (d, J = 6.1 Hz, 3H), 7.71 (t, J = 7.6 Hz, 1H), 7.55 (d, J = 7.4 Hz, 2H), 7.49 (s, 1H), 7.38 (d, J = 4.8 Hz, 2H), 7.22 (s, 2H), 6.35 (d, J = 4.8 Hz, 1H), 4.00 (t, J = 5.3 Hz, 2H), 3.93 (s, 3H), 2.90 (m, 6H), 2.24 (s, 2H), 1.80 (s, 4H), 1.49 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 170.91, 160.07, 159.51, 155.12, 153.47, 151.78, 149.63, 148.77, 146.56, 142.36, 138.49, 137.02, 136.80, 134.76, 133.90, 131.25, 130.05, 128.26, 127.33, 125.94, 125.60, 123.65, 121.62, 117.46, 116.62, 115.67, 109.97, 109.81, 108.83, 102.36, 99.71, 66.55, 56.05, 55.34, 53.81 (2C), 24.64, 23.89 (2C), 22.91; MS (ESI) m/z (%): 691.3 $[M + H]^+$; Anal. calcd. for $C_{40}H_{36}ClFN_4O_4$ (%): C, 69.51; H, 5.25; N, 8.11. Found (%): C, 69.55; H, 5.30; N, 8.10.

*5.13.6. 2-(3,4-Chlorophenyl)-N-3-fluoro-4-6-methoxy-7-(3-(piperdin-1-yl)propoxy)quinoline-4-carboxamide (**15f**)*

Yield: 55%; M.p.: 195–196 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.91 (s, 1H), 8.36 (d, J = 5.3 Hz, 1H), 8.11 (m, 3H), 7.93 (d, J = 11.9 Hz, 1H), 7.82 (m, 2H), 7.72 (t, J = 7.7 Hz, 1H), 7.54 (d, J = 7.1 Hz, 1H), 7.47 (d, J = 8.3 Hz, 3H), 7.24 (d, J = 10.5 Hz, 2H), 6.33 (d, J = 5.1 Hz, 1H), 4.05 (t, J = 6.6 Hz, 2H), 3.95 (s, 3H), 2.47 (t, J = 6.1 Hz, 2H), 2.38 (s, 4H), 2.03 (m, 2H), 1.53 (m, 4H), 1.38 (d, J = 4.4 Hz, 2H); MS (ESI) m/z (%): 724.9 $[M + H]^+$; Anal. calcd. for $C_{40}H_{35}Cl_2FN_4O_4$ (%): C, 66.21; H, 4.86; N, 7.72. Found (%): C, 66.25; H, 4.88; N, 7.70.

*5.13.7. N-(3-Fluoro-4-(6-methoxy-7-(3-morpholinopropoxy) quinolin-4-yloxy)phenyl)-2-phenylquinoline-4-carboxamide (**15g**)*

Yield: 63%; M.p.: 140–141 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.92 (s, 1H), 8.49 (d, J = 5.3 Hz, 1H), 8.18 (d, J = 8.3 Hz,1H), 8.12 (d, J = 8.4 Hz, 1H), 8.04 (m, 3H), 7.85 (s, 1H), 7.77 (m, 1H), 7.57 (m, 3H), 7.50 (m, 3H), 7.39 (s, 1H), 7.33 (t, J = 8.7 Hz, 1H), 6.46 (d, J = 5.1 Hz, 1H), 4.23 (t, J = 6.6 Hz, 2H), 4.07 (s, 3H), 3.73 (m, 4H), 2.57 (t, J = 7.1 Hz, 2H), 2.49 (m, 4H), 2.12 (p, J = 6.7 Hz, 2H); MS (ESI) m/z (%): 658.9 $[M + H]^+$; Anal. calcd. for $C_{39}H_{35}FN_4O_5$ (%): C, 71.11; H, 5.36; N, 8.51. Found (%): C, 71.15; H, 5.34; N, 8.48.

*5.13.8. N-(3-Fluoro-4-(6-methoxy-7-(3-morpholinopropoxy) quinolin-4-yloxy)phenyl)-2-(4-methoxyphenyl)quinoline-4-carboxamide (**15h**)*

Yield: 63%; M.p.: 162–163 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.74 (s, 1H), 8.50 (d, J = 5.2 Hz, 1H), 8.12 (d, J = 8.4 Hz, 1H), 8.03 (m, 4H), 7.74 (m, 2H), 7.57 (d, J = 6.8 Hz, 2H), 7.49 (t, J = 7.2 Hz, 1H), 7.41 (s, 1H), 7.33 (t, J = 8.6 Hz, 1H), 6.99 (d, J = 8.8 Hz, 2H), 6.46 (d, J = 5.2 Hz, 1H), 4.24 (t, J = 6.6 Hz, 2H), 4.05 (s, 3H), 3.89 (s, 3H), 3.72 (m, 4H), 2.57 (t, J = 7.1 Hz, 2H), 2.48 (m, 4H), 2.12 (p, J = 6.8 Hz, 2H); MS (ESI) m/z (%): 689.0 $[M + H]^+$; Anal. calcd. for $C_{40}H_{37}FN_4O_6$ (%): C, 69.75; H, 5.41; N, 8.13. Found (%): C, 69.77; H, 5.38; N, 8.12.

*5.13.9. N-(3-Fluoro-4-(6-methoxy-7-(3-morpholinopropoxy)quinolin-4-yloxy)phenyl)-2-(3-methoxyphenyl)quinoline-4-carboxamide (**15i**)*

Yield: 65%; M.p.: 166–167 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.52 (d, J = 5.3 Hz, 1H), 8.47 (s, 1H), 8.22 (t, J = 7.9 Hz, 2H), 8.03 (d, J = 11.8 Hz, 1H), 7.96 (s, 1H), 7.81 (t, J = 7.7 Hz, 1H), 7.74 (m, 1H), 7.66 (d, J = 7.9 Hz, 1H), 7.60 (m, 2H), 7.53 (d, J = 8.2 Hz, 1H), 7.44 (m, 2H), 7.34 (t, J = 8.7 Hz, 1H), 7.06 (dd, J = 8.0, 2.2 Hz, 1H), 6.47 (d, J = 5.1 Hz, 1H), 4.27 (t, J = 6.6 Hz, 2H), 4.07 (s, 3H), 3.94 (s, 3H), 3.74 (m, 4H), 2.60 (t, J = 7.1 Hz, 2H), 2.51 (m, 4H), 2.15 (m, 2H); MS (ESI) m/z (%): 689.0 $[M + H]^+$; Anal. calcd. for $C_{40}H_{37}FN_4O_6$ (%): C, 69.75; H, 5.41; N, 8.13. Found (%): C, 69.74; H, 5.41; N, 8.15.

*5.13.10. 2-(3-Chlorophenyl)-N-3-fluoro-4-6-methoxy-7-(3-morpholinopropoxy)quinoline-4-carboxamide (**15j**)*

Yield: 58%; M.p.: 193–194 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.52 (d, J = 5.3 Hz, 1H), 8.47 (s, 1H), 8.22 (t, J = 7.9 Hz, 2H), 8.03 (d, J = 11.8 Hz, 1H), 7.96 (s, 1H), 7.81 (t, J = 7.7 Hz, 1H), 7.74 (m, 1H), 7.66 (d, J = 7.9 Hz, 1H), 7.60 (m, 2H), 7.53 (d, J = 8.2 Hz, 1H), 7.44 (m, 2H), 7.34 (t, J = 8.7 Hz, 1H), 7.06 (dd, J = 8.0, 2.2 Hz, 1H), 6.47 (d, J = 5.1 Hz, 1H), 4.27 (t, J = 6.6 Hz, 2H), 4.07 (s, 3H), 3.94 (s, 3H), 3.74 (m, 4H), 2.60 (t, J = 7.1 Hz, 2H), 2.51 (m, 4H), 2.15 (m, 2H); ^{13}C NMR (DMSO-d_6) δ: 169.82, 160.28, 159.65, 154.78, 153.15, 152.40, 150.04, 149.28, 146.85, 142.56, 139.49, 138.63, 137.52, 136.71, 135.70, 135.41, 132.22, 131.00, 128.70, 127.65, 126.64, 125.51, 125.26, 124.74, 124.20, 118.17, 117.19, 114.93, 108.98, 102.55, 99.48, 67.13, 66.67 (2C), 56.23, 55.26, 53.83 (2C), 26.14; MS (ESI) m/z (%): 692.9 $[M + H]^+$; Anal. calcd. for $C_{39}H_{34}ClFN_4O_5$ (%): C, 67.58; H, 4.94; N, 8.08. Found (%): C, 67.60; H, 4.95; N, 8.05.

*5.13.11. N-(3-Fluoro-4-(6-methoxy-7-(3-morpholinopropoxy) quinolin-4-yloxy)phenyl)-2-(4-(trifluoromethyl)phenyl)quinoline-4-carboxamide (**15k**)*

Yield: 51%; M.p.: 191–192 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.81 (s, 1H), 8.40 (d, J = 5.2 Hz, 1H), 8.17 (t, J = 8.1 Hz, 4H), 7.94 (d, J = 14.8 Hz, 2H), 7.73 (m, 3H), 7.57 (t, J = 7.6 Hz, 1H), 7.47 (d, J = 11.5 Hz, 2H), 7.27 (d, J = 10.9 Hz, 2H), 6.36 (d, J = 5.3 Hz, 1H), 4.12 (t, J = 6.5 Hz, 2H), 3.98 (s, 3H), 3.66 (m, 4H), 2.50 (t, J = 7.0 Hz, 2H), 2.42 (s, 4H), 2.05 (m, 2H); MS (ESI) m/z (%): 726.8 $[M + H]^+$; Anal. calcd. for $C_{40}H_{34}F_4N_4O_5$ (%): C, 66.11; H, 4.72; N, 7.71. Found (%): C, 66.13; H, 4.70; N, 7.70.

*5.13.12. N-(3-Fluoro-4-(6-methoxy-7-(3-morpholinopropoxy) quinolin-4-yloxy)phenyl)-2-p-tolylquinoline-4-carboxamide (**15l**)*

Yield: 67%; M.p.: 171–173 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.76 (s, 1H), 8.51 (d, J = 5.2 Hz, 1H), 8.17 (d, J = 8.4 Hz, 1H), 8.08 (m, 2H), 7.97 (d, J = 8.1 Hz, 2H), 7.84 (s, 1H), 7.76 (t, J = 7.7 Hz, 1H), 7.59 (d, J = 8.5 Hz, 2H), 7.52 (t, J = 7.7 Hz, 1H), 7.43 (s, 1H), 7.34 (q, J = 8.3 Hz, 3H), 6.48 (d, J = 5.2 Hz, 1H), 4.26 (t, J = 6.6 Hz, 2H), 4.08 (s, 3H), 3.74 (m, 4H), 2.59 (t, J = 7.1 Hz, 2H), 2.51 (m, 4H), 2.46 (s, 3H), 2.14 (m, 2H); MS (ESI) m/z (%): 672.9 $[M + H]^+$; Anal. calcd. for $C_{40}H_{37}FN_4O_5$ (%): C, 71.41; H, 5.54; N, 8.33. Found (%): C, 71.44; H, 5.50; N, 8.35.

*5.13.13. 2-(3-Chlorophenyl)-N-(3-fluoro-4-(6-methoxy-7-(3-(4-methylpiperidin-1-yl)propoxy)quinolin-4-yloxy)phenyl)quinoline-4-carboxamide (**15m**)*

Yield: 63%; M.p.: 195–196 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.00 (s, 1H), 8.44 (d, J = 5.3 Hz, 1H), 8.17 (d, J = 8.9 Hz, 2H), 8.07 (s, 1H), 8.01 (m, 1H), 7.91 (m, 1H), 7.85 (s, 1H), 7.78 (t, J = 7.6 Hz, 1H), 7.57 (m, 3H), 7.44 (m, 2H), 7.32 (d, J = 6.3 Hz, 2H), 6.41 (d, J = 5.1 Hz, 1H), 4.13 (t, J = 6.5 Hz, 2H), 4.03 (s, 3H), 2.95 (d, J = 11.4 Hz, 2H), 2.57 (t, J = 5.3 Hz, 2H), 2.11 (m, 2H), 2.02 (t, J = 12.0 Hz, 2H), 1.63 (d, J = 12.1 Hz, 2H), 1.31 (m, 3H), 0.92 (d, J = 6.0 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ 176.01, 162.38, 159.64, 154.77, 153.14, 152.12, 149.91, 149.65, 149.30, 146.73, 143.19, 142.31, 139.02, 135.66, 132.25, 131.43, 129.91, 128.72, 126.87, 125.11, 124.66, 124.18, 123.35, 118.06, 117.15, 115.01, 111.52, 109.13, 104.94, 102.57, 99.50, 66.81, 56.21 (2C), 54.21, 52.80, 32.55, 29.23, 24.94, 21.64, 18.76; MS (ESI) m/z (%): 704.9 $[M + H]^+$; Anal. calcd. for $C_{41}H_{38}ClFN_4O_4$ (%): C, 69.83; H, 5.43; N, 7.94. Found (%): C, 69.87; H, 5.42; N, 7.97.

*5.13.14. N-(3-Fluoro-4-(6-methoxy-7-(3-(4-methylpiperidin-1-yl)propoxy)quinolin-4-yloxy)phenyl)-2-phenylquinoline-4-carboxamide (**15n**)*

Yield: 65%; M.p.: 142–143 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.33 (s, 1H), 8.48 (d, J = 5.2 Hz, 1H), 8.37 (m, 3H), 8.20 (m, 2H), 8.11 (dd, J = 13.0, 2.3 Hz, 1H), 7.84 (m, 1H), 7.74 (d, J = 9.9 Hz, 1H), 7.67 (m, 1H), 7.53 (m, 5H), 7.42 (s, 1H), 6.48 (d, J = 4.6 Hz, 1H), 4.22 (t, J = 6.1 Hz, 2H), 3.94 (s, 3H), 3.26 (d, J = 12.0 Hz, 2H), 2.97 (m, J = 6.1 Hz, 2H), 2.63 (m, 2H), 2.20 (m, 2H), 1.69 (d, J = 10.6 Hz, 2H), 1.45 (s, 1H), 1.37 (m, 2H), 0.87 (t, J = 6.5 Hz, 3H); MS (ESI) m/z (%): 671.0 $[M + H]^+$; Anal. calcd. for $C_{41}H_{39}FN_4O_4$ (%): C, 73.41; H, 5.86; N, 8.35. Found (%): C, 73.44; H, 5.90; N, 8.33.

*5.13.15. N-(3-Fluoro-4-(6-methoxy-7-(3-(4-methylpiperidin-1-yl)propoxy)quinolin-4-yloxy)phenyl)-2-(4-methoxyphenyl)quinoline-4-carboxamide (**15o**)*

Yield: 68%; M.p.: 138–139 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.68 (s, 1H), 8.41 (t, J = 7.9 Hz, 2H), 8.14 (d, J = 8.1 Hz, 1H), 8.03 (m, 4H), 7.92 (s, 1H), 7.62 (q, 2H), 7.48 (d, J = 6.2 Hz, 1H), 7.43 (m, 1H), 7.24 (s, 1H), 6.93 (s, 1H), 6.90 (s, 1H), 6.36 (d, J = 5.3 Hz, 1H), 4.01 (s, 2H), 3.94 (s, 3H), 3.78 (s, 3H), 3.17 (d, J = 9.9 Hz, 2H), 2.84 (d, J = 7.1 Hz, 2H), 2.37 (s, 2H), 2.17 (s, 2H), 1.61 (s, 2H), 1.51 (s, 1H), 1.47 (s, 2H), 0.87 (d, J = 4.7 Hz, 3H); MS (ESI) m/z (%): 701.2 $[M + H]^+$; Anal. calcd. for $C_{42}H_{41}FN_4O_5$ (%): C, 71.98; H, 5.90; N, 7.99. Found (%): C, 72.01; H, 5.90; N, 8.03.

*5.13.16. N-(3-Fluoro-4-(6-methoxy-7-(3-(4-methylpiperidin-1-yl)propoxy)quinolin-4-yloxy)phenyl)-2-p-tolylquinoline-4-carboxamide (**15p**)*

Yield: 67%; M.p.: 132–134 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.57 (s, 1H), 8.06 (d, J = 7.3 Hz, 2H), 8.00 (d, J = 11.5 Hz, 2H), 7.91 (d, J = 8.1 Hz, 2H), 7.82 (s, 1H), 7.61 (q, 2H), 7.49 (s, 1H), 7.41 (t, J = 7.6 Hz, 1H), 7.22 (d, J = 5.4 Hz, 2H), 7.18 (s, 2H), 6.36 (d, J = 4.7 Hz, 1H), 3.99 (t, J = 5.9 Hz, 2H), 3.94 (s, 3H), 2.99 (d, J = 5.4 Hz, 2H), 2.64 (m, 2H), 2.34 (s, 3H), 2.13 (s, 2H), 2.06 (t, J = 7.4 Hz, 2H), 1.56 (d, J = 9.2 Hz, 2H), 1.34 (s, 3H), 0.84 (d, J = 3.6 Hz, 3H); MS (ESI) m/z (%): 685.3 $[M + H]^+$; Anal. calcd. for $C_{42}H_{41}FN_4O_4$ (%): C, 73.66; H, 6.03; N, 8.18. Found (%): C, 73.70; H, 6.00; N, 8.20.

*5.13.17. 2-(3,4-Dichlorophenyl)-N-(3-fluoro-4-(6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy)quinolin-4-yloxy)phenyl)quinoline-4-carboxamide (**15q**)*

Yield: 54%; M.p.: 195–196 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.64 (s, 1H), 8.39 (d, J = 5.3 Hz, 1H), 8.21 (d, J = 2.1 Hz, 1H), 8.14 (t, J = 5.3 Hz, 2H), 7.92 (m, 1H), 7.88 (m, 2H), 7.74 (m, 1H), 7.58 (m, 1H), 7.53 (m, 1H), 7.49 (d, J = 2.8 Hz, 1H), 7.43 (d, J = 8.5 Hz, 1H), 7.28 (s, 1H), 7.25 (d, J = 8.7 Hz, 1H), 6.35 (d, J = 5.5 Hz, 1H), 4.13 (t, J = 6.5 Hz, 2H), 3.96 (s, 3H), 2.72 (t, J = 3.5 Hz, 2H), 2.63 (s, 4H), 2.12 (m, 2H), 1.78 (s, 4H); MS (ESI) m/z (%): 710.9 $[M + H]^+$; Anal. calcd. for $C_{39}H_{33}Cl_2FN_4O_4$ (%): C, 65.83; H, 4.67; N, 7.87. Found (%): C, 65.80; H, 4.66; N, 7.89.

*5.13.18. N-(3-Fluoro-4-(6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy)quinolin-4-yloxy)phenyl)-2-(3-methoxyphenyl)quinoline-4-carboxamide (**15r**)*

Yield: 63%; M.p.: 173–174 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.34 (s, 1H), 8.48 (d, J = 5.1 Hz, 1H), 8.40 (s, 1H), 8.15 (m, 3H), 7.93 (d, J = 7.8 Hz, 2H), 7.83 (t, J = 7.5 Hz, 1H), 7.74 (d, J = 7.4 Hz, 1H), 7.66 (t, J = 7.5 Hz, 1H), 7.53 (d, J = 4.3 Hz, 1H), 7.47 (m, 2H), 7.40 (s, 1H), 7.08 (d, J = 7.6 Hz, 1H), 6.47 (d, J = 4.9 Hz, 1H), 4.21 (t, J = 6.0 Hz, 2H), 3.94 (s, 3H), 3.87 (s, 3H), 2.85 (m, 6H), 2.10 (m, 2H), 1.78 (s, 4H); MS (ESI) m/z (%): 673.4 $[M + H]^+$; Anal. calcd. for $C_{40}H_{37}FN_4O_5$ (%): C, 71.41; H, 5.54; N, 8.33. Found (%): C, 71.45; H, 5.53; N, 8.30.

*5.13.19. N-(3-Fluoro-4-(6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy)quinolin-4-yloxy)phenyl)-2-p-tolylquinoline-4-carboxamide (**15s**)*

Yield: 67%; M.p.: 169–170 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.02 (s, 1H), 8.19 (d, J = 8.3 Hz, 1H), 8.03 (m, 6H), 7.64 (m, 2H), 7.50 (s, 1H), 7.44 (d, J = 8.0 Hz, 1H), 7.22 (d, J = 8.1 Hz, 3H), 7.14 (d, J = 8.8 Hz, 1H), 6.36 (s, 1H), 3.96 (s, 2H), 3.93 (s, 3H), 3.07 (s, 4H), 2.83 (m, 2H), 2.34 (s, 3H), 2.19 (s, 2H), 1.92 (s, 4H); MS (ESI) m/z (%): 657.5 $[M + H]^+$; Anal. calcd. for $C_{40}H_{37}FN_4O_5$ (%): C, 73.15; H, 5.68; N, 8.53. Found (%): C, 73.18; H, 5.66; N, 8.51.

*5.13.20. 6-Fluoro-N-(3-fluoro-4-(6-methoxy-7-(3-(piperidin-1-yl)propoxy)quinolin-4-yloxy)phenyl)-2-phenylquinoline-4-carboxamide (**16a**)*

Yield: 62%; M.p.: 148–149 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.38 (s, 1H), 8.52 (s, 2H), 8.40 (d, J = 7.1 Hz, 2H), 8.28 (m, 1H), 8.14 (d, J = 13.6 Hz, 1H), 7.99 (m, 1H), 7.80 (m, 2H), 7.57 (m, 5H), 7.47 (s, 1H), 6.52 (d, J = 4.9 Hz, 1H), 4.28 (s, 2H), 3.99 (s, 3H), 3.16 (s, 6H), 2.30 (s, 2H), 1.80 (s, 4H), 1.57 (s, 2H); MS (ESI) m/z (%): 675.4 $[M + H]^+$; Anal. calcd. for $C_{40}H_{36}F_2N_4O_4$ (%): C, 71.20; H, 5.38; N, 8.30. Found (%): C, 70.12; H, 5.41; N, 8.35.

*5.13.21. 6-Fluoro-N-(3-fluoro-4-(6-methoxy-7-(3-(piperidin-1-yl)propoxy)quinolin-4-yloxy)phenyl)-2-(3-methoxyphenyl)quinoline-4-carboxamide (**16b**)*

Yield: 49%; M.p.: 164–165 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.39 (s, 1H), 8.52 (m, 2H), 8.27 (dd, J = 9.3, 5.7 Hz, 1H), 8.15 (dd, J = 12.9, 2.3 Hz, 1H), 7.98 (m, 3H), 7.81 (m, 2H), 7.57 (m, 2H), 7.50 (d, J = 7.7 Hz, 1H), 7.45 (s, 1H), 7.13 (m, 1H), 6.51 (d, J = 4.7 Hz, 1H), 4.25 (t, J = 6.3 Hz, 2H), 3.99 (s, 3H), 3.91 (s, 3H), 2.90 (s, 6H), 2.19 (s, 2H), 1.69 (m, 4H), 1.50 (s, 2H); MS (ESI) m/z (%): 705.8 $[M + H]^+$; Anal. calcd. for $C_{41}H_{38}F_2N_4O_5$ (%): C, 69.87; H, 5.43; N, 7.95. Found (%): C, 69.84; H, 5.45; N, 7.99.

*5.13.22. 6-Fluoro-N-(3-fluoro-4-(6-methoxy-7-(3-(piperidin-1-yl)propoxy)quinolin-4-yloxy)phenyl)-2-p-tolylquinoline-4-carboxamide (**16c**)*

Yield: 60%; M.p.: 196–197 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.36 (s, 1H), 8.48 (s, 1H), 8.42 (s, 1H), 8.26 (s, 1H), 8.23 (s, 1H), 8.18 (m, 1H), 8.09 (d, J = 11.5 Hz, 1H), 7.91 (dd, J = 10.3, 2.6 Hz, 1H), 7.73 (m, 2H), 7.43 (m, 5H), 6.48 (d, J = 5.3 Hz, 1H), 4.22 (t, J = 5.8 Hz, 2H), 3.92 (s, 3H), 3.16 (s, 4H), 2.87 (s, 2H), 2.36 (s, 3H), 2.28 (s, 2H), 1.75 (s, 6H); MS (ESI) m/z (%): 689.1 $[M + H]^+$; Anal. calcd. for $C_{41}H_{38}F_2N_4O_4$ (%): C, 71.50; H, 5.56; N, 8.13. Found (%): C, 71.42; H, 5.58; N, 8.15.

*5.13.23. 6-Fluoro-N-(3-fluoro-4-(6-methoxy-7-(3-(piperidin-1-yl)propoxy)quinolin-4-yloxy)phenyl)-2-(4-methoxyphenyl)quinoline-4-carboxamide (**16d**)*

Yield: 61%; M.p.: 134–135 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.24 (s, 1H), 8.48 (d, J = 5.2 Hz, 1H), 8.41 (s, 1H), 8.34 (s, 1H), 8.31

(s, 1H), 8.19 (m, 1H), 8.08 (m, 1H), 7.90 (m, 1H), 7.74 (m, 2H), 7.55 (s, 1H), 7.49 (d, J = 9.0 Hz, 1H), 7.42 (s, 1H), 7.11 (d, J = 8.9 Hz, 2H), 6.47 (d, J = 4.8 Hz, 1H), 4.23 (t, J = 6.1 Hz, 2H), 3.95 (s, 3H), 3.84 (s, 3H), 3.03 (m, 6H), 2.22 (s, 2H), 1.72 (s, 4H), 1.50 (s, 2H); MS (ESI) m/z (%): 705.5 $[M + H]^+$; Anal. calcd. for $C_{41}H_{38}F_2N_4O_5$ (%): C, 69.87; H, 5.43; N, 7.95; Found (%): C, 69.83; H, 5.44; N, 7.95.

*5.13.24. 2-(2,4-Dichlorophenyl)-6-fluoro-N-(3-fluoro-4-(6-methoxy-7-(3-(piperidin-1-yl)propoxy)quinolin-4-yloxy)phenyl)quinoline-4-carboxamide (**16e**)*

Yield: 56%; M.p.: 196–198 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.18 (s, 1H), 8.45 (d, J = 5.2 Hz, 1H), 8.22 (dd, J = 9.3, 5.6 Hz, 1H), 8.00 (m, 3H), 7.81 (m, 3H), 7.61 (m, 2H), 7.50 (d, J = 5.6 Hz, 1H), 7.45 (d, J = 9.0 Hz, 1H), 7.38 (s, 1H), 6.44 (d, J = 5.2 Hz, 1H), 4.18 (t, J = 6.2 Hz, 2H), 3.91 (d, J = 7.2 Hz, 3H), 2.76 (m, 6H), 2.10 (s, 2H), 1.61 (d, J = 5.2 Hz, 4H), 1.42 (s, 2H); MS (ESI) m/z (%): 743.0 $[M + H]^+$; Anal. calcd. for $C_{40}H_{34}Cl_2F_2N_4O_4$ (%): C, 64.61; H, 4.61; N, 7.53. Found (%): C, 64.62; H, 4.58; N, 7.55.

*5.13.25. 6-Fluoro-N-(3-fluoro-4-(6-methoxy-7-(3-morpholinopropoxy)quinolin-4-yloxy)phenyl)-2-(4-fluorophenyl)quinoline-4-carboxamide (**16f**)*

Yield: 54%; M.p.: 147–148 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.19 (s, 1H), 8.51 (s, 2H), 8.45 (m, 2H), 8.26 (m, 1H), 8.09 (d, J = 12.6 Hz, 1H), 7.97 (d, J = 9.8 Hz, 1H), 7.82 (m, 1H), 7.71 (d, J = 7.6 Hz, 1H), 7.54 (m, 2H), 7.44 (m, 3H), 6.49 (d, J = 5.0 Hz, 1H), 4.22 (s, 2H), 3.97 (s, 3H), 3.61 (s, 4H), 2.44 (s, 6H), 2.00 (s, 2H); MS (ESI) m/z (%): 695.8 $[M + H]^+$; Anal. calcd. for $C_{39}H_{33}F_3N_4O_5$ (%): C, 67.43; H, 4.79; N, 8.06. Found (%): C, 67.39; H, 4.81; N, 8.10.

*5.13.26. 2-(3-Chlorophenyl)-6-fluoro-N-(3-fluoro-4-(6-methoxy-7-(3-morpholinopropoxy)quinolin-4-yloxy)phenyl)quinoline-4-carboxamide (**16g**)*

Yield: 65%; M.p.: 175–176 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.28 (s, 1H), 8.58 (s, 1H), 8.52 (d, J = 5.2 Hz, 1H), 8.45 (s, 1H), 8.37 (m, 1H), 8.29 (m, 1H), 8.12 (m, 1H), 8.01 (dd, J = 10.2, 2.8 Hz, 1H), 7.83 (m, 1H), 7.75 (d, J = 10.1 Hz, 1H), 7.63 (m, 2H), 7.55 (m, 2H), 7.41 (d, J = 14.7 Hz, 1H), 6.49 (t, J = 4.4 Hz, 1H), 4.23 (t, J = 6.6 Hz, 2H), 3.97 (s, 3H), 3.62 (m, 4H), 2.48 (d, J = 17.0 Hz, 6H), 2.01 (m, 2H); MS (ESI) m/z (%): 711.2 $[M + H]^+$; Anal. calcd. for $C_{39}H_{33}ClF_2N_4O_5$ (%): C, 65.87; H, 4.68; N, 7.88. Found (%): C, 65.82; H, 4.69; N, 7.86.

*5.13.27. 6-Fluoro-N-(3-fluoro-4-(6-methoxy-7-(3-morpholinopropoxy)quinolin-4-yloxy)phenyl)-2-p-tolylquinoline-4-carboxamide (**16h**)*

Yield: 69%; M.p.: 173–174 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.18 (s, 1H), 8.52 (d, J = 5.2 Hz, 1H), 8.48 (s, 1H), 8.27 (m, 3H), 8.10 (dd, J = 13.0, 2.3 Hz, 1H), 7.97 (dd, J = 10.2, 2.8 Hz, 1H), 7.81 (m, 1H), 7.72 (d, J = 8.0 Hz, 1H), 7.55 (m, 2H), 7.41 (m, 3H), 6.51 (d, J = 4.4 Hz, 1H), 4.23 (t, J = 6.5 Hz, 2H), 3.99 (s, 3H), 3.62 (m, 4H), 2.47 (m, 9H), 2.01 (m, 2H); MS (ESI) m/z (%): 691.2 $[M + H]^+$; Anal. calcd. for $C_{40}H_{36}F_2N_4O_5$ (%): C, 69.55; H, 5.25; N, 8.11. Found (%): C, 69.53; H, 5.27; N, 8.13.

*5.13.28. 2-(3-Chlorophenyl)-6-fluoro-N-(3-fluoro-4-(6-methoxy-7-(3-(4-methylpiperdin-1-yl)propoxy)quinolin-4-yloxy)phenyl)quinoline-4-carboxamide (**16i**)*

Yield: 49%; M.p.: 181–182 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.36 (s, 1H), 8.55 (s, 1H), 8.48 (d, J = 5.2 Hz, 1H), 8.42 (s, 1H), 8.33 (m, 1H), 8.26 (dd, J = 9.2, 5.6 Hz, 1H), 8.09 (m, 1H), 7.97 (dd, J = 10.2, 2.8 Hz, 1H), 7.79 (d, J = 2.5 Hz, 1H), 7.74 (d, J = 8.4 Hz, 1H), 7.59 (m, 2H), 7.55 (s, 1H), 7.49 (m, 1H), 7.42 (s, 1H), 6.47 (d, J = 5.0 Hz, 1H), 4.24 (t, J = 6.3 Hz, 2H), 3.93 (s, 3H), 3.10 (s, 4H), 2.80 (s, 2H), 2.25 (s, 2H), 1.74 (d, J = 12.5 Hz, 2H), 1.45 (m, 3H), 0.90 (d, J = 6.0 Hz, 3H); MS (ESI) m/z (%): 723.6 $[M + H]^+$; Anal. calcd. for $C_{41}H_{37}ClF_2N_4O_4$ (%): C, 68.09; H, 5.16; N, 7.75. Found (%): C, 68.10; H, 5.17; N, 7.77.

*5.13.29. 6-Fluoro-N-(3-fluoro-4-(6-methoxy-7-(3-(4-methylpiperidin-1-yl)propoxy)quinolin-4-yloxy)phenyl)-2-(3-methoxyphenyl)quinoline-4-carboxamide (**16j**)*

Yield: 54%; M.p.: 175–177 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.28 (s, 1H), 8.46 (s, 2H), 8.22 (m, 1H), 8.08 (m, 1H), 7.92 (m, 3H), 7.77 (dd, J = 11.5, 4.0 Hz, 1H), 7.70 (m, 1H), 7.52 (s, 1H), 7.47 (m, 2H), 7.37 (s, 1H), 7.09 (m, 1H), 6.45 (d, J = 4.7 Hz, 1H), 4.17 (t, J = 4.7 Hz, 2H), 3.93 (s, 3H), 3.86 (s, 3H), 3.13 (s, 2H), 2.93 (d, J = 10.6 Hz, 2H), 2.56 (s, 2H), 2.01 (m, 2H), 1.58 (d, J = 10.6 Hz, 2H), 1.34 (s, 1H), 1.19 (s, 2H), 0.85 (d, J = 6.5 Hz, 3H); MS (ESI) m/z (%): 719.3 $[M + H]^+$; Anal. calcd. for $C_{42}H_{40}F_2N_4O_5$ (%): C, 70.18; H, 5.61; N, 7.79. Found (%): C, 70.11; H, 5.62; N, 7.82.

*5.13.30. 6-Fluoro-N-(3-fluoro-4-(6-methoxy-7-(3-(4-methylpiperidin-1-yl)propoxy)quinolin-4-yloxy)phenyl)-2-p-tolylquinoline-4-carboxamide (**16k**)*

Yield: 57%; M.p.: 183–184 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.40 (s, 1H), 8.51 (m, 2H), 8.32 (s, 1H), 8.29 (s, 1H), 8.23 (d, J = 7.3 Hz, 1H), 8.11 (s, 1H), 7.97 (dd, J = 10.2, 3.0 Hz, 1H), 7.79 (m, 2H), 7.58 (s, 1H), 7.53 (d, J = 9.2 Hz, 1H), 7.43 (s, 1H), 7.40 (s, 1H), 7.36 (d, J = 8.1 Hz, 1H), 6.51 (d, J = 4.7 Hz, 1H), 4.23 (t, J = 6.4 Hz, 2H), 3.98 (s, 3H), 3.05 (s, 2H), 2.73 (d, J = 6.9 Hz, 2H), 2.42 (s, 3H), 2.25 (s, 2H), 2.10 (s, 2H), 1.66 (d, J = 11.0 Hz, 2H), 1.45 (s, 1H), 1.30 (m, 2H), 0.92 (d, J = 6.3 Hz, 3H); MS (ESI) m/z (%): 703.4 $[M + H]^+$; Anal. calcd. for $C_{42}H_{40}F_2N_4O_4$ (%): C, 71.78; H, 5.74; N, 7.97. Found (%): C, 71.75; H, 5.77; N, 7.98.

*5.13.31. 6-Fluoro-N-(3-fluoro-4-(6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy)quinolin-4-yloxy)phenyl)-2-phenylquinoline-4-carboxamide (**16l**)*

Yield: 67%; M.p.: 134–135 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.34 (s, 1H), 8.48 (m, 2H), 8.35 (d, J = 6.9 Hz, 2H), 8.23 (q, 1H), 8.10 (d, J = 13.0 Hz, 1H), 7.95 (dd, J = 10.1, 2.7 Hz, 1H), 7.77 (m, 2H), 7.54 (m, 5H), 7.43 (s, 1H), 6.48 (d, J = 5.1 Hz, 1H), 4.26 (t, J = 6.1 Hz, 2H), 3.95 (s, 3H), 3.54 (s, 2H), 3.01 (d, J = 6.1 Hz, 4H), 2.27 (m, 2H), 1.96 (s, 4H); MS (ESI) m/z (%): 661.6 $[M + H]^+$; Anal. calcd. for $C_{39}H_{34}F_2N_4O_4$ (%): C, 70.90; H, 5.19; N, 8.48. Found (%): C, 70.83; H, 5.61; N, 8.50.

*5.13.32. 2-(3-Chlorophenyl)-6-fluoro-N-(3-fluoro-4-(6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy)quinoline-4-yloxy)phenyl)quinoline-4-carboxamide (**16m**)*

Yield: 71%; M.p.: 166–167 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.30 (s, 1H), 8.59 (s, 1H), 8.53 (d, J = 5.4 Hz, 1H), 8.47 (s, 1H), 8.38 (d, J = 5.2 Hz, 1H), 8.31 (q, 1H), 8.13 (d, J = 15.4 Hz, 1H), 8.01 (dd, J = 10.2, 2.8 Hz, 1H), 7.85 (m, 1H), 7.75 (d, J = 9.7 Hz, 2H), 7.65 (d, J = 5.3 Hz, 1H), 7.59 (s, 1H), 7.54 (d, J = 9.0 Hz, 1H), 7.46 (s, 1H), 6.51 (d, J = 5.2 Hz, 1H), 4.28 (t, J = 5.9 Hz, 2H), 4.00 (s, 3H), 3.07 (s, 6H), 2.20 (s, 2H), 1.89 (s, 4H); ^{13}C NMR ($CDCl_3$) δ 170.94, 160.03, 159.47, 155.17, 153.52, 152.03, 149.73, 148.81, 146.79, 142.37, 138.52, 137.21, 136.88, 134.72, 133.86, 131.22, 130.04, 128.28, 127.29, 125.99, 125.62, 123.65, 123.43, 117.44, 116.61, 115.52, 109.99, 109.83, 108.83, 102.28, 99.55, 67.06, 56.10, 54.07 (2C), 52.97, 27.73, 23.44 (2C); MS (ESI) m/z (%): 695.6 $[M + H]^+$; Anal. calcd. for $C_{39}H_{33}ClF_2N_4O_4$ (%): C, 67.38; H, 4.78; N, 8.06. Found (%): C, 67.42; H, 4.80; N, 8.07.

*5.13.33. 6-Fluoro-N-(3-fluoro-4-(6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy)quinolin-4-yloxy)phenyl)-2-(4-methoxyphenyl)quinoline-4-carboxamide (**16n**)*

Yield: 60%; M.p.: 158–159 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.31 (s, 1H), 8.49 (d, J = 5.3 Hz, 1H), 8.42 (s, 1H), 8.33 (d, J = 8.7 Hz, 2H), 8.18 (q, 1H), 8.09 (d, J = 13.3 Hz, 1H), 7.91 (dd, J = 10.1, 2.8 Hz, 1H), 7.74 (m, 2H), 7.55 (s, 1H), 7.50 (t, J = 9.1 Hz, 1H), 7.43 (s, 1H), 7.11 (d, J = 8.8 Hz, 2H), 6.48 (d, J = 5.3 Hz, 1H), 4.26 (t, J = 6.0 Hz, 2H), 3.95 (s, 3H), 3.83 (s, 3H), 3.21 (s, 4H), 3.01 (m, 2H), 2.24 (s, 2H), 1.93 (s, 4H); MS(ESI) m/z (%): 691.3 $[M + H]^+$; Anal. calcd. for $C_{40}H_{36}F_2N_4O_5$ (%): C, 69.55; H, 5.25; N, 8.11. Found (%): C, 69.49; H, 5.27; N, 8.12.

5.14. Pharmacology

5.14.1. MTT assay in vitro

The anti-proliferative activities of compounds **15a**–**s** and **16a**–**n** were evaluated against H460, HT-29, MKN-45, U-87MG and SMMC-7721 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% foetal 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 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.

5.14.2. c-Met kinase assay

The c-Met kinase activity was evaluated using homogeneous time-resolved fluorescence (HTRF) assays as previously reported [29,30]. Briefly, 20 μg/mL poly (Glu, Tyr) 4:1 (Sigma) was precoated 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 wells. The plates were read using Envision (Perkin Elmer) 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.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejmech.2013.04.001.

References

[1] A. Gilman, Am. J. Surg. 105 (1963) 574–578.
[2] K.W. Kohn, Cancer Res. 56 (1996) 5533–5546.
[3] A.A. Mohamed, A.W. EI-Harby, J. Mol. Struct. Theochem 817 (2007) 125–136.
[4] J. He, X. Wang, X. Zhao, Y. Liang, H. He, L. Fu, Eur. J. Med. Chem. 55 (2012) 925–930.
[5] B.B.S. Zhou, H. Huang, M. Damelin, K.G. Geles, J.C. Grindley, P.B. Dirks, Nat. Rev. Drug Discov. 8 (2009) 506–523.
[6] P. John, Expert Opin. Ther. Pat. 20 (2010) 159–177.
[7] X. Liu, R.C. Newton, P.A. Scherle, Trends Mol. Med. 16 (2009) 37–45.
[8] C.M. Stellrecht, V. Gandhi, Cancer Lett. 280 (2009) 1–14.
[9] M. Zillhardt, S.M. Park, I.L. Romero, K. Sawada, A. Montag, T. Krausz, S.D. Yamada, M.E. Peter, E. Lengyel, Clin. Cancer Res. 17 (2011) 4042–4051.
[10] F. Qian, S. Engst, K. Yamaguchi, P. Yu, K.A. Won, L. Mock, T. Lou, J. Tan, C. Li, D. Tam, J. Lougheed, F.M. Yakes, F. Bentzien, W. Xu, T. Zaks, R. Wooster, J. Greshock, A.H. Joly, Cancer Res. 69 (2009) 8009–8016.
[11] M.H. Norman, L. Liu, M.R. Lee, N. Xi, N. D'Angelo, I. Fellows, C. Dominguez, K. Rex, S.F. Bellon, T.S. Kim, I. Dussault, J. Med. Chem. 55 (2012) 1858–1867.
[12] G.M. Schroeder, Y. An, Z.W. Cai, X.T. Chen, C. Clark, L.A.M. Cornelius, J. Dai, J.G. Brown, A. Gupta, B. Henley, J.T. Hunt, R. Jeyaseelan, A. Kamath, K. Kim, J. Lippy, L.J. Lombardo, V. Manne, S. Oppenheimer, J.S. Sack, R.J. Schmidt, G. Shen, K. Stefanski, J.S. Tokarski, G.L. Trainor, B.S. Wautlet, D. Wei, D.K. Williams, Y. Zhang, Y. Zhang, J. Fargnoli, R.M. Borzilleri, J. Med. Chem. 52 (2009) 1251–1254.
[13] J. Caballero, M. Quiliano, J.H. Alzate-Morales, M. Zimic, E. Deharo, J. Comput. Aided Mol. Des. 25 (2011) 349–369.
[14] O. Saavedra, S. Claridge, L. Zhan, F. Raeppel, M.C. Granger, S. Raeppel, M. Mannion, F. Gaudette, N. Zhou, L. Isakovic, N. Bernstein, R. Deziel, H. Nguyen, N. Beaulieu, C. Beaulieu, I. Dupont, J. Wang, A.R. Macleod, J.M. Besterman, A. Vaisburg, Bioorg. Med. Chem. Lett. 19 (2009) 6836–6839.
[15] K.S. Kim, L. Zhang, R. Schmidt, Z.W. Cai, D. Wei, D.K. Williams, L.J. Lombardo, G.L. Trainor, D. Xie, Y. Zhang, Y. An, J.S. Sack, J.S. Tokarski, C. Darienzo, A. Kamath, P. Marathe, Y. Zhang, J. Lippy, R. Jeyaseelan, B. Wautlet, B. Henley, J. Gullo-Brown, V. Manne, J.T. Hunt, J. Fargoli, R.M. Borzilleri, J. Med. Chem. 51 (2008) 5330–5341.
[16] M. Pradeep, R.K. Agrawal, U.K. Maini, Indian J. Pharm. Sci. 50 (1988) 269–271.
[17] T. Ashizawa, H. Miyata, H. Ishii, C. Oshita, K. Matsuno, Y. Masuda, T. Furuya, T. Okawara, M. Otsuka, N. Ogo, A. Asai, Y. Akiyama, Int. J. Oncol. 38 (2011) 1245–1252.
[18] K. Matsuno, Y. Masuda, Y. Uehara, H. Sato, A. Muroya, O. Takahashi, T. Yokotagawa, T. Furuya, T. Okawara, M. Otsuka, N. Ogo, T. Ashizawa, C. Oshita, S. Tai, H. Ishii, Y. Akiyama, A. Asai, ACS Med. Chem. Lett. 1 (2010) 371–375.
[19] P.P. Jumade, S.J. Wadher, A.J. Chourasia, U.V. Kharabe, D. Mude, P.G. Yeole, Int. J. Chem. Sci. 7 (2009) 1518–1530.
[20] B. Anna, M. Carlo, S. Isabella, S. Maria, T. Luciana, D. Giudice, M. Rosaria, Arch. Pharm. Chem. Life Sci. 340 (2007) 17–25.
[21] A.D. Walsh, K.S. Franzyshen, M.J.J. Yanni, J. Med. Chem. 32 (1989) 105–108.
[22] M. Wilcox, R.W. Viola, K.W. Johnson, A.P. Billington, B.K. Carpenter, J.A. McCray, A.P. Guzikowski, G.P.J. Hess, Org. Chem. 55 (1990) 1585–1589.
[23] S. Hernández, I. Moreno, R.S. Martin, M.T. Herrero, E. Domínguez, Org. Biomol. Chem. 9 (2011) 2251–2257.
[24] J. Tois, M. Vahermo, A. Koskinen, Tetrahedron Lett. 46 (2005) 735–737.
[25] N.D. D'Angelo, S.F. Belllon, S.K. Booker, Y. Cheng, A. Coxon, C. Dominguez, I. Fellows, D. Hoffman, R. Hungate, P. Kaplan-Lefko, M.R. Lee, C. Li, L.B. Liu, E. Rainbeau, P.J. Reider, K. Rex, A. Siegmund, Y. Sun, A.S. Tasler, N. Xi, S.M. Xu, Y.J. Yang, Y.H. Zhang, T.L. Burgess, I. Dussault, T.S.J. Kim, Med. Chem. 51 (2008) 5766–5779.
[26] D.Y. Zhang, J. Ai, Z.J. Liang, C.P. Li, P. Xia, Y.C. Ji, H.L. Jiang, M.Y. Geng, C. Luo, H. Liu, Bioorg. Med. Chem. 20 (2012) 5169–5180.
[27] S. DasGupta, P.R. Murumkar, R. Giridhar, M.R. Yadav, Bioorg. Med. Chem. 17 (2009) 3604–3617.
[28] E.A. EI Sayed, R. EI Sayed, A.H. Hamida, H. Mohamed, Synth. Commun. 35 (2005) 2243–2250.
[29] L.B. Liu, A. Siegmund, N. Xi, P. Kaplan-Lefko, K. Rex, A. Chen, J. Lin, J. Moriguchi, L. Berry, L.Y. Huang, Y. Teffera, Y.J. Yang, Y.H. Zhang, S.F. Bellon, M. Lee, R. Shimanovich, A. Bak, C. Dominguez, M.H. Norman, J.C. Harmange, I. Dussault, T.S. Kim, J. Med. Chem. 51 (2008) 3688–3691.
[30] B.K. Albrecht, J.C. Harmange, D. Bauer, L. Berry, C. Bode, A.A. Boezio, A. Chen, D. Choquette, I. Dussault, C. Fridrich, R. Shimanovich, S.K. Springer, Y. Teffera, Y. Yang, Y. Zhang, S.F. Bellon, J. Med. Chem. 51 (2008) 2879–2882.