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Full Paper

Design and Synthesis of Novel 4-Phenoxyquinolines Bearing 3-Hydrosulfonylacrylamido or 1*H*-Imidazole-4-carboxamido Scaffolds as c-Met Kinase Inhibitors

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A series of novel 6,7-disubstituted-4-phenoxyquinoline derivatives bearing (*E*)-3-hydrosulfonylacrylamido or 1*H*-imidazole-4-carboxamido moieties were designed, synthesized and evaluated for their cytotoxicity against A549, MKN-45, and HT-29 cancer cell lines *in vitro*. All the target compounds showed moderate to significant cytotoxic activity against the tested cells with IC_{50} values ranging from 0.13 to 2.65 μM. Five of them were further examined for their inhibitory activity against c-Met kinase, which identified compound **30** as a promising agent (c-Met $IC_{50} = 1.52$ nM) with IC_{50} values of 0.24, 0.45, and 0.13 μM against HT-29, MKN-45, and A549 cells, respectively.

Keywords: Antitumor activity / c-Met inhibitors / QSAR / Synthesis

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Introduction

c-Met, a receptor tyrosine kinase, is normally activated by binding its natural ligand hepatocyte growth factor (HGF) which induces several complex signaling pathways and results in cell proliferation, motility, migration, and survival [1–3]. Thus, the aberrant activation of HGF/c-Met signaling can lead to a variety of malignancies [4].

Recently, c-Met as a potential target has drawn considerable attention for cancer treatment [5–7], prompting a number of c-Met inhibitors with diverse molecular scaffolds. Among them, novel 6,7-disubstituted-4-phenoxyquinoline derivatives with remarkable antitumor activity have been discovered, such as foretinib (**1**), cabozantinib (**2**), AM7 (**3**), MG10 (**4**), Amgen (**5**), etc. (**1–5** in Fig. 1) [8–11].

The c-Met inhibitors undergoing clinical trials or launched suggested that quinoline pharmacophores were essential for furnishing hydrogen bonds with the backbone of c-Met kinase, and the aryl fragment (moiety B) probably generated hydrophobic binds. Importantly, there should be two structural characteristics on the linkage (moiety C) between moiety A and B, one is 5-atoms regulation and the other is possessing hydrogen-bond donors or acceptors simultaneously [12–14]. In our previous studies, a variety of pharmacodynamics skeletons were introduced as the linker, which resulted in various derivatives **6–10** (Fig. 2) with excellent c-Met inhibition potency [12–18].

As an extension of our work on the discovery of novel potent c-Met inhibitors based on the 5-atom regulation, two kinds of new frameworks, namely (*E*)-3-hydrosulfonylacrylamido and 1*H*-imidazole-4-carboxamido scaffolds (Fig. 3) [19–21], were introduced into moiety C. Based on the above design, we reserved the 3-carbon tether at the 7-position of quinoline skeleton, further replaced the morpholinyl group (moiety A) by other alicyclic tertiary

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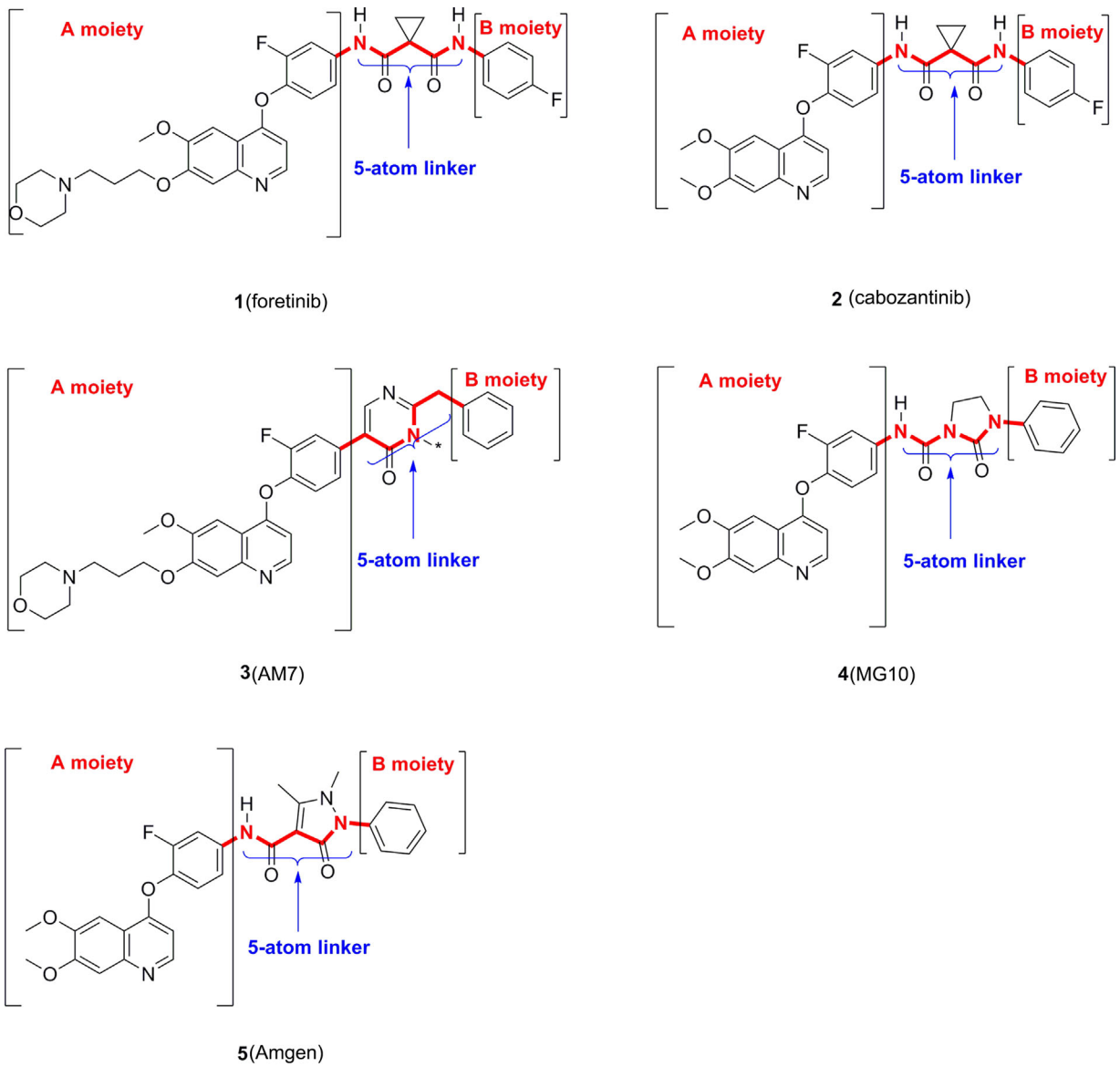

Figure 1. Representative c-Met inhibitors based on 6,7-disubstituted-4-phenoxyquinoline scaffolds.

amino groups to optimal cellular potency via improving water solubility. Furthermore, various substituents were introduced into the phenyl ring (moiety B) with the purpose of enriching the structural diversity. Therefore, a series of novel 6,7-disubstituted-4-phenoxyquinoline derivatives possessing (*E*)-3-hydrosulfonylacrylamido or 1*H*-imidazole-4-carboxamido motifs as c-Met kinase inhibitors were designed and synthesized. In the current study, all target compounds were evaluated for their cytotoxicity against A549, MKN-45, and HT-29 cancer cell lines *in vitro*. Additionally, enzymatic assays of five active compounds are also presented in this study.

Results and discussion

Chemistry

Scheme 1 depicts the preparation of compounds **20–29**. The key intermediates of 4-(2-fluorophenoxy)quinolones **12a–e** were synthesized through an eight-step reaction starting from commercially available 1-(4-hydroxy-3-methoxyphenyl)-ethanone which has been illustrated in detail in our previous study [12–18].

Various substituted anilines were refluxed with sodium format in formic acid for 12 h to afford *N*-phenylformamides **13a–d**, which were converted to benzonitriles **14a–d** on

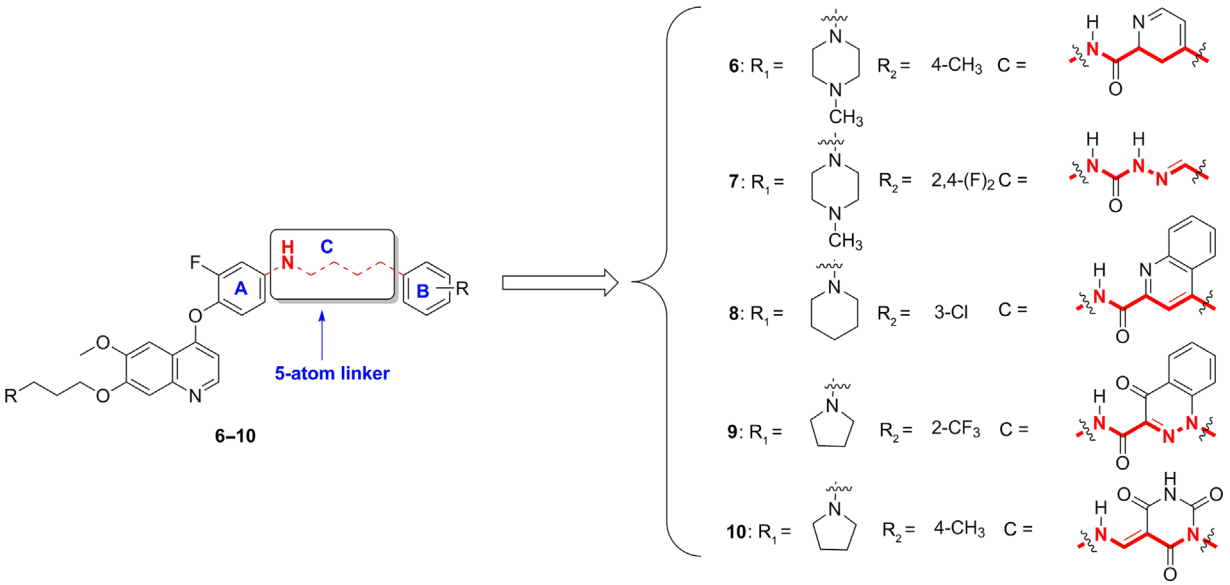

Figure 2. Representative c-Met inhibitors in our previous studies.

exposure to phosphorus oxychloride in the presence of triethylamine in tetrahydrofuran at room temperature. Treatment of **14a–d** with 4-methoxy-3-oxobutanenitrile under the catalysis of 1,10-phenanthroline monohydrate and cuprous oxide in tetrahydrofuran furnished **15a–d**, which were then reacted with lithium hydroxide monohydrate in tetrahydrofuran/water (4:1) at room temperature to give the key intermediates **16a–d**. Finally, **16a–d** were chlorinated by thionyl chloride and subsequently condensed with **12a–e** in the existence of potassium carbonate in dichloromethane to generate the target compounds **20–29**.

The synthesis of target compounds **30–40** is described in Scheme 2. Sulfur-alkylation of commercially available various benzenethiols with ethyl propiolate provided intermediates **17a–d**, which were oxidized by hydrogen peroxide to afford **18a–d**. Subsequently, **18a–d** were subjected to hydrolyzation by lithium hydroxide monohydrate in tetrahydrofuran/water (5:1) to obtain the key intermediates **19a–d**. The synthesis of

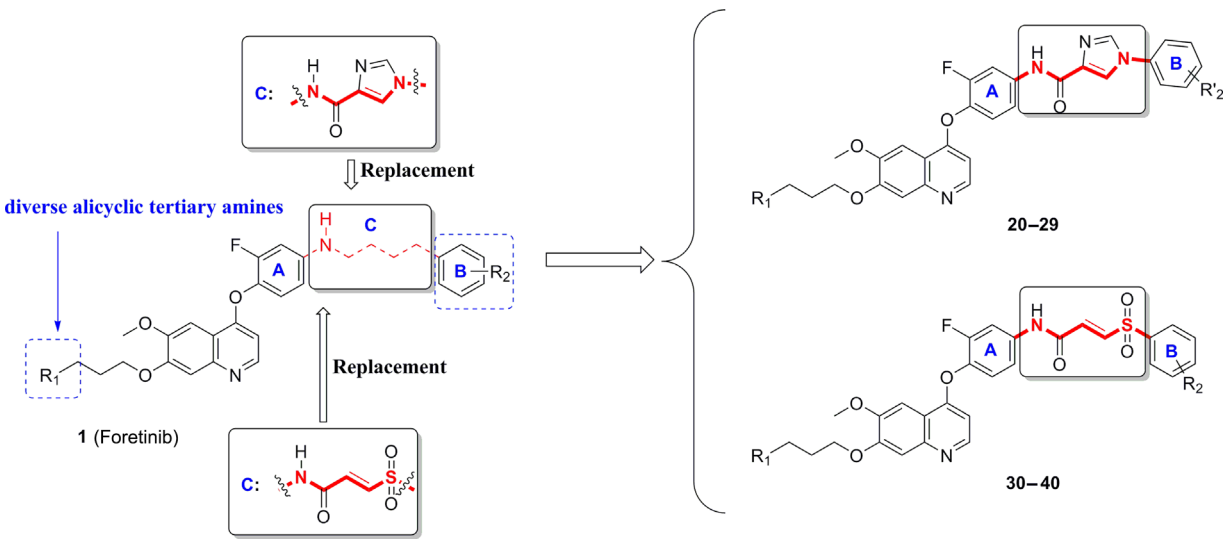

Figure 3. General structures of target compounds **20–40**.

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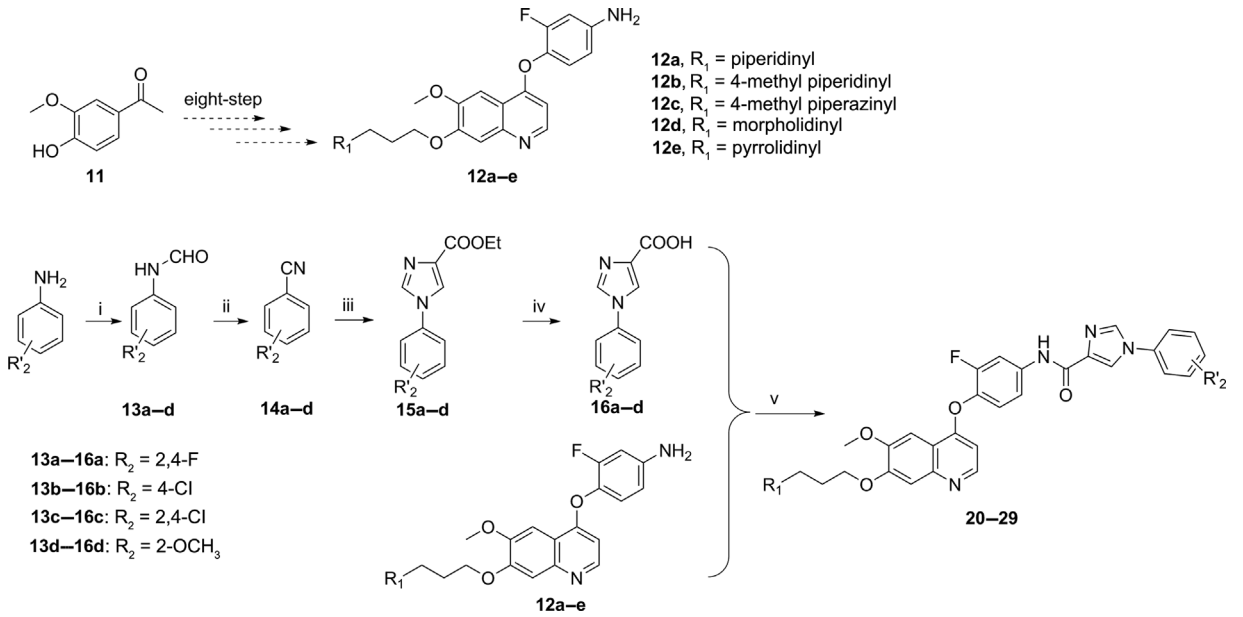


Scheme 1. Reagents and conditions: (i) HCOONa, HCOOH, reflux, 12 h; (ii) $POCl_3$, Et_3N, THF, 0°C, 30 min, r.t., 1 h; (iii) Cu_2O, THF, 4-methoxy-3-oxobutanenitrile, 1,10-phenanthroline, reflux, 3 h; (iv) lithium hydroxide, THF/ H_2O, r.t., 20 h; (v) $SOCl_2$, K_2CO_3, r.t., 5 h.

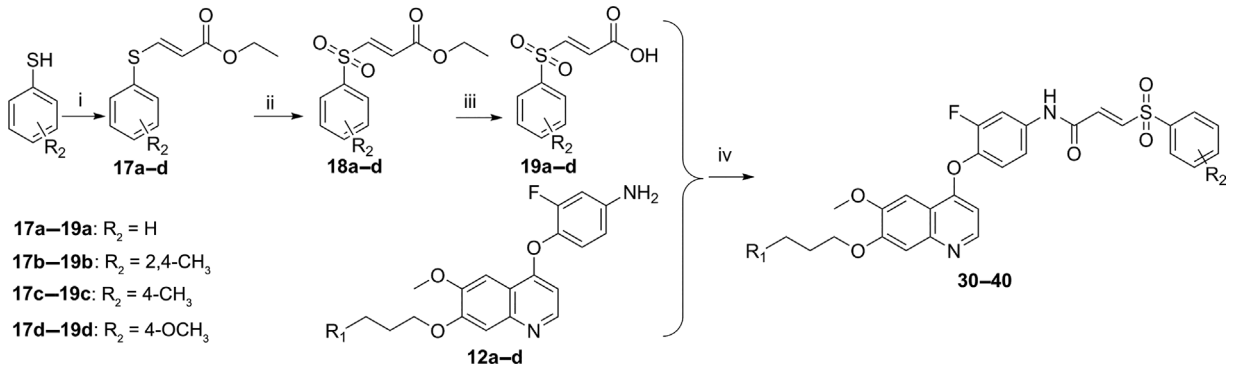
compounds **30–40** was progressed as previously described reactions from **19a–d** and **12a–d** in Scheme 1.

The existing carbon–carbon double bonds in compounds **30–40** could lead to *E* or *Z* isomeric forming. According to the reported motif of 3-(arylsulfonyl)-2-propiolates, the coupling constants of olefinic protons were observed for the *E* configuration ($^3J > 12.00$ Hz) and *Z* configuration ($^3J < 11.00$ Hz) (Fig. 4) [22, 23]. The coupling constants of compound **33** were furtherly identified using ^{1}H NMR (400 MHz) and the resulting coupling values of 12.0 Hz verified that its configuration is exclusive *E* isomer.

Biological assays

In vitro cytotoxicity and structure–activity relationships (SAR)

All the target compounds (**20–40**) were screened for their *in vitro* cytotoxic activity against three human cancer cell lines containing human colon cancer cell line (HT-29), human lung adenocarcinoma cell line (A549), and human gastric cancer cell line (MKN-45) with the positive control foretinib by MTT assay. The results were conveyed as IC_{50} values which were the average of at least three independent experiments, and are summarized in Table 1.



Scheme 2. Reagents and conditions: (i) Ethyl propionate, THF, 65°C, 1 h; (ii) H_2O_2, HOAc, 90°C, 1 h; (iii) lithium hydroxide, THF/ H_2O, r.t., 1 h.

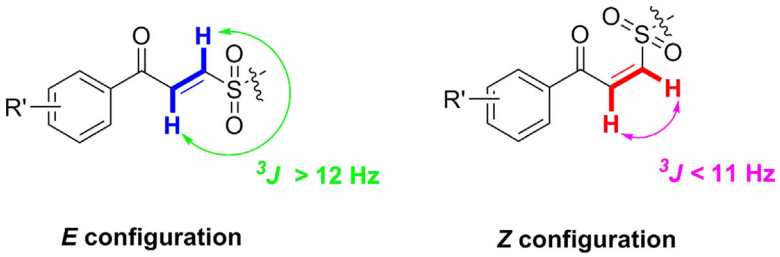


Figure 4. The configurations of (*E*)- or (*Z*)-3-(arylsulfonyl)-2-propiolate isomers.

As illustrated in Table 1, most of compounds showed moderate to excellent cytotoxic activity against tested cancer cells with IC_{50} ranging from 0.13 to 2.65 μM, which demonstrated that the introduction of (*E*)-3-hydrosulfonylacrylamido or 1*H*-imidazole-4-carboxamido moieties as the linker maintained antitumor potency. Among them, compound **30** exhibited the most promising cytotoxicity with the IC_{50} values of 0.24, 0.45, and 0.13 μM against HT-29, MKN-45, and A549 cells as comparable to foretinib (0.25, 0.32, 0.15 μM). It was noticeable that the majority of compounds were more effective against A549 than other two cell lines which reflected good selectivity for lung adenocarcinoma.

The data in Table 1 disclosed that a tether linkage of (*E*)-3-hydrosulfonylacrylamido motif was superior to the cyclic linker of 1*H*-imidazole-4-carboxamido moiety. Preliminary SAR study focused on 6,7-disubstituted-4-phenoxyquinoline derivatives bearing 1*H*-imidazole-4-carboxamido moiety (**20–29**) and indicated that the introduction of various tertiary amines groups at R_1 group had a moderate influence on activity. For example, compounds **20** or **21** with pyrrolidinyl or 4-methyl piperidinyl groups were better than the morpholinyl derivatives **22** in the antiproliferative activities, and the same trend was observed for compounds **24–26**.

In addition, further analysis clearly revealed that different biological properties were observed when diverse R_2 groups were introduced into the phenyl ring (moiety B). The introduction of mono-electron-withdrawing groups (**20**, R_2' = 4-chloride, IC_{50} = 0.25 μM against A549) exhibited improved cytotoxic activity compared to double-EWGs (**24**, R_2' = 2,4-dichloro, IC_{50} = 0.44 μM against A549) by 1.45-fold. Moreover, the incorporation of different double-EWGs made a negative contribution to potency, such as compound **26** (R_2' = 2,4-dichloro, IC_{50} = 1.13 μM against A549) was more active than **29** (R_2' = 2,4-1,2-difluoro, IC_{50} = 1.43 μM against A549).

To further verify the optimized structural skeleton and explore the SAR, our attention was converted to compounds **30–40** with (*E*)-3-hydrosulfonylacrylamido linkage. It can be noted that compound **35** with *N*-methylpiperazinyl at R_1 group afforded the improved antitumor potency than the derivatives **36–38** with morpholinyl, 4-methylpiperidinyl, or piperidinyl groups, respectively. The introduction of electron-donating groups (EDGS) into the phenyl ring (B moiety) resulted in a decrease in antitumor activity. For instance, compounds with 4-methoxy (**34**, IC_{50} = 0.63 μM against A549) or 2,4-dimethyl (**37**, IC_{50} = 1.00 μM against A549) brought about 1.2-fold less in activity in contrast with the compound **31** (IC_{50} = 0.58 μM against A549) than with no substituent on the phenyl ring.

In vitro enzymatic assays

Based on the cellular assays, five compounds (**20**, **21**, **30**, **31**, and **33**) were selected for further *in vitro* c-Met inhibitory studies. In parallel with the cellular results, all of the tested compounds displayed good to significant potency against c-Met with values ranging from 1.52 to 30.15 nM. As shown in Table 2, the most potent compound **30** exhibited prominent potency against c-Met kinase with an IC_{50} value of 1.52 nM, which was similar to the positive control foretinib (IC_{50} = 1.48 nM).

For examining the selectivity of the most potent compound **30** on c-Met over other kinases, it was sifted against five other tyrosine kinases (Table 3). The data showed that **30** expressed little inhibitory effects against c-Kit, Flt-3, PDGFRa, and VEGFR-2 kinase with the potency 58.6- to 352.1-fold lower than that against c-Met. Likewise, **30** showed barely inhibited kinase activity against EGFR kinase (IC_{50} > 3 μM). The pharmacological data in Tables 2 and 3 indicated that 6,7-disubstituted-4-phenoxyquinoline derivatives possessing (*E*)-3-hydrosulfonylacrylamido moiety are novel selectivity c-Met inhibitors, which deserves further study with respect to its application in the treatment of cancer.

Binding model analysis

To further elucidate the binding mode of compounds, the docking simulation was conducted using Discovery Studio 3.0 software. The co-crystal structure of foretinib (GSK 1363089) with c-Met was selected as the docking model (PDB ID code: 3LQ8). The binding model was exemplified by the interaction of compounds **20** and **30** with c-Met. As shown in Fig. 5, the oxygen atom of 1*H*-imidazole-4-carboxamido moiety and the nitrogen atom of the quinoline ring in **20** formed two hydrogen binds with protein residues Lys1110 and Met1160. It can be observed that compound **30** bound well to c-Met domain via four hydrogen bonds. The nitrogen atom of 2-position and oxygen atom at 6-position of quinoline interacted with

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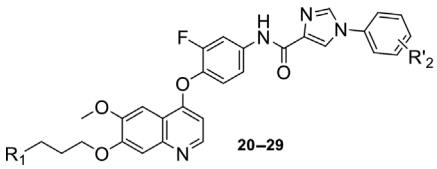
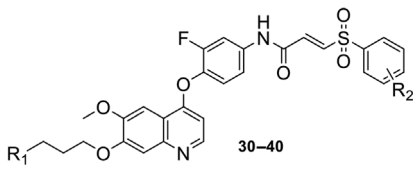
Table 1. **Structures and cytotoxicities of compounds 20–40 against HT-29, MKN-45, A549 cell lines *in vitro*.**



20–29



30–40

Compd.	R_1	R_2/R_2'	IC_{50} (μmol/L) ± SD		
			HT29	MKN45	A549
20	Pyrrolidinyl	4-Cl	0.29 ± 0.01	0.33 ± 0.03	0.25 ± 0.08
21	4-Methylpiperidinyl	4-Cl	0.33 ± 0.04	0.38 ± 0.02	0.32 ± 0.01
22	Morpholinyl	4-Cl	0.78 ± 0.004	0.87 ± 0.02	0.50 ± 0.05
23	Pyrrolidinyl	2-OCH_3	0.45 ± 0.01	0.37 ± 0.11	0.35 ± 0.03
24	Pyrrolidinyl	2,4-Cl	0.54 ± 0.22	0.48 ± 0.03	0.44 ± 0.11
25	4-Methylpiperidinyl	2,4-Cl	0.90 ± 0.002	0.98 ± 0.04	0.71 ± 0.05
26	Morpholinyl	2,4-Cl	1.63 ± 0.01	1.35 ± 0.02	1.13 ± 0.17
27	4-Methylpiperazinyl	2,4-F	1.34 ± 0.30	1.43 ± 0.01	1.28 ± 0.02
28	Piperidinyl	2,4-F	1.50 ± 0.05	2.41 ± 0.03	1.42 ± 0.12
29	Morpholinyl	2,4-F	1.67 ± 0.16	1.49 ± 0.03	1.43 ± 0.09
30	4-Methylpiperazinyl	H	0.24 ± 0.01	0.45 ± 0.01	0.13 ± 0.11
31	4-Methylpiperidinyl	H	0.63 ± 0.002	0.65 ± 0.02	0.58 ± 0.10
32	Piperidinyl	H	0.60 ± 0.08	0.83 ± 0.02	0.60 ± 0.03
33	Morpholinyl	4-OCH_3	0.35 ± 0.13	0.41 ± 0.03	0.34 ± 0.03
34	4-Methylpiperidinyl	4-OCH_3	0.93 ± 0.01	1.18 ± 0.12	0.63 ± 0.17
35	4-Methylpiperazinyl	2,4-CH_3	0.92 ± 0.11	0.89 ± 0.04	0.62 ± 0.11
36	Morpholinyl	2,4-CH_3	1.12 ± 0.07	0.92 ± 0.02	0.78 ± 0.13
37	4-Methylpiperidinyl	2,4-CH_3	1.30 ± 0.004	0.85 ± 0.01	1.00 ± 0.05
38	Piperidinyl	2,4-CH_3	1.57 ± 0.16	2.65 ± 0.03	1.30 ± 0.07
39	Morpholinyl	4-CH_3	0.84 ± 0.08	0.60 ± 0.01	0.70 ± 0.05
40	4-Methylpiperidinyl	4-CH_3	0.88 ± 0.04	0.93 ± 0.01	0.85 ± 0.02
Foretinib			0.25 ± 0.01	0.32 ± 0.03	0.15 ± 0.01

Met1160 and Asp1164 via two hydrogen bonds, and the (*E*)-3-hydrosulfonylacrylamido moiety formed two hydrogen-bonding with Met1131 and Asp1222, respectively. Hence, **30** contained more hydrogen bonds as compared with **20**, suggesting that the much stronger binding force with c-Met could be the reason for that (*E*)-3-hydrosulfonylacrylamido-based derivatives (**30–40**) were superior to the cyclic linker of 1*H*-imidazole-4-carboxamido-based derivatives (**20–29**).

Conclusion

In summary, 21 novel 6,7-disubstituted-4-phenoxyquinoline derivatives conjugated with 1*H*-imidazole-4-carboxamido or

Table 2. **c-Met kinase activity of selected compounds 20, 21, 30, 31, 33, and foretinib *in vitro*.**

Compd.	IC_{50} on c-Met (nM)
20	10.79
21	30.15
30	1.52
31	18.65
33	14.55
Foretinib	1.48

Table 3. **Inhibition of tyrosine kinases by compound 30.**

Kinase	Enzyme IC_{50} (nM)
c-Kit	89.0
Flt-3	124.5
PDGFRa	535.2
VEGFR-2	1323
EGFR	>3000

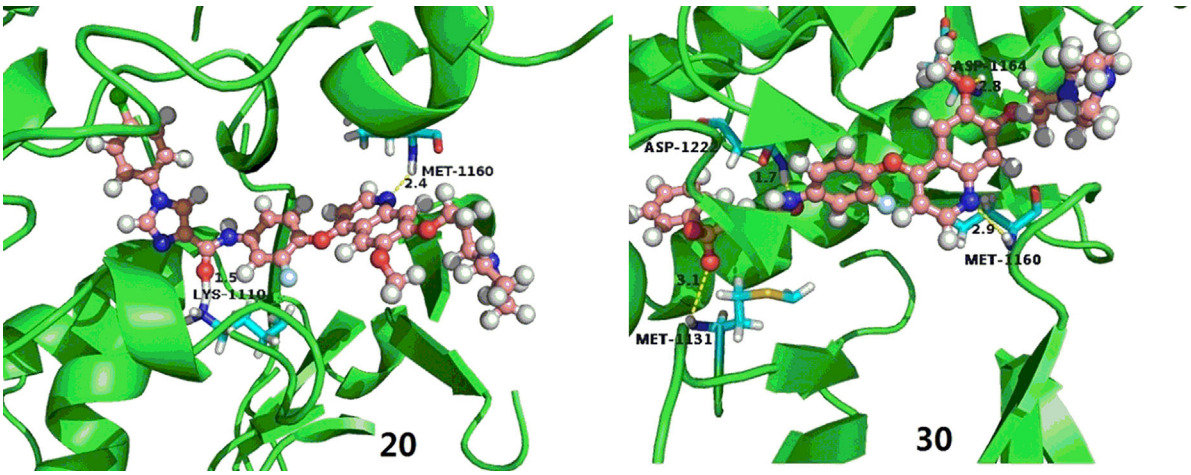


Figure 5. The proposed binding model of compounds **20** or **30** with c-Met. The protein is displayed by secondary structure. Compounds **20** and **30** are shown in colored sticks (pink: carbon atom, blue: nitrogen atom, red: oxygen atom, white: hydrogen atom). The hydrogen-bond is shown in yellow-dotted lines.

(*E*)-3-hydrosulfonylacrylamido moieties as c-Met inhibitors were designed, synthesized and evaluated for their biological activity. The screening of cytotoxicity and enzyme activities led to the identification of a most promising compound **30** (c-Met $IC_{50} = 1.52$ nM) with IC_{50} values of 0.24, 0.45, 0.13 μM against HT-29, MKN-45, and A549 cells, representing a promising lead for further optimization. The initial SARs analysis disclosed that the (*E*)-3-hydrosulfonylacrylamido scaffolds as the preferred linkage was benefit to the improvement of antitumor activity, and the introduction of *N*-methylpiperazinyl at R_1 group is indispensable for good cytotoxicity. Meanwhile, differences in various substituents on phenyl ring (B moiety) would result in lower or complete loss of antitumor potency. Further studies on structural optimization and the mechanisms of action are still underway and will be reported in the future.

Experimental

Chemistry

General

All melting points were obtained on a Büchi Melting Point B-540 apparatus (Büchi Labortechnik, Flawil, Switzerland). Mass spectra (MS) were taken in ESI mode on Agilent 1100 LC-MS (Agilent, Palo Alto, CA). ^{1}H NMR was recorded on Bruker ARX-400, 400 MHz (Bruker Bioscience, Billerica, MA) with TMS as an internal standard. All materials were obtained from commercial suppliers and were used without further purification. Reaction times 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).

Some NMR spectra as well as the InChI codes of the investigated compounds together with some biological activity data are provided as Supporting Information.

*Preparation of 3-fluoro-4-(6,7-disubstituted quinolin-4-yloxy)anilines **12a–e***

The preparation of the key intermediates (**12a–e**) has been illustrated in detail in our laboratory previous study, so the synthesis method would not be listed here.

*3-Fluoro-4-(6-methoxy-7-(3-(piperdine-1-yl)propoxy)-quinolin-4-yloxy)aniline (**12a**)*

Gray solid; yield: 85.5%; m.p.: 196–197°C; MS (ESI) *m/z*: 426.3 $[M+H]^+$.

*3-Fluoro-4-(6-methoxy-7-(3-(4-methylpiperdine-1-yl)-propoxy)quinolin-4-yl-oxy)aniline (**12b**)*

White solid; yield: 77.4%; m.p.: 193–194°C; MS (ESI) *m/z*: 440.3 $[M+H]^+$.

*3-Fluoro-4-(6-methoxy-7-(3-(4-methylpiperazine-1-yl)-propoxy)quinolin-4-yl-oxy)aniline (**12c**)*

White solid; yield: 77%; m.p.: 201–202°C; MS (ESI) *m/z*: 441.4 $[M+H]^+$, 463.3 $[M+Na]^+$.

*3-Fluoro-4-(6-methoxy-7-(3-morpholinopropoxy)quinolin-4-yloxy)aniline (**12d**)*

White solid; yield: 81.8%; m.p.: 217–218°C; MS (ESI) *m/z*: 428.2 $[M+H]^+$, 450.1 $[M+Na]^+$.

*3-Fluoro-4-(6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy)-quinolin-4-yloxy)aniline (**12e**)*

Light yellow solid; yield: 72.3%; m.p.: 208–209°C; MS (ESI) *m/z*: 412.5 $[M+H]^+$.

*General procedure for the preparation of the intermediates of N-phenylformamide (**13a–d**)*
Commercially available substituted aniline (40.7 mmol) and sodium formate were added portionwise to a solution of formic acid (12.5 mL). The above mixture was stirred at room temperature for 12 h. The reaction mixture was evaporated, dissolved in ethyl acetate (50 mL), washed by water (20 mL), and then was evaporated to afford light yellow solids (**13a–d**).

*N-(2,4-Difluorophenyl)formamide (**13a**)*
Light yellow solid; yield: 83%; MS (ESI) *m/z*: 158.0 $[M+H]^+$.

*N-(4-Chlorophenyl)formamide (**13b**)*
Light yellow solid; yield: 81.5%; MS (ESI) *m/z*: 157.0 $[M+H]^+$.

*N-(2,4-Dichlorophenyl)formamide (**13c**)*
Yellow solid; yield: 78.9%; MS (ESI) *m/z*: 191.1 $[M+H]^+$.

*N-(2-Methoxyphenyl)formamide (**13d**)*
Yellow solid; yield: 85.0%; MS (ESI) *m/z*: 152.1 $[M+H]^+$.

*General procedure for the preparation of benzonitriles (**14a–d**)*
A mixture of appropriate substituted benzonitrile **13a–d** (33.1 mmol) and triethylamine (128.7 mmol) in THF was cooled to 0°C. A solution of $POCl_3$ (41.4 mmol) in THF (20 mL) was slowly added thereto for 30 min. The reaction mixture was stirred at room temperature for 1 h. The reaction mixture was cooled to 0°C, was added to water (250 mL), filtered, and dried under vacuum to afford the title compounds **14a–d**.

*2,4-Difluorobenzonitrile (**14a**)*
Yellow solid; yield: 85.6%; MS (ESI) *m/z*: 140.0 $[M+H]^+$.

*4-Chlorobenzonitrile (**14b**)*
Yellow solid; yield: 88.2%; MS (ESI) *m/z*: 139.0 $[M+H]^+$.

*2,4-Dichlorobenzonitrile (**14c**)*
Yellow solid; yield: 86.2%; MS (ESI) *m/z*: 173.0 $[M+H]^+$.

*2-Methoxybenzonitrile (**14d**)*
Yellow solid; yield: 87.4%; MS (ESI) *m/z*: 134.1 $[M+H]^+$.

*General procedure for the preparation of ethyl 1-phenyl-1H-imidazole-4-carboxylates (**15a–d**)*
A mixture of appropriate **14a–d** (24.8 mmol), 4-methoxy-3-oxobutanenitrile (35.4 mmol), cuprous oxide (3.5 mmol), and 1,10-phenanthroline (5.1 mmol) in THF (50 mL) was refluxed for 3 h. The reaction mixture was concentrated under reduced pressure, dissolved into ethyl acetate (50 mL), filtered, evaporated the most solution, and then was cooled to separate out solid. The solid was washed with cool methanol to afford **15a–d**.

*Ethyl 1-(2,4-difluorophenyl)-1H-imidazole-4-carboxylate (**15a**)*
Light yellow solid; yield: 63.2%; MS (ESI) *m/z*: 253.1 $[M+H]^+$.

*Ethyl 1-(4-chlorophenyl)-1H-imidazole-4-carboxylate (**15b**)*
Light yellow solid; yield: 53.8%; MS (ESI) *m/z*: 252.0 $[M+H]^+$.

*Ethyl 1-(2,4-dichlorophenyl)-1H-imidazole-4-carboxylate (**15c**)*
Light yellow solid; yield: 66.4%; MS (ESI) *m/z*: 285.0 $[M+H]^+$.

*Ethyl 1-(2-methoxyphenyl)-1H-imidazole-4-carboxylate (**15d**)*
Light yellow solid; yield: 87.4%; MS (ESI) *m/z*: 247.1 $[M+H]^+$.

*General procedure for the preparation of 1-phenyl-1H-imidazole-4-carboxylic acids (**16a–d**)*
To a solution of an appropriate intermediate **15a–d** (4.1 mmol) dissolved in THF/H_2O (10 mL, 4:1) was added 2 eq of lithium hydroxide monohydrate, and the resulting suspension was stirred for 20 h at room temperature. Then, most of the solvent was evaporated, and the residue was poured into water (5 mL) and the resulting solution was extracted with ethyl acetate two times (20 mL × 2). The aqueous layer was acidified by addition of 6 N hydrogen chloride solutions until pH 3. The solid which precipitated was collected by filtration to afford substituted acids (**16a–d**).

*1-(2,4-Difluorophenyl)-1H-imidazole-4-carboxylic acid (**16a**)*
White solid; yield: 73.2%; m.p.: 144.4–146.0°C; MS (ESI) *m/z*: 225.0 $[M+H]^+$.

*1-(4-Chlorophenyl)-1H-imidazole-4-carboxylic acid (**16b**)*
White solid; yield: 80.2%; m.p.: 154.4–156.0°C; MS (ESI) *m/z*: 223.0 $[M+H]^+$.

*1-(2,4-Dichlorophenyl)-1H-imidazole-4-carboxylic acid (**16c**)*
White solid; yield: 78.0%; m.p.: 160.0–162.8°C; MS (ESI) *m/z*: 257.0 $[M+H]^+$.

*1-(2-Methoxyphenyl)-1H-imidazole-4-carboxylic acid (**16d**)*
White solid; yield: 86.2%; m.p.: 161.0–163.0°C; MS (ESI) *m/z*: 219.1 $[M+H]^+$.

*General procedure for the preparation of ethyl (E)-3-(phenylthio)acrylates (**17a–d**)*
A mixture of commercially available substituted benzenethiol (21.4 mmol), ethyl propionate (23.6 mmol), and THF (5 mL) was heated at 65°C for 1 h. Upon cooling to room temperature, the solvent was evaporated in vacuum to afford compounds (**17a–d**).

*Ethyl (E)-3-(phenylthio)acrylate (**17a**)*
White solid; yield: 71.2%; MS (ESI) *m/z*: 209.1 $[M+H]^+$.

*Ethyl (E)-3-((2,4-dimethylphenyl)thio)acrylate (**17b**)*
White solid; yield: 83.2%; MS (ESI) *m/z*: 237.1 $[M+H]^+$.

*Ethyl (E)-3-(p-tolylthio)acrylate (**17c**)*
White solid; yield: 69.7%; MS (ESI) *m/z*: 223.1 $[M+H]^+$.

*Ethyl (E)-3-((4-methoxyphenyl)thio)acrylate (**17d**)*
White solid; yield: 86.2%; MS (ESI) *m/z* (%): 239.1 $[M+H]^+$.

*General procedure for the preparation of ethyl (E)-3-(phenylsulfonyl)acrylates (**18a–d**)*
To a solution of **17a–d** (12.6 mmol) in acetic acid (60 mL), 30% hydrogen peroxide (208.8 mmol) was added dropwise while maintaining the temperature below 50°C. After the addition was completed, the mixture was heated to 90°C for 1 h. After cooling, the reaction mixture was evaporated to give compounds **18a–d**.

*Ethyl (E)-3-(phenylsulfonyl)acrylate (**18a**)*
Light yellow solid; yield: 83.2%; MS (ESI) *m/z*: 241.0 $[M+H]^+$.

*Ethyl (E)-3-((2,4-dimethylphenyl)sulfonyl)acrylate (**18b**)*
Light yellow solid; yield: 85.2%; MS (ESI) *m/z*: 269.1 $[M+H]^+$.

*Ethyl (E)-3-tosylacrylate (**18c**)*
Light yellow solid; yield: 80.2%; MS (ESI) *m/z*: 255.1 $[M+H]^+$.

*Ethyl (E)-3-((2-methoxyphenyl)sulfonyl)acrylate (**18d**)*
Light yellow solid; yield: 73.2%; MS (ESI) *m/z*: 271.1 $[M+H]^+$.

*General procedure for the preparation of (E)-3-(phenylsulfonyl)acrylic acids (**19a–d**)*
To a solution of an appropriate intermediate **18a–d** (7.1 mmol) dissolved in THF/H_2O (25 mL, 3:2) was added 2 eq of lithium hydroxide monohydrate, and the resulting suspension was stirred for 1 h at room temperature. Then, most of the solvent was evaporated, and the residue was poured into water (5 mL). The aqueous layer was acidified by addition of 6 N hydrochloric acid solutions until pH 3, and then separated out from hydraulic. The mixture was filtered to collected substituted acids (**19a–d**).

*(E)-3-(Phenylsulfonyl)acrylic acid (**19a**)*
Yellow solid; yield: 73.2%; m.p.: 117.0–119.4°C; MS (ESI) *m/z*: 213.0 $[M+H]^+$.

*(E)-3-((2,4-Dimethylphenyl)sulfonyl)acrylic acid (**19b**)*
Yellow solid; yield: 74.0%; m.p.: 118.0–119.4°C; MS (ESI) *m/z*: 241.0 $[M+H]^+$.

*(E)-3-Tosylacrylic acid (**19c**)*
Yellow solid; yield: 83.2%; m.p.: 100.2–102.4°C; MS (ESI) *m/z*: 227.0 $[M+H]^+$.

*(E)-3-((2-Methoxyphenyl)sulfonyl)acrylic acid (**19d**)*
Yellow solid; yield: 76.2%; m.p.: 97.0–99.4°C; MS (ESI) *m/z*: 243.0 $[M+H]^+$.

*General procedure for the preparation of the target compounds **20–29***
A mixture of the corresponding acid (**16a–d**) (1.0 mmol), toluene (10 mL), and $SOCl_2$ (10 mL) was heated at 85°C for 5 h. Upon cooling to room temperature, the solvent was evaporated in vacuum. The residue was dissolved in dried dichloromethane (20 mL) and dropwise added to a mixture of the corresponding aniline (**12a–e**) (1.3 mmol), K_2CO_3 (4.4 mmol) and dichloromethane (20 mL) in an ice bath for 30 min, which was then removed to raise the temperature to room temperature and stirred for 2 h. The resulting mixture was sequentially washed with water (100 mL) and 1% K_2CO_3 (100 mL), and the organic phase was separated, dried, and evaporated. The crude product obtained was purified by silica gel chromatography using a mixture of CH_2Cl_2/MeOH (25:1) to afford **20–29** as white solids.

*1-(4-Chlorophenyl)-N-(3-fluoro-4-((6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl)-1H-imidazole-4-carboxamide (**20**)*
Yield: 79.7%; m.p.: 157.9–160.0°C; MS (ESI) *m/z*: 616.2 $[M+H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 9.10 (s, 1H), 8.49 (d, $J = 5.2$ Hz, 1H), 8.00 (s, 1H), 7.95 (dd, $J = 1.2$ Hz, 1H), 7.82 (s, 1H), 7.58 (s, 1H), 7.53 (d, $J = 8.5$ Hz, 2H), 7.43 (s, 1H), 7.40 (d, $J = 8.9$ Hz, 1H), 7.41 (s, 1H), 7.26 (s, 1H), 6.44 (d, $J = 5.1$ Hz, 1H), 4.27 (t, $J = 6.2$ Hz, 2H), 4.04 (s, 3H), 2.94 (m, 4H), 2.81 (m, 2H), 2.32 (s, 2H), 1.94 (s, 4H). Anal. calcd. for $C_{33}H_{31}ClFN_5O_4$ (%): C, 64.34; H, 5.07; N, 11.37. Found (%): C, 64.32; H, 5.02; N, 11.34.

*1-(4-Chlorophenyl)-N-(3-fluoro-4-((6-methoxy-7-(3-(4-methylpiperidin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl)-1H-imidazole-4-carboxamide (**21**)*
Yield: 80.7%; m.p.: 167.9–169.0°C; MS (ESI) *m/z*: 644.2 $[M+H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 9.09 (s, 1H), 8.49 (d, $J = 5.2$ Hz, 1H), 8.00 (d, $J = 1.2$ Hz, 1H), 7.95 (dd, $J = 12.1$, 2.4 Hz, 1H), 7.81 (d, $J = 1.2$ Hz, 1H), 7.58 (s, 1H), 7.52 (d, $J = 8.7$ Hz, 2H), 7.40 (t, $J = 6.3$ Hz, 4H), 7.27 (s, 1H), 6.43 (d, $J = 5.2$ Hz, 1H), 4.25 (t, $J = 6.5$ Hz, 2H), 4.04 (s, 3H), 3.02 (s, 2H), 2.66 (s, 1H), 2.14 (m, 4H), 1.66 (d, $J = 10.1$ Hz, 2H), 1.39 (m, 4H), 0.95 (s, 3H). Anal. calcd. for $C_{35}H_{35}ClFN_5O_4$ (%): C, 65.26; H, 5.48; N, 10.87. Found (%): C, 65.23; H, 5.42; N, 10.86.

*1-(4-Chlorophenyl)-N-(3-fluoro-4-((6-methoxy-7-(3-morpholinopropoxy)quinolin-4-yl)oxy)phenyl)-1H-imidazole-4-carboxamide (**22**)*
Yield: 83.7%; m.p.: 157.9–159.0°C; MS (ESI) *m/z*: 632.2 $[M+H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 9.09 (s, 1H), 8.49 (d, $J = 5.3$ Hz, 1H), 8.00 (d, $J = 1.1$ Hz, 1H), 7.95 (dd, $J = 2.3$, 1.7 Hz, 1H), 7.81 (d, $J = 1.0$ Hz, 1H), 7.59 (s, 1H), 7.53 (d, $J = 8.7$ Hz, 2H), 7.44 (s, 1H), 7.40 (d, $J = 8.7$ Hz, 2H), 7.24 (s, 1H), 6.44 (d, $J = 5.2$ Hz, 1H), 4.28 (t, $J = 6.6$ Hz, 2H), 4.05 (s, 3H), 3.79–3.67 (m, 4H), 2.59 (t, $J = 6.8$ Hz, 4H), 2.47 (m, 2H), 2.18–2.11 (m,

$J = 6.8$ Hz, 2H). Anal. calcd. for $C_{33}H_{31}ClFN_5O_5$ (%): C, 62.71; H, 4.94; N, 11.08. Found (%): C, 62.70; H, 4.93; N, 11.09.

*N-(3-Fluoro-4-((6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy)-quinolin-4-yl)oxy)phenyl)-1-(2-(trifluoromethoxy)phenyl)-1H-imidazole-4-carboxamide (**23**)*
Yield: 80.1%; m.p.: 157.9–160.0°C; MS (ESI) *m/z*: 666.2 $[M+H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 9.14 (s, 1H), 8.51 (s, 1H), 7.96 (d, $J = 13.0$ Hz, 1H), 7.92 (s, 1H), 7.74 (s, 1H), 7.59 (s, 1H), 7.54 (m, 1H), 7.52 (s, 1H), 7.49 (d, $J = 3.2$ Hz, 2H), 7.42 (d, $J = 8.4$ Hz, 2H), 7.23 (s, 1H), 6.46 (s, 1H), 4.27 (s, 2H), 4.03 (s, 3H), 3.32 (s, 6H), 2.54 (s, 2H), 2.15 (s, 4H). Anal. calcd. for $C_{34}H_{31}F_4N_5O_5$ (%): C, 61.35; H, 4.69; N, 10.52. Found (%): C, 61.33; H, 4.71; N, 10.54.

*1-(2,4-Dichlorophenyl)-N-(3-fluoro-4-((6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl)-1H-imidazole-4-carboxamide (**24**)*
Yield: 79.7%; m.p.: 157.9–160.0°C; MS (ESI) *m/z*: 650.2 $[M+H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 9.05 (s, 1H), 8.44 (d, $J = 8.0$ Hz, 1H), 7.89 (d, $J = 16.0$ Hz, 1H), 7.80 (s, 1H), 7.61 (s, 1H), 7.57 (d, $J = 1.76$ Hz, 1H), 7.53 (s, 1H), 7.37 (d, $J = 4.0$ Hz, 1H), 7.34 (s, 1H), 7.29 (d, $J = 8.4$ Hz, 1H), 7.16 (s, 1H), 7.08 (t, $J = 9.0$ Hz, 1H), 6.39 (d, $J = 5.1$ Hz, 1H), 4.20 (t, $J = 5.7$ Hz, 2H), 3.97 (s, 3H), 3.12 (s, 2H), 2.37 (s, 2H), 2.01 (s, 4H), 1.61 (s, 4H). Anal. calcd. for $C_{33}H_{30}Cl_2FN_5O_4$ (%): C, 60.93; H, 4.65; N, 10.77. Found (%): C, 60.91; H, 4.67; N, 10.73.

*1-(2,4-Dichlorophenyl)-N-(3-fluoro-4-((6-methoxy-7-(3-(4-methylpiperidin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl)-1H-imidazole-4-carboxamide (**25**)*
Yield: 80.1%; m.p.: 145.9–147.6°C; MS (ESI) *m/z*: 678.2 $[M+H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 9.11 (s, 1H), 8.49 (d, $J = 5.2$ Hz, 1H), 7.95 (dd, $J = 12.1$, 2.0 Hz, 1H), 7.86 (s, 1H), 7.67 (s, 1H), 7.63 (d, $J = 2.0$ Hz, 1H), 7.58 (s, 1H), 7.44 (d, $J = 2.1$ Hz, 1H), 7.42 (d, $J = 2.0$ Hz, 1H), 7.40 (m, 1H), 7.35 (d, $J = 8.5$ Hz, 1H), 7.24 (s, 1H), 6.43 (d, $J = 5.2$ Hz, 1H), 4.25 (t, $J = 6.4$ Hz, 2H), 4.03 (s, 3H), 3.05 (s, 2H), 2.70 (s, 1H), 2.17 (m, 4H), 1.67 (d, $J = 10.4$ Hz, 2H), 1.40 (s, 4H), 0.94 (d, $J = 4.9$ Hz, 3H). Anal. calcd. for $C_{35}H_{34}Cl_2FN_5O_4$ (%): C, 61.95; H, 5.05; N, 10.32. Found (%): C, 61.93; H, 5.07; N, 10.30.

*1-(2,4-Dichlorophenyl)-N-(3-fluoro-4-((6-methoxy-7-(3-morpholinopropoxy)quinolin-4-yl)oxy)phenyl)-1H-imidazole-4-carboxamide (**26**)*
Yield: 80.1%; m.p.: 110.0–110.2°C; MS (ESI) *m/z*: 666.2 $[M+H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 9.12 (s, 1H), 8.49 (s, 1H), 7.95 (d, $J = 11.7$ Hz, 1H), 7.86 (s, 1H), 7.67 (s, 1H), 7.63 (d, $J = 2.0$ Hz, 1H), 7.58 (s, 1H), 7.44 (d, $J = 2.1$ Hz, 1H), 7.42 (d, $J = 2.0$ Hz, 1H), 7.40 (m, 1H), 7.35 (d, $J = 8.5$ Hz, 1H), 7.24 (s, 1H), 6.44 (s, 1H), 4.27 (s, 2H), 4.04 (s, 3H), 3.73 (s, 4H), 2.59 (s, 2H), 2.50 (s, 4H), 2.14 (s, 2H). Anal. calcd. for $C_{33}H_{30}Cl_2FN_5O_5$ (%): C, 59.47; H, 4.54; N, 10.51. Found (%): C, 59.49; H, 4.52; N, 10.51.

*1-(2,4-Difluorophenyl)-N-(3-fluoro-4-((6-methoxy-7-(3-(4-methylpiperazin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl)-1H-imidazole-4-carboxamide (**27**)*
Yield: 82.1%; m.p.: 116.0–118.2°C; MS (ESI) *m/z*: 647.3 $[M+H]^+$; ^{1}H NMR (400 MHz, Acetic) δ (ppm) 9.86 (s, 1H), 8.85 (d, $J = 6.6$ Hz, 1H), 8.58 (s, 1H), 8.34 (s, 1H), 8.16 (dd, $J = 12.6$, 2.1 Hz, 1H), 7.94 (s, 1H), 7.90 (d, $J = 8.8$ Hz, 1H), 7.80 (s, 1H), 7.51 (t, $J = 8.8$ Hz, 1H), 7.34 (d, $J = 5.5$ Hz, 2H), 7.05 (t, $J = 9.0$ Hz, 1H), 6.97 (d, $J = 6.4$ Hz, 1H), 4.45 (t, $J = 4.5$ Hz, 2H), 3.92 (s, 3H), 2.48 (d, $J = 11.6$ Hz, 2H), 2.29 (t, $J = 7.1$ Hz 8H), 2.14 (s, 3H), 1.83 (d, $J = 11.6$ Hz, 2H). Anal. calcd. for $C_{34}H_{33}F_3N_6O_4$ (%): C, 63.15; H, 5.14; N, 13.00. Found (%): C, 63.14; H, 5.15; N, 13.01.

*1-(2,4-Difluorophenyl)-N-(3-fluoro-4-((6-methoxy-7-(3-(piperidin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl)-1H-imidazole-4-carboxamide (**28**)*
Yield: 77.8%; m.p.: 145.9–147.6°C; MS (ESI) *m/z*: 632.2 $[M+H]^+$; ^{1}H NMR (400 MHz, Acetic) δ (ppm) 8.85 (d, $J = 6.6$ Hz, 1H), 8.59 (s, 1H), 8.34 (s, 1H), 8.15 (dd, $J = 12.6$, 2.1 Hz, 1H), 7.94 (s, 1H), 7.88 (d, $J = 8.8$ Hz, 1H), 7.84 (s, 1H), 7.51 (t, $J = 8.8$ Hz, 1H), 7.38 (d, $J = 5.5$ Hz, 2H), 7.08 (t, $J = 9.0$ Hz, 1H), 6.99 (d, $J = 6.4$ Hz, 1H), 4.45 (t, $J = 4.5$ Hz, 2H), 4.12 (s, 3H), 3.79 (d, $J = 11.6$ Hz, 2H), 3.45 (t, $J = 7.3$ Hz, 2H), 2.98 (t, $J = 11.2$ Hz, 2H), 2.50 (s, 2H), 1.95 (s, 6H). Anal. calcd. For $C_{34}H_{32}F_3N_5O_4$ (%): C, 64.65; H, 5.11; N, 11.09. Found (%): C, 64.65; H, 5.13; N, 11.08.

*1-(2,4-Difluorophenyl)-N-(3-fluoro-4-((6-methoxy-7-(3-morpholinopropoxy)quinolin-4-yl)oxy)phenyl)-1H-imidazole-4-carboxamide (**29**)*
Yield: 81.7%; m.p.: 146.2–148.7°C; MS (ESI) *m/z*: 634.2 $[M+H]^+$; ^{1}H NMR (400 MHz, Acetic) δ (ppm) 8.85 (d, $J = 6.6$ Hz, 1H), 8.59 (s, 1H), 8.34 (s, 1H), 8.15 (dd, $J = 12.6$, 2.1 Hz, 1H), 7.94 (s, 1H), 7.88 (d, $J = 8.8$ Hz, 1H), 7.84 (s, 1H), 7.51 (t, $J = 8.8$ Hz, 1H), 7.38 (d, $J = 5.5$ Hz, 2H), 7.08 (t, $J = 9.0$ Hz, 1H), 6.99 (d, $J = 6.4$ Hz, 1H), 4.27 (s, 2H), 4.04 (s, 3H), 3.73 (s, 4H), 2.54 (d, $J = 35.1$ Hz, 6H), 2.14 (s, 2H). Anal. calcd. for $C_{33}H_{30}F_3N_5O_5$ (%): C, 62.55; H, 4.77; N, 11.05. Found (%): C, 62.52; H, 4.80; N, 11.03.

*General procedure for the preparation of the target compounds **30–40***
The compounds **19a–d** (1.5 mmol) were each dissolved in dried dichloromethane (15 mL), and refluxed with $SOCl_2$ (15 mL) for 3 h. Upon cooling to room temperature, the solvent was evaporated in vacuum. The residue was dissolved in dried dichloromethane (10 mL) and dropwise added to a mixture of the corresponding aniline (**12a–d**) (1 mmol), K_2CO_3 (2.1 mmol) and CH_2Cl_2 (15 mL) in an ice bath for 30 min, which was then removed to raise the temperature to room temperature and stirred for 5 h. The resulting mixture was evaporated and extracted with ethyl acetate (3×75 mL). The organic phase was sequentially washed with 5% K_2CO_3 (2×15 mL) and saturated sodium chloride solution (2×15 mL), and the organic phase was separated, dried, and evaporated. The crude product obtained was purified by silica gel chromatography using a mixture of CH_2Cl_2/MeOH (25:1) to afford **30–40**.

*(E)-N-(3-Fluoro-4-((6-methoxy-7-(3-(4-methylpiperazin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl)-3-(phenylsulfonyl) acrylamide (**30**)*
Yield: 83.4%; m.p.: 114.2–116.0°C; MS (ESI) *m/z*: 635.2 $[M+H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 10.22 (s, 1H), 8.43 (d, *J* = 8.0 Hz, 1H), 7.92 (m, *J* = 12.0, 1.4 Hz, 4H), 7.66 (t, *J* = 8.0 Hz, 1H), 7.58 (d, *J* = 4.0 Hz, 2H), 7.56 (s, 1H), 7.50 (s, 1H), 7.46 (s, 1H), 7.42 (d, *J* = 12.0 Hz, 1H), 7.16 (t, *J* = 8.0 Hz, 1H), 6.36 (d, *J* = 4.0 Hz, 1H), 4.25 (t, *J* = 6.4 Hz, 2H), 4.02 (s, 3H), 3.67 (d, *J* = 4.0 Hz, 2H), 2.89 (s, 3H), 2.70 (m, *J* = 7.0 Hz, 8H), 2.14 (t, *J* = 7.0 Hz, 2H). Anal. calcd. for $C_{33}H_{35}FN_4O_6S$ (%): C, 62.45; H, 5.56; N, 8.83. Found (%): C, 62.43; H, 5.58; N, 8.85.

*(E)-N-(3-Fluoro-4-((6-methoxy-7-(3-(4-methylpiperidin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl)-3-(phenylsulfonyl)-acrylamide (**31**)*
Yield: 62.4%; m.p.: 157.2–159.0°C; MS (ESI) *m/z*: 634.2 $[M+H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 9.10 (s, 1H), 8.43 (d, *J* = 4.0 Hz, 1H), 7.90 (d, *J* = 8.0 Hz, 2H), 7.83 (d, *J* = 12.0 Hz, 1H), 7.71 (d, *J* = 8.0 Hz, 1H), 7.61 (dd, *J* = 8.0 Hz, 2H), 7.56 (s, 1H), 7.49 (d, *J* = 12.0 Hz, 1H), 7.43 (s, 1H), 7.32 (d, *J* = 8.0 Hz, 1H), 7.28 (s, 1H), 7.21 (d, *J* = 8.0 Hz, 1H), 4.07 (t, *J* = 8.0 Hz, 2H), 3.92 (s, 3H), 2.57 (t, *J* = 8.0 Hz, 2H), 2.53 (s, 3H), 2.05 (m, *J* = 8.0 Hz, 2H), 2.40 (t, *J* = 8.0 Hz, 4H), 1.62 (m, *J* = 8.0 Hz, 1H), 1.33 (m, *J* = 8.0 Hz, 4H), 0.86 (s, 3H). Anal. calcd. for $C_{34}H_{36}FN_3O_6S$ (%): C, 64.44; H, 5.73; N, 6.63. Found (%): C, 64.46; H, 5.71; N, 6.59.

*(E)-N-(3-Fluoro-4-((6-methoxy-7-(3-(piperidin-1-yl)-propoxy)quinolin-4-yl)oxy)phenyl)-3-(phenylsulfonyl)-acrylamide (**32**)*
Yield: 87.0%; m.p.: 219.0–220.0°C; MS (ESI) *m/z*: 620.2 $[M+H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 9.03 (s, 1H), 8.48 (d, *J* = 4.0 Hz, 1H), 7.89 (d, *J* = 8.0 Hz, 2H), 7.76 (d, *J* = 12.0 Hz, 1H), 7.67 (d, *J* = 8.0 Hz, 1H), 7.60 (dd, *J* = 8.0 Hz, 2H), 7.56 (s, 1H), 7.49 (d, *J* = 12.0 Hz, 1H), 7.36 (s, 1H), 7.32 (d, *J* = 8.0 Hz, 1H), 7.20 (s, 1H), 7.12 (d, *J* = 8.0 Hz, 1H), 4.45 (t, *J* = 4.5 Hz, 2H), 4.12 (s, 3H), 3.79 (d, *J* = 11.6 Hz, 2H), 3.45 (t, *J* = 7.3 Hz, 2H), 2.98 (t, *J* = 11.2 Hz, 2H), 2.50 (s, 2H), 1.95 (s, 6H). Anal. calcd. for $C_{33}H_{34}FN_3O_6S$ (%): C, 63.96; H, 5.53; N, 6.78. Found (%): C, 63.94; H, 5.55; N, 6.78.

*(E)-N-(3-Fluoro-4-((6-methoxy-7-(3-morpholinopropoxy)-quinolin-4-yl)oxy)phenyl)-3-((4-methoxyphenyl)sulfonyl)-acrylamide (**33**)*
Yield: 82.1%; m.p.: 112.0–113.2°C; MS (ESI) *m/z*: 652.2 $[M+H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 9.13 (s, 1H), 8.45 (d, *J* = 4.0 Hz, 1H), 7.88 (d, *J* = 8.0 Hz, 2H), 7.83 (d, *J* = 12.0 Hz, 1H), 7.56 (s, 1H), 7.49 (d, *J* = 12.0 Hz, 1H), 7.43 (s, 1H), 7.32 (d, *J* = 8.0 Hz, 1H), 7.28 (s, 1H), 7.21 (d, *J* = 8.0 Hz, 1H), 7.06 (d, *J* = 8.0 Hz, 2H), 4.27 (t, *J* = 8.0 Hz, 2H), 4.04 (s, 3H), 3.91 (s, 3H), 3.74 (s, 4H), 2.59 (t, *J* = 8.0 Hz, 2H), 2.50 (s, 4H), 2.07 (m, *J* = 8.0 Hz, 2H). Anal. calcd. for $C_{33}H_{34}FN_3O_8S$ (%): C, 60.82; H, 5.26; N, 6.45. Found (%): C, 60.80; H, 5.28; N, 6.47.

*(E)-N-(3-Fluoro-4-((6-methoxy-7-(3-(4-methylpiperidin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl)-3-((4-methoxyphenyl)sulfonyl)acrylamide (**34**)*
Yield: 7.9%; m.p.: 129.0–131.1°C; MS (ESI) *m/z*: 664.2 $[M+H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 9.12 (s, 1H), 8.58 (d, *J* = 4.0 Hz, 1H), 7.96 (d, *J* = 8.0 Hz, 2H), 7.64 (d, *J* = 12.0 Hz, 1H), 7.52 (s, 1H), 7.49 (d, *J* = 12.0 Hz, 1H), 7.39 (s, 1H), 7.32 (d, *J* = 8.0 Hz, 1H), 7.26 (s, 1H), 7.10 (d, *J* = 8.0 Hz, 1H), 6.94 (d, *J* = 8.0 Hz, 2H), 4.27 (t, *J* = 8.0 Hz, 2H), 3.98 (s, 3H), 2.53 (t, *J* = 8.0 Hz, 2H), 2.46 (t, *J* = 8.0 Hz, 4H), 2.39 (s, 3H), 2.07 (m, *J* = 8.0 Hz, 2H), 1.60 (m, *J* = 8.0 Hz, 1H), 1.40 (m, *J* = 8.0 Hz, 4H), 0.90 (s, 3H). Anal. calcd. for $C_{35}H_{38}FN_3O_7S$ (%): C, 63.33; H, 5.77; N, 6.33. Found (%): C, 63.35; H, 5.75; N, 6.35.

*(E)-3-((2,4-Dimethylphenyl)sulfonyl)-N-(3-fluoro-4-((6-methoxy-7-(3-(4-methylpiperazin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl)acrylamide (**35**)*
Yield: 84.4%; m.p.: 104.2–106.0°C; MS (ESI) *m/z*: 663.3 $[M+H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 9.09 (s, 1H), 8.32 (d, *J* = 4.0 Hz, 1H), 7.91 (d, *J* = 12.0 Hz, 1H), 7.68 (d, *J* = 8.0 Hz, 1H), 7.52 (s, 1H), 7.48 (d, *J* = 12.0 Hz, 1H), 7.42 (s, 1H), 7.37 (s, 1H), 7.34 (d, *J* = 8.0 Hz, 1H), 7.32 (d, *J* = 8.0 Hz, 1H), 7.28 (s, 1H), 7.21 (d, *J* = 8.0 Hz, 1H), 6.48 (s, 1H), 4.27 (t, *J* = 8.0 Hz, 2H), 4.04 (s, 3H), 2.64 (s, 3H), 2.59 (t, *J* = 8.0 Hz, 2H), 2.36 (s, 3H), 2.30 (t, *J* = 8.0 Hz, 8H), 2.14 (s, 3H), 2.07 (m, *J* = 8.0 Hz, 2H). Anal. calcd. for $C_{35}H_{39}FN_4O_6S$ (%): C, 63.43; H, 5.93; N, 8.45. Found (%): C, 63.40; H, 5.96; N, 8.47.

*(E)-3-((2,4-Dimethylphenyl)sulfonyl)-N-(3-fluoro-4-((6-methoxy-7-(3-morpholinopropoxy)quinolin-4-yl)oxy)-phenyl)acrylamide (**36**)*
Yield: 82.3%; m.p.: 106.0–108.2°C; MS (ESI) *m/z*: 650.2 $[M+H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.98 (s, 1H), 8.62 (d, *J* = 4.0 Hz, 1H), 7.80 (d, *J* = 12.0 Hz, 1H), 7.70 (d, *J* = 8.0 Hz, 1H), 7.56 (s, 1H), 7.49 (d, *J* = 12.0 Hz, 1H), 7.42 (s, 1H), 7.43 (s, 1H), 7.34 (d, *J* = 8.0 Hz, 1H), 7.32 (d, *J* = 8.0 Hz, 1H), 7.28 (s, 1H), 7.21 (d, *J* = 8.0 Hz, 1H), 4.27 (t, *J* = 8.0 Hz, 2H), 4.04 (s, 3H), 3.74 (s, 4H), 2.64 (s, 3H), 2.59 (t, *J* = 8.0 Hz, 2H), 2.50 (s, 4H), 2.31 (s, 3H), 2.07 (m, *J* = 8.0 Hz, 2H). Anal. calcd. for $C_{34}H_{36}FN_3O_7S$ (%): C, 62.85; H, 5.59; N, 6.47. Found (%): C, 62.87; H, 5.61; N, 6.49.

*(E)-3-((2,4-Dimethylphenyl)sulfonyl)-N-(3-fluoro-4-((6-methoxy-7-(3-(4-methylpiperidin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl)acrylamide (**37**)*
Yield: 78.8%; m.p.: 111.0–113.2°C; MS (ESI) *m/z*: 662.3 $[M+H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 9.11 (s, 1H), 8.45 (d, *J* = 4.0 Hz, 1H), 7.83 (d, *J* = 12.0 Hz, 1H), 7.70 (d, *J* = 8.0 Hz, 1H), 7.56 (s, 1H), 7.49 (d, *J* = 12.0 Hz, 1H), 7.42 (s, 1H), 7.43 (s, 1H), 7.34 (d, *J* = 8.0 Hz, 1H), 7.32 (d, *J* = 8.0 Hz, 1H), 7.28 (s, 1H), 7.21 (d, *J* = 8.0 Hz, 1H), 4.27 (t, *J* = 8.0 Hz, 2H), 4.04 (s, 3H), 4.04 (s, 3H), 2.59 (t, *J* = 8.0 Hz, 2H), 2.43 (s, 3H), 2.07 (m, *J* = 8.0 Hz, 2H), 2.46 (t, *J* = 8.0 Hz, 4H), 1.60 (m, *J* = 8.0 Hz, 1H), 1.48 (m, *J* = 8.0 Hz, 4H), 0.86 (s, 3H). Anal. calcd. for $C_{36}H_{40}FN_3O_6S$ (%): C, 65.34; H, 6.09; N, 6.35. Found (%): C, 65.30; H, 6.13; N, 6.33.

*(E)-3-((2,4-Dimethylphenyl)sulfonyl)-N-(3-fluoro-4-((6-methoxy-7-(3-(piperidin-1-yl)propoxy)quinolin-4-yl)oxy)-phenyl)acrylamide (**38**)*
Yield: 65.0%; m.p.: 154.0–156.2°C; MS (ESI) *m/z*: 648.2 $[M+H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 9.14 (s, 1H), 8.45 (d, *J* = 4.0 Hz, 1H), 7.83 (d, *J* = 12.0 Hz, 1H), 7.70 (d, *J* = 8.0 Hz, 1H), 7.56 (s, 1H), 7.49 (d, *J* = 12.0 Hz, 1H), 7.42 (s, 1H), 7.43 (s, 1H), 7.34 (d, *J* = 8.0 Hz, 1H), 7.32 (d, *J* = 8.0 Hz, 1H), 7.28 (s, 1H), 7.21 (d, *J* = 8.0 Hz, 1H), 4.45 (t, *J* = 4.5 Hz, 2H), 4.12 (s, 3H), 3.79 (d, *J* = 11.6 Hz, 2H), 3.45 (t, *J* = 7.3 Hz, 2H), 2.98 (t, *J* = 11.2 Hz, 2H), 2.50 (s, 2H), 1.95 (s, 6H). Anal. calcd. for $C_{35}H_{38}FN_3O_6S$ (%): C, 64.90; H, 5.91; N, 6.49. Found (%): C, 64.93; H, 5.88; N, 6.47.

*(E)-N-(3-Fluoro-4-((6-methoxy-7-(3-morpholinopropoxy)-quinolin-4-yl)oxy)phenyl)-3-tosylacrylamide (**39**)*
Yield: 83.4%; m.p.: 116.2–118.0°C; MS (ESI) *m/z*: 636.2 $[M+H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 9.65 (s, 1H), 8.45 (d, *J* = 4.0 Hz, 1H), 7.88 (dd, *J* = 2.2 Hz, 1H), 7.80 (d, *J* = 8.0 Hz, 2H), 7.55 (s, 1H), 7.45 (s, 1H), 7.44 (s, 1H), 7.40 (s, 1H), 7.37 (d, *J* = 8.0 Hz, 2H), 7.16 (t, *J* = 12.0 Hz, 1H), 6.38 (d, *J* = 4.0 Hz, 1H), 4.29 (t, *J* = 8.0 Hz, 2H), 4.01 (s, 3H), 3.82 (m, *J* = 4.0 Hz, 4H), 2.76 (m, *J* = 8.0 Hz, 2H), 2.68 (d, *J* = 2.8 Hz, 4H), 2.45 (s, 3H), 2.22 (m, *J* = 8.0 Hz, 2H). Anal. calcd. for $C_{33}H_{34}FN_3O_7S$ (%): C, 62.35; H, 5.39; N, 6.61. Found (%): C, 62.30; H, 5.44; N, 6.63.

*(E)-N-(3-Fluoro-4-((6-methoxy-7-(3-(4-methylpiperidin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl)-3-tosylacrylamide (**40**)*
Yield: 75.9%; m.p.: 120.1–123.5°C; MS (ESI) *m/z*: 648.2 $[M+H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 10.81 (s, 1H), 8.35 (d, *J* = 4.0 Hz, 1H), 7.91 (dd, *J* = 4.0 Hz, 1H), 7.76 (d, *J* = 8.0 Hz, 2H), 7.68 (d, *J* = 16.0 Hz, 1H), 7.52 (s, 1H), 7.51 (s, 1H), 7.44 (s, 1H), 7.41 (d, *J* = 12.0 Hz, 1H), 7.31 (d, *J* = 8.0 Hz, 2H), 7.08 (t, *J* = 8.0 Hz, 1H), 6.33 (d, *J* = 8.0 Hz, 1H), 4.34 (d, *J* = 4.0 Hz, 2H), 3.96 (s, 3H), 3.76 (d, *J* = 12.0 Hz, 2H), 3.39 (m, *J* = 8.0, 4.0 Hz, 2H), 2.56 (s, 3H), 2.39 (d, *J* = 12.0 Hz, 2H), 1.92 (s, 4H), 1.25 (s, 1H), 1.05 (d, *J* = 8.0 Hz, 3H). Anal. calcd. for $C_{35}H_{38}FN_3O_6S$ (%): C, 64.90; H, 5.91; N, 6.49. Found (%): C, 64.93; H, 5.88; N, 6.52.

Pharmacology

MTT assay in vitro
The anti-proliferative activities of compounds **20–40** were evaluated against HT-29, A549, and MKN-45 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). Approximately 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 tested compounds 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 mg/mL, and incubated with cells at 37°C for 4 h. The formazan crystals were dissolved in 100 mL 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 of the cell lines. 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.

c-Met kinase assay
The c-Met kinase activity was evaluated using homogeneous time-resolved fluorescence (HTRF) assays as previously reported protocol [24, 25]. 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 plate was read using Envision (Perkin Elmer) at 320 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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