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Research paper

Discovery of a novel 6,7-disubstituted-4-(2-fluorophenoxy)quinolines bearing 1,2,3-triazole-4-carboxamide moiety as potent c-Met kinase inhibitors

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ABSTRACT

A series of 6,7-disubstituted-4-(2-fluorophenoxy)quinoline derivatives possessing 1,2,3-triazole-4-carboxamide moiety were designed, synthesized and evaluated for their *in vitro* cytotoxic activities against four typical cancer cell lines (A549, H460, HT-29, and MKN-45). Most compounds showed moderate-to-excellent antiproliferative activity. Compounds **32, 36, 37, 45, 51,** and **52** were further examined for their inhibitory activity against c-Met kinase. The promising compound **37**, with a c-Met IC_{50} value of 2.27 nM, was identified as a multitargeted receptor tyrosine kinase inhibitor. The analysis of their structure–activity relationships indicated that compounds with EWGs, especially chloro group, at 2-position on the phenyl ring (moiety B) have potent antitumor activity.

1. Introduction

Mesenchymal–epithelial transition factor (c-Met), a member of a structurally distinct family of receptor tyrosine kinases (RTK) [1,2], was discovered in 1984 as an oncogenic fusion protein TPR-MET [3]. In normal cells, the activation of c-Met occurs through the extracellular binding to its natural ligand, hepatocyte growth factor/scatter factor (HGF/SF). A variety of human cancers involve aberrant HGF/SF or c-Met expression or the activation of c-Met kinase mutations [4]. Consequently, inhibiting the activation of c-Met activity is a potentially impactful approach to the treatment of cancers caused by the activation of the c-Met [5].

There has been a significant interest in the development of small molecule c-Met inhibitors for the treatment of cancer [6]. Several quinoline derivatives have been reported recently as small-molecule c-Met inhibitors such as Foretinib (**1**), Cabozantinib (**2**) and AM 7 (**3**) (Fig. 1). These compounds are multikinase inhibitors, which usually exert strong inhibitory effect on VEGFR and other homological kinases as well [7–10]. From the structures, we can see that their main modification was focused on the 5-atom linker containing hydrogen-bond donors or acceptors between moiety A and B, which is known as "**5-atom regulation**". In the light of the results mentioned above, our research group has introduced different 5-atom linkers, such as 1, 4-dihydrocinnoline-3-carboxamide, pyridine/pyrimidine-based, *N*-acylhydrazine and pyrimidine-2, 4,6-trione and the resulting derivatives **7**–**10** (Fig. 2) showed excellent potency [11–14].

To our knowledge, compounds bearing 1,2,3-triazole-4-carboxamide fragment have been reported to exhibit a large field of biological activities, including antitumor, antibacterial, and anti-inflammatory activities, etc (**11**–**13,** Fig. 3) [15–20]. Therefore, we introduced 1,2,3-triazole-4-carboxamide fragment to the target quinoline derivatives as the 5-atom linker in an effort to provide more potent antitumor agents.

Taking Foretinib as the leading compound, we designed and synthesized a novel series of 6, 7-disubstituted-4-(2-fluorophenoxy) quinoline derivatives (Fig. 4), in which moiety A was preserved and the 1,2,3-triazole-4-carboxamide fragment was attached into the C-4′ position.

The target compounds synthesized were evaluated for their inhibitory activities against c-Met kinase and antiproliferative activities against 4 cancer cell lines including the HT-29 (human colon

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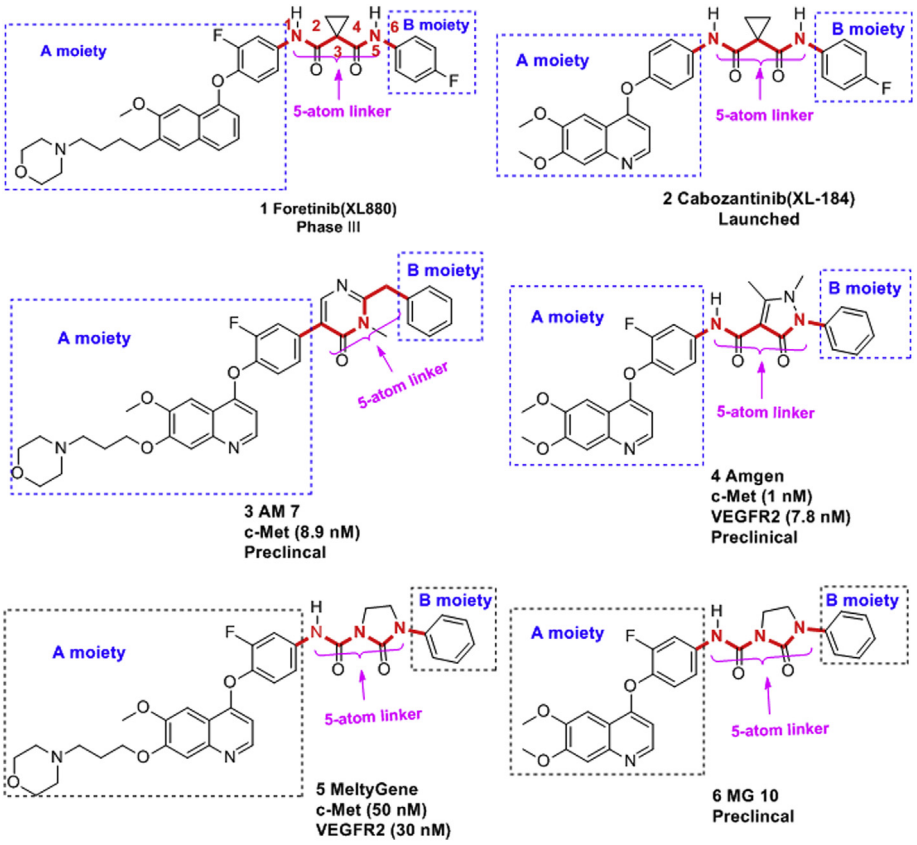


Fig. 1. The representative 4-phenoxyquinoline derivatives as small-molecule c-Met kinase inhibitors.

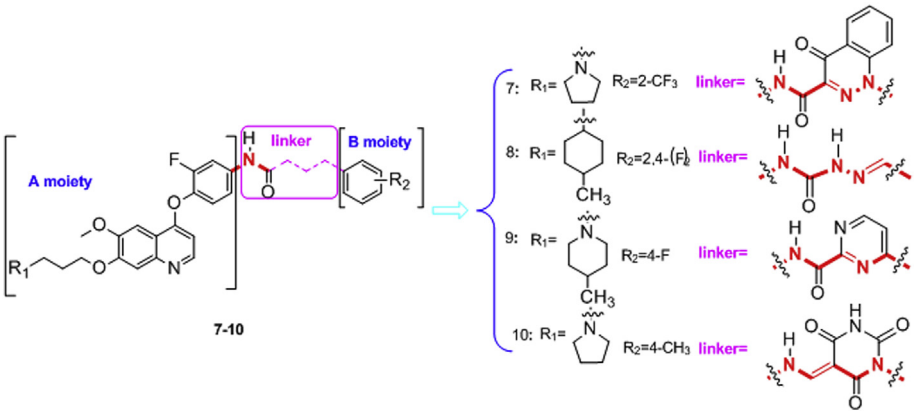


Fig. 2. Representative compounds in our previous work as small-molecule c-Met kinase inhibitors.

cancer), H460 (human lung cancer), A549 (human lung adenocarcinoma), MKN-45 (human gastric cancer).

2. Chemistry

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

The key intermediates 6,7-disubstituted-4-phenoxyquinolines **21a**–**e** were synthesized using a convenient eight-step procedure starting from 1-(4-hydroxy-3-methoxyphenyl)ethanone as shown in Scheme 1, which was illustrated in detail in our previous study [21,22].

2.2. Synthesis of the target compounds

The synthesis of target compounds **26**–**56** is summarized in Scheme 2. Condensation of commercially available substituted phenylamines with sodium nitrite ($NaNO_2$) and sodium azide (NaN_3) in H_2O/HCl at 0 °C resulted in high yield of intermediates **22a-h** as brown oil. Acylation of the aryl azides **22a-h** with 2-chloroacrylonitrile in water at 80 °C afforded intermediates **23a-h**, which were converted to acids **24a-h** using 10% sodium hydroxide solution at 80 °C for 4 h. Subsequently, intermediates **24a-h** were refluxed in toluene and $SOCl_2$ for 6 h to afford acyl chlorides **25a-h**, which were condensed with intermediates **21a-e** in the presence of sodium carbonate in dichloromethane at room

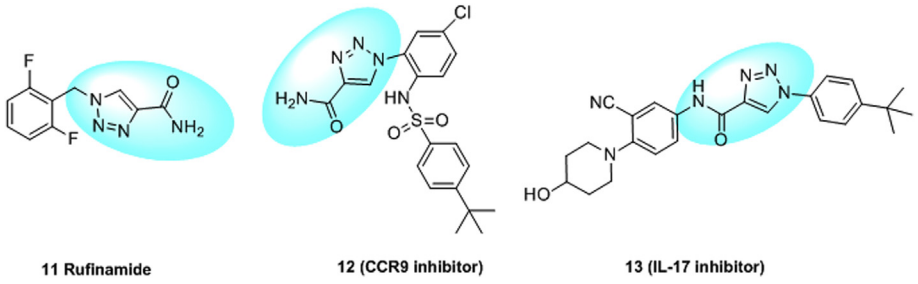


Fig. 3. Active compounds bearing 1,2,3-triazole-4-carboxamide framework.

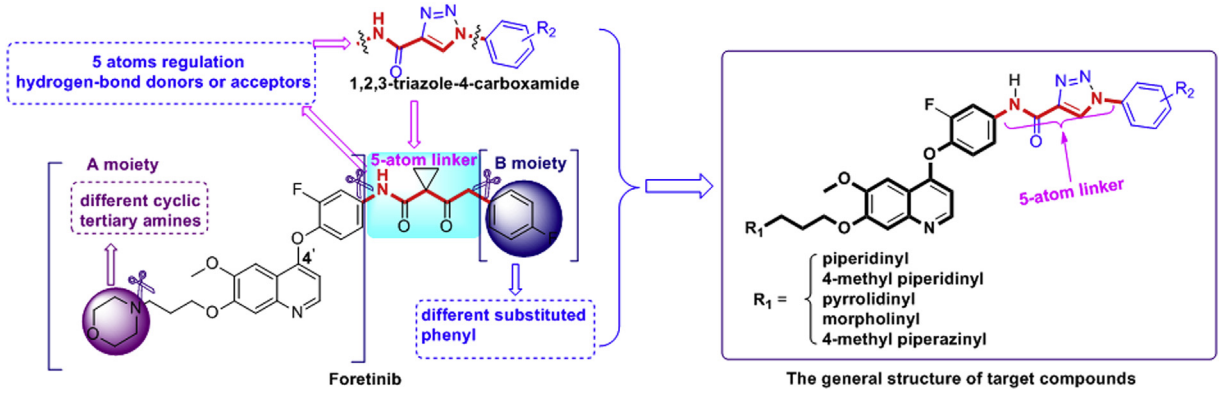
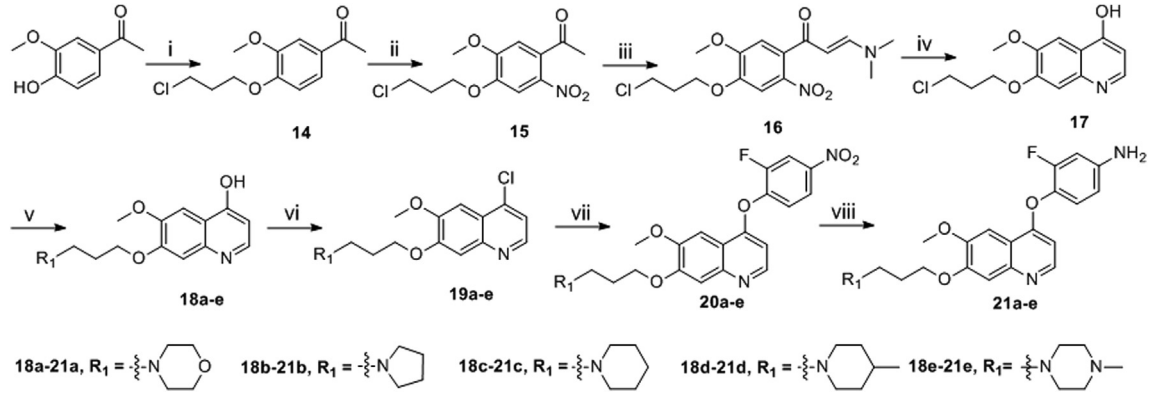


Fig. 4. Design strategy for the 4-phenoxyquinoline derivatives bearing 1,2,3-triazole-4-carboxamide moiety.



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

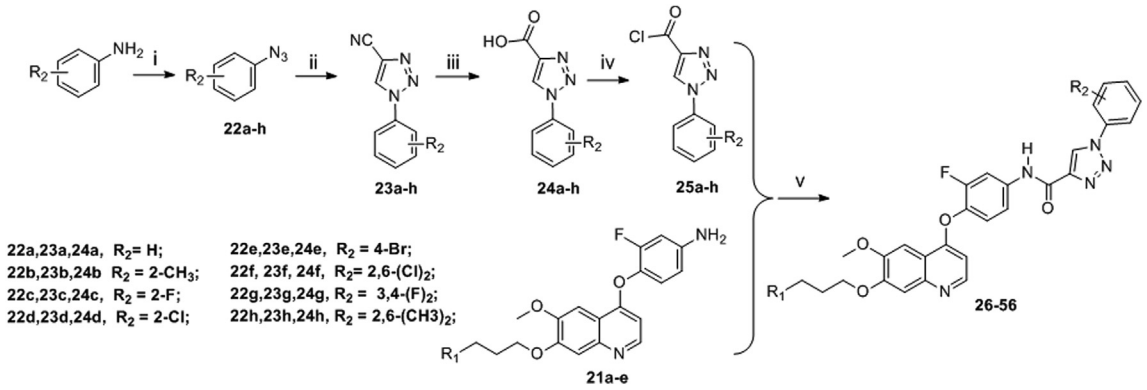
temperature overnight to obtain the target compounds **26**–**56**, respectively.

3. Results and discussion

3.1. In vitro cytotoxicity and structure–activity relationships

The cytotoxicity of the target compounds were evaluated against the cancer cell lines HT-29, H460, A549, and MKN-45 by using MTT assay with Foretinib as the positive control. The results were expressed as IC_{50} values and summarized in Table 1. The IC_{50} values were the average of at least three independent experiments.

As illustrated in Table 1, all the target compounds showed moderate-to-excellent cytotoxic activity against different cancer cells with potencies in the single-digit μM range, indicating that the introduction of 1,2,3-triazole-4-carboxamide moiety as the linker maintained potent cytotoxicity. In contrast, the introduction of different R_1 groups only slightly affected cytotoxicity, indicating that the R_1 group was insignificant. For example, compounds **27** (R_1 = morpholinyl, R_2 = 2-chloro), **32** (R_1 = pyrrolidinyl, R_2 = 2-chloro), **39** (R_1 = piperidinyl, R_2 = 2-fluoro), **46** (R_1 = 4-methylpiperidinyl, R_2 = 2-fluoro), and **53** (R_1 = 4-methylpiperazinyl, R_2 = 2-fluoro) exhibited comparable cytotoxicity with IC_{50} values in the range from 0.18 to 0.23 μM against H460 cells. In general, the target compounds were more potent against HT-29 and H460 compared to the other two cell lines. Notably, the IC_{50} values of the most promising compound **37** were 0.10 μM, 0.18 μM, 0.07 μM and 0.03 μM against HT-29, H460, A549



Scheme 2. Reagents and conditions: (i) $NaNO_2$, HCl, NaN_3, H_2O, 0 °C, 2 h, rt., 1 h; (ii) 2-Chloroacrylonitrile, H_2O, 80 °C, 12 h; (iii) 10% NaOH, EtOH/THF, 80 °C, 4 h; (iv) PhMe, $SOCl_2$, 85 °C, 6 h; (v) appropriate anilines, Na_2CO_3, CH_2Cl_2, rt.

and MKN-45 cell lines, respectively.

Different R_2 groups on the phenyl ring (moiety B) would have different cytotoxic activity. Introduction of mono-electron-withdrawing groups (mono-EWGs) exhibited a positive effect on the cytotoxic activity. However, the mono-electron-donating groups (mono-EDGs) exhibited a negative effect. For example, compound **31** (IC_{50} = 0.18 μM), with no substituent on the phenyl ring, showed potent cytotoxicity against HT29 cells. The introduction of mono-EWGs to the phenyl ring (**32**, R_2 = 2-chloro, IC_{50} = 0.15 μM) improved the activity, which could be further confirmed by introduction of these groups in compounds **34**, **45**, and **52**. On the contrary, the introduction of mono-EDGs (**33**, R_2 = 2-methyl, IC_{50} = 1.20 μM) reduced the activity, and the same trend was observed in compounds **38**, **47**, and **54**.

Further studies revealed that the number of R_2 group was closely related to antitumor activity as well. Incorporation of double groups and mono group showed opposite trend in potency. Incorporation of mono-EWGs and mono-EDGs increased the c-Met inhibitory efficacy; in contrast, the double-EWGs and double-EDGs clearly decreased the potency, such as **45** (R_2 = 2- chloro, IC_{50} = 0.13 μM) and **49** (R_2 = 2, 6-dichloro, IC_{50} = 1.39 μM); **54** (R_2 = 2-methyl, IC_{50} = 1.43 μM) and **55** (R_2 = 2, 6-dimethyl, IC_{50} = 2.17 μM).

Then the subsequent molecular docking studies of compounds 29 (R_2 = 2,6-$(CH_3)_2$), 32 (R_2 = 2-chloro), 33 (R_2 = 2-methyl). As shown in Fig. 5, the introduction of mono-EWGs to the phenyl ring 32 (R_2 = 2-chloro, IC_{50} = 0.15 μM) improved the activity, which could be validated by the interaction between chlorine atom and ILE1130. However, the introduction of EDGs 29 (R_2 = 2,6-$(CH_3)_2$, IC_{50} = 6.14 μM), 33 (R_2 = 2-methyl, IC_{50} = 1.2 μM) reduced the activity, because of the absence of any interaction between R_2 (R_2 = methyl) and Amino Acid.

These pharmacological data indicated that an appropriate amount of electron density on the pyridazinone ring and the number of the substituent on the phenyl ring were probably essential to the antitumor activity. The triazole ring, which was a part of the 5-atom linker, required EWGs (such as a chloro group) to reduce its electron density and ensure the mold.

3.2. In vitro enzymatic assays

As shown in Table 2, the six tested compounds all exhibited excellent c-Met enzymatic potency, suggesting that the inhibition of c-Met may be a mechanism for the antitumor effect of these derivatives. Compound **37** showed the most potent activity with an IC_{50} value of 2.27 nM, which was comparable to that of the positive control Foretinib (IC_{50} = 1.84 nM), and this compound should be studied further.

3.3. Enzymatic selectivity assays

To examine whether compound **37** is a selective c-Met inhibitor, this compound was screened against other 5 tyrosine kinases (Table 3). Compared with its high potency against c-Met (IC_{50} = 2.27 nM), **37** also exhibited high inhibitory effects against c-kit (IC_{50} = 9.36 nM) and Flt-3 (IC_{50} = 8.91 nM). Moreover, compound **37** showed inhibitory effects against VEGFR-2, Ron, and EGFR although the potency was 42.6-, 152.3-, and 233.2- fold lower than that of c-Met. These data suggested that compound **37** is a promising multitarget inhibitor of tyrosine kinases.

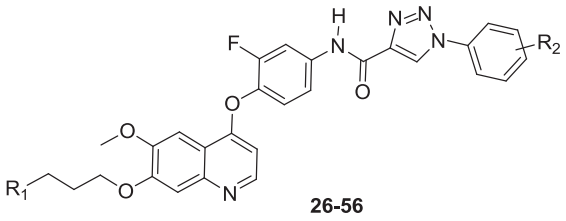
3.4. Binding model analysis

To further elucidate the binding mode of compounds, a detail docking analysis was performed. In our study, the co-crystal structure of Foretinib (GSK1363089) with c-Met was selected as the docking model (PDB ID code: 3LQ8). The docking simulation was conducted using Glide XP (Schrödinger 2014), since Glide uses a hierarchical series of filters to search for possible locations of the ligand in the active-site region of the receptor. The shape and properties of the receptor are represented on a grid by several different sets of fields that provide progressively more accurate scoring of the ligand poses. The image files were generated using Accelrys DS visualizer 4.0 system. The binding model was exemplified by the interaction of compound **37** with c-Met. As shown in Fig. 6, the protonated nitrogen atom of piperidine and the nitrogen atom of the quinoline ring in **37** formed one hydrogen-bonding interactions with MET1160. The π−π hydrophobic interactions had been formed between the quinoline ring and TYR1159. In addition, the oxygen atom of carbonyl group forms a conventional hydrogen bond with LYS1110. The π-sigma interaction was forged between the phenyl ring (moiety B) in **37** with ILE1130.

4. Conclusions

In summary, a series of 6,7-disubstituted-4-(2-fluorophenoxy) quinoline derivatives possessing 1,2,3-triazole-4-carboxamide moiety were designed, synthesized and evaluated as novel c-Met inhibitors. c-Met kinase and four human cancer cell lines (HT-29, H460, A549, and MKN-45) were used to evaluate the potency of the synthesized compounds. The pharmacological data indicated that most of them exhibited moderate-to-excellent cytotoxicity and

Table 1
Structures and cytotoxic activities of compounds **26**–**56** against HT-29, H460, A549 and MKN-45 cell lines *in vitro*.



26-56

Compd.	R_1	R_2	IC_{50} (μmol/L) ± SD[a]			
			HT-29	H460	A549	MKN-45
26		H	0.35 ± 0.03	0.45 ± 0.05	0.72 ± 0.05	0.11 ± 0.08
27		2-Cl	0.24 ± 0.01	**0.21 ± 0.01**	0.53 ± 0.05	0.27 ± 0.03
28		4-Br	0.26 ± 0.01	0.13 ± 0.002	0.18 ± 0.01	0.09 ± 0.001
29		2,6-$(CH_3)_2$	6.14 ± 0.25	4.32 ± 0.53	ND	ND
30		2,6-$(Cl)_2$	0.27 ± 0.01	0.29 ± 0.01	ND	0.11 ± 0.02
31		H	**0.18 ± 0.02**	0.28 ± 0.02	0.36 ± 0.03	0.26 ± 0.05
32		2-Cl	**0.15 ± 0.02**	**0.19 ± 0.05**	0.33 ± 0.05	0.07 ± 0.03
33		2-CH_3	**1.20 ± 0.04**	1.26 ± 0.06	0.90 ± 0.08	ND
34		4-Br	0.19 ± 0.03	0.20 ± 0.03	0.37 ± 0.03	0.12 ± 0.07
35		2,6-$(CH_3)_2$	2.24 ± 0.11	1.56 ± 0.12	1.24 ± 0.02	3.49 ± 0.12
36		H	**0.18 ± 0.03**	0.21 ± 0.03	0.13 ± 0.002	0.10 ± 0.01
37		2-Cl	**0.10 ± 0.003**	**0.18 ± 0.03**	**0.07 ± 0.01**	**0.03 ± 0.01**
38		2-CH_3	1.34 ± 0.15	2.10 ± 0.15	3.23 ± 0.05	3.25 ± 0.25
39		2-F	0.29 ± 0.03	**0.21 ± 0.07**	2.77 ± 0.12	1.29 ± 0.12
40		4-Br	0.26 ± 0.02	0.36 ± 0.01	0.23 ± 0.07	0.15 ± 0.11
41		2,6-$(CH_3)_2$	3.69 ± 0.02	3.52 ± 0.05	ND	2.14 ± 0.23
42		2,6-$(Cl)_2$	0.24 ± 0.04	0.28 ± 0.03	0.15 ± 0.01	ND
43		3,4-$(F)_2$	0.21 ± 0.04	0.25 ± 0.02	0.22 ± 0.03	0.31 ± 0.08
44		H	**0.19 ± 0.02**	0.21 ± 0.02	0.14 ± 0.003	0.09 ± 0.002
45		2-Cl	**0.13 ± 0.005**	0.23 ± 0.01	0.37 ± 0.01	0.24 ± 0.01
46		2-F	0.21 ± 0.04	**0.19 ± 0.03**	0.25 ± 0.07	0.13 ± 0.01
47		2-CH_3	2.38 ± 0.15	2.73 ± 0.05	3.50 ± 0.13	ND
48		2,6-$(CH_3)_2$	2.45 ± 0.33	2.36 ± 0.01	3.34 ± 0.05	4.31 ± 0.21
49		2,6-$(Cl)_2$	**1.39 ± 0.12**	0.27 ± 0.02	0.32 ± 0.02	0.12 ± 0.01
50		3,4-$(F)_2$	0.81 ± 0.02	0.26 ± 0.02	1.46 ± 0.07	1.29 ± 0.08
51		H	**0.18 ± 0.04**	0.20 ± 0.02	0.16 ± 0.01	0.06 ± 0.03

Table 1 (*continued*)

Compd.	R_1	R_2	IC_{50} (μmol/L) ± SD[a]			
			HT-29	H460	A549	MKN-45
52		2-Cl	**0.16 ± 0.01**	0.29 ± 0.01	0.15 ± 0.01	0.07 ± 0.01
53		2-F	0.30 ± 0.05	**0.23 ± 0.01**	0.25 ± 0.01	0.14 ± 0.01
54		2-CH_3	**1.43 ± 0.09**	3.65 ± 0.08	3.10 ± 0.22	ND
55		2,6-$(CH_3)_2$	**2.17 ± 0.05**	4.54 ± 0.11	2.18 ± 0.07	ND
56		3,4-$(F)_2$	0.43 ± 0.03	0.25 ± 0.01	0.20 ± 0.03	0.16 ± 0.01
Foretinib[b]			0.19 ± 0.01	0.21 ± 0.03	0.11 ± 0.01	0.032 ± 0.005

Bold values show the IC50 values of target compounds lower than the values of the positive control. ND: Not determined.

[a] IC_{50}: concentration of the compound (μM) producing 50% cell growth inhibition after 72 h of drug exposure, as determined by the MTT assay. Each experiment was carried out in triplicate.

[b] Used as a positive control.

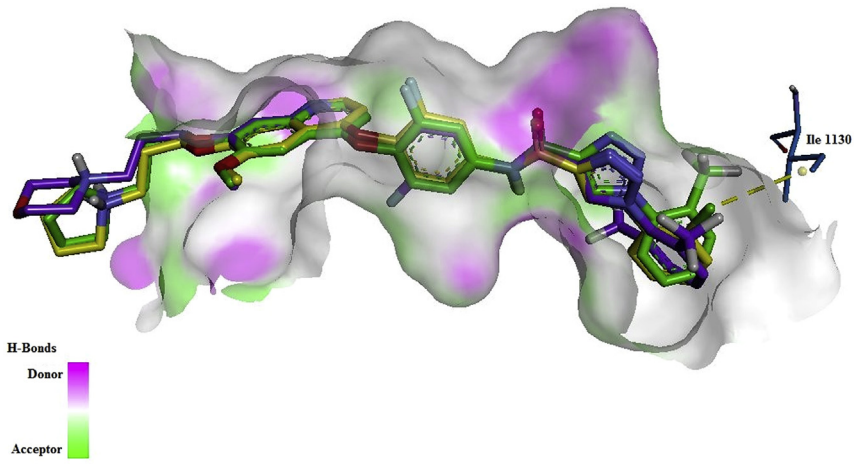


Fig. 5. The docking model of cytotoxic activity with R_2 groups (29-blue, 32-yellow, 33-green). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 2
Inhibitory activity against c-Met kinase of compounds **32, 36, 37, 45, 51, 52,** and Foretinib *in vitro*.

Compd.	IC_{50} on c-Met (nM)
32	6.68
36	8.75
37	2.27
45	3.08
51	9.45
52	10.37
Foretinib	1.84

Table 3
Inhibition of tyrosine kinases by compound **37**.

Kinase	Enzyme IC_{50} (nM)
VEGFR-2	96.68
c-kit	9.36
Flt-3	8.91
Ron	345.7
EGFR	529.4

high selectivity against one or more cell lines. The most promising compound **37**, showed excellent inhibition on c-Met kinase (IC_{50} = 2.27 nM) compared to the 5 other tyrosine kinases screened in this report; its cytotoxic activity against the HT-29, H460, A549, and MKN-45 cell lines (IC_{50} values: 0.10, 0.18, 0.07, and 0.03 μM, respectively) were 1.9-, 1.2-, 1,6-, and 1.1- times more active than that of Foretinib, respectively. Analysis of SARs indicated that EWGs on the phenyl ring (moiety B) were required to reduce the electron density on the 1,2,3-triazole-4-carboxamide moiety. In addition, the hydrophobic pocket of c-Met was probably not sufficiently large to accommodate moiety B with bulky groups. Therefore, a chloro group was the most favorable substituent on the phenyl ring. Further studies on the structural optimization about these derivatives are still underway in our laboratory.

5. Experimental

5.1. Docking study

To validate the docking methodology, the co-crystal ligand was extracted and re-docked into the protein binding pocket, and the docked pose was overlapped onto the conformation observed in

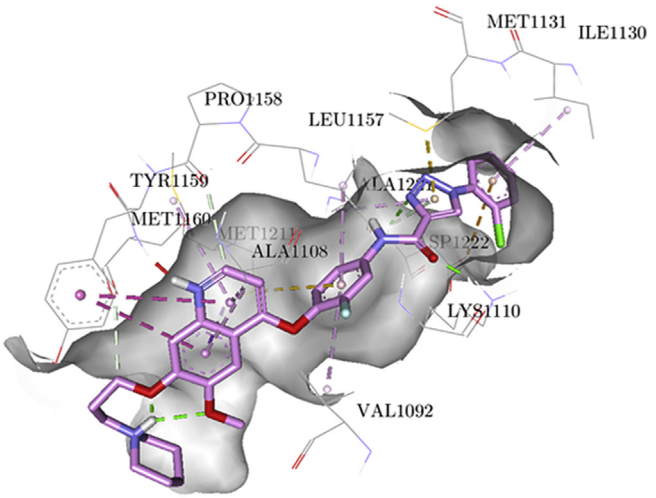


Fig. 6. The c-Met active site in complex with compound **37**. Compound **37** was shown in colored sticks (purple: carbon atom, blue: nitrogen atom, red: oxygen atom, green: chlorine atom). H-bonding interactions between the **37** and c-Met were indicated with dashed lines in red and green. π–π and π-sigma interactions were shown in light purple dotted line. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

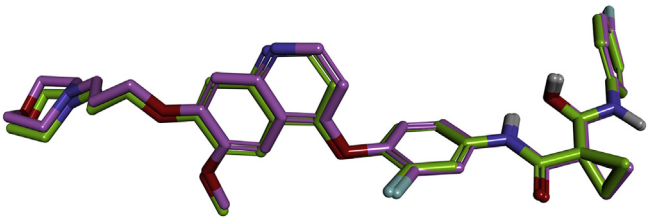


Fig. 7. The validation of the docking methodology (Foretinib: a. calculation: purple; b. cocrystallization: green). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

the crystal structure. According to the calculated RMSD value (0.3781), it's supposed that the Glide XP (Schrödinger 2014) is able to repose a perfect binding pose for the enzyme (Fig. 7).

5.2. Chemistry

Unless otherwise noted, all materials were obtained from commercial suppliers and were used without further purification. Reactions' time and purity of the products were monitored by TLC on FLUKA silica gel aluminum cards (0.2 mm thickness) with fluorescent indicator 254 nm. Column chromatography was run on silica gel (200–300 mesh) from Qingdao Ocean Chemicals (Qingdao, Shandong, China). All melting points were obtained on a Büchi Melting Point B-540 apparatus (Büchi Labortechnik, Flawil, Switzerland) and were uncorrected. Mass spectra (MS) were taken in ESI mode on Agilent 1100 LC–MS (Agilent, Palo Alto, CA, USA). ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker ARX-400, 400 MHz spectrometers (Bruker Bioscience, Billerica, MA, USA) with TMS as an internal standard. The IR spectra were recorded by means of the KBr pellet technique on a Bruker FTS 135 spectrometer. Elemental analysis was determined on a Carlo-Erba 1106 Elemental analysis instrument (Carlo Erba, Milan, Italy). (In the mode of measurement C, H, and N, the sample into the combustion tube in pure oxygen atmosphere static combustion and products by a specific reagent after formation of CO_2, H_2O, N_2 and nitrogen oxides, uniform mixing under the atmospheric pressure. The thermal conductivity detector is used for determining the content of C, H and N from mixed gases.).

5.3. General procedure for preparation of 3-fluoro-4-(6,7-disubstituted quinolin-4-yloxy)anilines (**21a**–**e**)

The preparation of the key intermediates **21a**–**e** has been illustrated in detail in our laboratory previous study, so their synthetic methods would not be listed here.

5.3.1. 3-Fluoro-4-(6-methoxy-7-(3-morpholinopropoxy)quinolin-4-yloxy)aniline (**21a**)

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

5.3.2. 3-Fluoro-4-(6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy) quinolin-4-yloxy)aniline (**21b**)

Gray solid; Yield: 85.5%; 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, 2H), 4.28 (t, J = 5.7 Hz, 2H), 3.96 (s, 3H), 3.59 (s, 2H), 3.35 (m, 4H), 3.04 (s, 2H), 2.28 (m, 2H), 1.96 (d, J = 28.0 Hz, 4H); MS (ESI) m/z (%): 412.5 $[M+H]^+$.

5.3.3. 3-Fluoro-4-(6-methoxy-7-(3-(piperdine-1-yl)propoxy) quinolin-4-yloxy)aniline (**21c**)

Gray 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 (s, 3H), 3.81 (s, 2H), 2.54 (m, 2H), 2.43 (s, 4H), 2.14 (m, 2H), 1.60 (m, 4H), 1.55 (m, 2H); MS (ESI) m/z (%): 426.3 $[M+H]^+$.

5.3.4. 3-Fluoro-4-(6-methoxy-7-(3-(4-methylpiperdine-1-yl) propoxy)quinolin-4-yl-oxy)aniline (**21d**)

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 $[M+H]^+$.

5.3.5. 3-Fluoro-4-(6-methoxy-7-(3-(4-methylpiperazine-1-yl) propoxy)quinolin-4-yl-oxy)aniline (**21e**)

White solid; yield: 77%; M.p.: 201–202 °C; ^{1}H NMR (300 MHz, CDCl3) δ 8.48 (d, J = 5.3 Hz, 1H), 7.61 (s, 1H), 7.41 (s, 1H), 7.06 (t, J = 8.7 Hz, 1H), 6.58 (dd, J = 11.8, 2.6 Hz, 1H), 6.54 (dd, J = 9.0, 2.9 Hz, 1H), 6.41 (dd, J = 5.3, 0.8 Hz, 1H), 4.28 (t, J = 6.7 Hz, 2H), 4.06 (s, 3H), 3.84 (s, 2H), 2.64–2.51 (m, 8H), 2.18 (s, 3H), 2.11 (t, J = 10.9 Hz, 2H), 1.88 (m, 2H); MS (ESI) m/z (%): 441.4 $[M+H]^+$, 463.3 $[M+Na]^+$.

5.4. General procedure for preparation intermediates of aryl azides (**22a**–**h**)

To a mixture of substituted phenyl amine (0.08 mol) and 15% HCl (80 mL), $NaNO_2$ (6.7 g, 0.096 mol) in H_2O (200 mL) was added dropwise at 0 °C. After the completion of addition, the reaction mixture was stirred at this temperature for 30 min. A solution of sodium

azide (7.9 g, 0.13 mol in 30 mL H_2O) was added dropwise to the reaction mixture at 0 °C. After addition the reaction mixture was maintained at 0 °C for 1 h. The product was extracted by using ethyl acetate followed by washing with water up to neutral pH. Organic layer was dried with anhydrous sodium sulfate and then concentrated by distillation to afford **22a-h** as yellow to brown oil.

*5.4.1. Azidobenzene (**22a**)*
Brown oil; Yield: 96%; MS (ESI) *m/z* (%): 120.1 $[M+H]^+$.

*5.4.2. 1-azido-2-methylbenzene (**22b**)*
Brown oil; Yield: 95%; MS (ESI) *m/z* (%): 134.1 $[M+H]^+$.

*5.4.3. 1-azido-2-fluorobenzene (**22c**)*
Red oil; Yield: 93%; MS (ESI) *m/z* (%): 138.1 $[M+H]^+$.

*5.4.4. 1-azido-2-chlorobenzene (**22d**)*
Yellow oil; Yield: 92.8%; MS (ESI) *m/z* (%): 153.6 $[M+H]^+$.

*5.4.5. 1-azido-4-bromobenzene (**22e**)*
Yellow oil; Yield: 94.5%; MS (ESI) *m/z* (%): 198.1 $[M+H]^+$.

*5.4.6. 2-azido-1,3-dichlorobenzene (**22f**)*
Yellow oil; Yield: 93.8%; MS (ESI) *m/z* (%): 188.0 $[M+H]^+$.

*5.4.7. 2-azido-1,3-dimethylbenzene (**22g**)*
Light yellow oil; Yield: 95.2%; MS (ESI) *m/z* (%): 148.1 $[M+H]^+$.

*5.4.8. 4-azido-1,2-difluorobenzene (**22h**)*
Light yellow oil; Yield: 96.1%; MS (ESI) *m/z* (%): 156.1 $[M+H]^+$.

*5.5. General procedure for the preparation of intermediates 1-substituted phenyl-1H-1,2, 3-triazole-4-carbonitrile (**23a–h**)*

To a solution of appropriate aryl azides **22a-h** (5 g, 0.033 mol) and 2-chloroacrylonitrile (1.9 g, 0.022 mol), were dissolved in H_2O (30 mL). Upon the completion of addition, the mixture was heated to 80 °C for 12 h. The solution was extracted with dichloromethane and the organic phase was separated, washed with brine, dried, filtered and concentrated. The crude product was purified by column chromatography on silica gel with a mixture of petroleum ether/ethyl acetate (10:1) to afford **23a-h** as white to yellow precipitates, respectively.

*5.5.1. 1-phenyl-1H-1,2,3-triazole-4-carbonitrile (**23a**)*
White solid; yield: 73.8%; M.p.: 80.1–81.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (s, 1H), 7.72 (dd, *J* = 8.4, 1.2 Hz, 2H), 7.57 (d, *J* = 1.6 Hz, 1H), 7.55 (dd, *J* = 3.9, 2.5 Hz, 1H), 7.52 (d, *J* = 7.4 Hz, 1H); MS (ESI) *m/z* (%): 171.1 $[M+H]^+$.

*5.5.2. 1-(o-tolyl)-1H-1,2,3-triazole-4-carbonitrile (**23b**)*
White solid; yield: 74.2%; M.p.: 81.2–83.4 °C; MS (ESI) *m/z* (%): 185.2 $[M+H]^+$.

*5.5.3. 1-(2-fluorophenyl)-1H-1,2,3-triazole-4-carbonitrile (**23c**)*
White solid; yield: 73.1%; M.p.: 75–78 °C; MS (ESI) *m/z* (%): 189.1 $[M+H]^+$.

*5.5.4. 1-(2-chlorophenyl)-1H-1,2,3-triazole-4-carbonitrile (**23d**)*
Yellow solid; yield: 73.4%; M.p.: 79.5–80.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (s, 1H), 7.73 (dd, *J* = 8.5, 1.3 Hz, 1H), 7.55 (d, *J* = 1.5 Hz, 1H), 7.51 (dd, *J* = 3.8, 2.4 Hz, 1H), 7.49 (d, *J* = 7.3 Hz, 1H); MS (ESI) *m/z* (%): 205.4 $[M+H]^+$

*5.5.5. 1-(4-bromophenyl)-1H-1,2,3-triazole-4-carbonitrile (**23e**)*
Brown solid; yield: 72.9%; M.p.: 81.2–82.3 °C; MS (ESI) *m/z* (%): 249.1 $[M+H]^+$.

*5.5.6. 1-(2,6-dichlorophenyl)-1H-1,2,3-triazole-4-carbonitrile (**23f**)*
Brown solid; yield: 71.7%; M.p.: 80.4–81.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (s, 1H), 7.13 (t, *J* = 7.6 Hz, 1H), 6.98 (t, *J* = 8.3 Hz, 2H), 1.74 (s, 6H); MS (ESI) *m/z* (%): 239.1 $[M+H]^+$.

*5.5.7. 1-(2,6-dimethylphenyl)-1H-1,2,3-triazole-4-carbonitrile (**23g**)*
White solid; yield: 72.5%; M.p.: 77.4–78.3 °C; MS (ESI) *m/z* (%): 198.2 $[M+H]^+$.

*5.5.8. 1-(3,4-difluorophenyl)-1H-1,2,3-triazole-4-carbonitrile (**23h**)*
Yellow solid; yield: 73.6%; M.p.: 78.4–79.8 °C; MS (ESI) *m/z* (%): 207.1 $[M+H]^+$.

*5.6. General procedure for the preparation of intermediates **24a–h***

To a solution of an appropriate intermediate **23a-h** (5 mmol) dissolved in methanol (30 mL), was added drop-wise 10% NaOH (8 mL) at room temperature. After the completion of addition, the mixture was heated to 80 °C for 4 h. Then, most of the solvent was evaporated, and the residue was poured into H_2O (70 mL) and extracted with ethyl acetate (100 mL). The aqueous layer was separated and acidified (6 Mol/L HCl) to afford substituted acids **24a-h** as white to yellow precipitate, respectively.

*5.6.1. 1-phenyl-1H-1,2,3-triazole-4-carboxylic acid (**24a**)*
White solid; Yield: 93.2%; M.p.: 136.2–138.1 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.24 (s, 1H), 8.49 (s, 1H), 7.62 (dd, *J* = 8.2, 1.3 Hz, 2H), 7.56 (d, *J* = 1.5 Hz, 1H), 7.52 (dd, *J* = 3.8, 2.4 Hz, 1H), 7.42 (d, *J* = 7.4 Hz, 1H); MS (ESI) *m/z* (%): 188.2 $[M-H]^-$.

*5.6.2. 1-(o-tolyl)-1H-1,2,3-triazole-4-carboxylic acid (**24b**)*
White solid; Yield: 92.6%; M.p.: 135.7–137.1 °C; MS (ESI) *m/z* (%): 202.1 $[M-H]^-$.

*5.6.3. 1-(2-fluorophenyl)-1H-1,2,3-triazole-4-carboxylic acid (**24c**)*
White solid; Yield: 93.0%; M.p.: 136.3–137.8 °C; MS (ESI) *m/z* (%): 206.4 $[M-H]^-$.

*5.6.4. 1-(2-chlorophenyl)-1H-1,2,3-triazole-4-carboxylic acid (**24d**)*
Yellow solid; Yield: 93.5%; M.p.: 137.3–138.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.26 (s, 1H) 8.46 (s, 1H), 7.64 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.55 (d, *J* = 1.5 Hz, 1H), 7.50 (dd, *J* = 3.7, 2.3 Hz, 1H), 7.41 (d, *J* = 7.4 Hz, 1H); MS (ESI) *m/z* (%): 222.1 $[M-H]^-$.

*5.6.5. 1-(4-bromophenyl)-1H-1,2,3-triazole-4-carboxylic acid (**24e**)*
Brown solid; Yield: 92.8%; M.p.: 138.9–140.2 °C; MS (ESI) *m/z* (%): 266.8 $[M-H]^-$.

*5.6.6. 1-(2,6-dichlorophenyl)-1H-1,2,3-triazole-4-carboxylic acid (**24f**)*
White solid; Yield: 91.7%; M.p.: 135.3–137.2 °C; ^{1}H NMR (400 MHz, DMSO) δ 13.28 (s, 1H), 9.00 (s, 1H), 7.44–7.35 (m, 1H), 7.29 (d, *J* = 7.6 Hz, 2H), 1.92 (s, 6H); MS (ESI) *m/z* (%): 256.7 $[M-H]^-$.

*5.6.7. 1-(2,6-dimethylphenyl)-1H-1,2,3-triazole-4-carboxylic acid (**24g**)*
Brown solid; Yield: 93.1%; M.p.: 132.5–134.1 °C; MS (ESI) *m/z* (%): 216.5 $[M-H]^-$.

*5.6.8. 1-(3,4-difluorophenyl)-1H-1,2,3-triazole-4-carboxylic acid (**24h**)*

White solid; Yield: 92.5%; M.p.: 134.7–136.1 °C; MS (ESI) *m*/*z* (%): 224.3 $[M-H]^-$.

*5.7. General procedure for preparation of the target compounds (**26**–**56**)*

A mixture of the corresponding acid **24a-h** (0.86 mmol), toluene (10 mL), and $SOCl_2$ (5 mL) was heated at 85 °C for 6 h. Upon cooling to room temperature, the solvent was evaporated in vacuum. The residue was dissolved in dried CH_2Cl_2 (15 mL) and added dropwise to a mixture of the corresponding aniline **21a-e** (0.49 mmol), Na_2CO_3 (0.97 mmol) and CH_2Cl_2 (15 mL) in an ice bath, which was then raised to room temperature and stirred for 3 h. The resulting mixture was sequentially washed with 20% K_2CO_3 (25 mL × 3) and brine (25 mL × 3), and 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 **26**–**56** as white solids in 72.3–80.2% yields.

*5.7.1. N-(3-fluoro-4-((6-methoxy-7-(3-morpholinopropoxy) quinolin-4-yl)oxy)phenyl)-1-phenyl- 1H-1,2,3-triazole-4-carboxamide (**26**)*

Yield: 79.6%; M.p.: 155–157 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.14 (s, 1H), 8.65 (s, 1H), 8.51 (d, *J* = 5.3 Hz, 1H), 7.97 (dd, *J* = 11.9, 2.4 Hz, 1H), 7.80 (d, *J* = 7.7 Hz, 2H), 7.60 (dd, *J* = 9.9, 5.2 Hz, 3H), 7.54 (t, *J* = 7.4 Hz, 1H), 7.44 (d, *J* = 5.6 Hz, 2H), 7.30 (d, *J* = 8.6 Hz, 1H), 6.44 (d, *J* = 5.1 Hz, 1H), 4.28 (t, *J* = 6.7 Hz, 2H), 4.05 (s, 3H), 3.78–3.68 (m, 4H), 2.58 (t, *J* = 7.1 Hz, 2H), 2.53–2.43 (m, 4H), 2.14 (t, *J* = 6.8 Hz, 2H); MS (ESI) *m*/*z* (%): 598.9 $[M+H]^+$; Anal. calcd. for $C_{32}H_{31}FN_6O_5$ (%): C, 64.20; H, 5.22; N, 14.04. Found (%): C, 64.23; H, 5.37; N, 14.06.

*5.7.2. 1-(2-chlorophenyl)-N-(3-fluoro-4-((6-methoxy-7-(3-morpholinopropoxy)quinolin-4-yl)oxy) phenyl)-1H-1,2,3-triazole-4-carboxamide (**27**)*

Yield: 75.6%; M.p.: 156–159 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.14 (s, 1H), 8.63 (s, 1H), 8.52 (d, *J* = 5.2 Hz, 1H), 7.98 (dd, *J* = 12.0, 2.4 Hz, 1H), 7.71–7.65 (m, 2H), 7.60 (s, 1H), 7.59–7.51 (m, 2H), 7.46 (s, 1H), 7.46–7.43 (m, 1H), 7.32 (t, *J* = 8.6 Hz, 1H), 6.46 (d, *J* = 5.3 Hz, 1H), 4.30 (t, *J* = 6.7 Hz, 2H), 4.07 (s, 3H), 3.77–3.72 (m, 4H), 2.60 (t, *J* = 7.1 Hz, 2H), 2.54–2.47 (m, 4H), 2.19–2.12 (m, 2H); MS (ESI) *m*/*z* (%): 631.1 $[M-H]^-$; Anal. calcd. for $C_{32}H_{30}ClFN_6O_5$ (%): C, 60.72; H, 4.78; N, 13.28. Found (%): C, 60.73; H, 4.81; N, 13.36.

*5.7.3. 1-(4-bromophenyl)-N-(3-fluoro-4-((6-methoxy-7-(3-morpholinopropoxy)quinolin-4-yl)oxy) phenyl)-1H-1,2,3-triazole-4-carboxamide (**28**)*

Yield: 74.6%; M.p.: 157–158 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.11 (s, 1H), 8.63 (s, 1H), 8.53 (d, *J* = 5.2 Hz, 1H), 7.98 (dd, *J* = 11.9, 2.3 Hz, 1H), 7.76 (d, *J* = 8.9 Hz, 2H), 7.71 (d, *J* = 8.9 Hz, 2H), 7.61 (s, 1H), 7.46 (d, *J* = 8.6 Hz, 2H), 7.32 (d, *J* = 8.7 Hz, 1H), 6.46 (d, *J* = 5.2 Hz, 1H), 4.31 (t, *J* = 6.6 Hz, 2H), 4.08 (s, 3H), 3.77–3.72 (m, 4H), 2.61 (t, *J* = 7.1 Hz, 2H), 2.52 (s, 4H), 2.16 (t, *J* = 7.0 Hz, 2H); MS (ESI) *m*/*z* (%): 678.7 $[M+H]^+$; Anal. calcd. for $C_{32}H_{30}BrFN_6O_5$ (%): C, 56.72; H, 4.46; N, 12.40. Found (%): C, 56.73; H, 4.47; N, 12.46.

*5.7.4. 1-(2,6-dimethylphenyl)-N-(3-fluoro-4-((6-methoxy-7-(3-morpholinopropoxy)quinolin-4-yl) oxy) phenyl)-1H-1,2,3-triazole-4-carboxamide (**29**)*

Yield: 72.3%; M.p.: 154.2–156.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.21 (s, 1H), 8.51 (d, *J* = 5.3 Hz, 1H), 8.29 (s, 1H), 7.98 (d, *J* = 9.6 Hz, 1H), 7.60 (s, 1H), 7.49–7.43 (m, 2H), 7.39 (t, *J* = 7.6 Hz, 1H), 7.31 (d, *J* = 8.6 Hz, 1H), 7.24 (d, *J* = 7.6 Hz, 2H), 6.47 (d, *J* = 5.2 Hz, 1H), 4.29 (t, *J* = 6.5 Hz, 2H), 4.05 (s, 3H), 3.83–3.74 (m, 4H), 2.73–2.64 (m, 2H), 2.63–2.46 (m, 4H), 2.25–2.13 (m, 2H), 2.05 (s, 6H); MS (ESI) *m*/*z* (%): 626.9 $[M+H]^+$; Anal. calcd. for $C_{34}H_{35}FN_6O_5$ (%): C, 65.16; H, 5.63; N, 13.41. Found (%): C, 65.23; H, 5.67; N, 13.46.

*5.7.5. 1-(2,6-dichlorophenyl)-N-(3-fluoro-4-((6-methoxy-7-(3-morpholinopropoxy)quinolin-4-yl) oxy)phenyl)-1H-1,2,3-triazole-4-carboxamide (**30**)*

Yield: 73.4%; M.p.: 156.3–157.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.22 (s, 1H), 8.52 (d, *J* = 5.2 Hz, 1H), 8.42 (s, 1H), 7.98 (dd, *J* = 11.9, 2.3 Hz, 1H), 7.58 (d, *J* = 12.8 Hz, 2H), 7.55–7.49 (m, 1H), 7.45 (d, *J* = 5.1 Hz, 2H), 7.31 (d, *J* = 8.6 Hz, 1H), 7.28 (s, 1H), 6.46 (d, *J* = 5.2 Hz, 1H), 4.29 (t, *J* = 6.7 Hz, 2H), 4.06 (s, 3H), 3.77–3.70 (m, 4H), 2.59 (t, *J* = 7.1 Hz, 2H), 2.50 (s, 4H), 2.20–2.10 (m, 2H); MS (ESI) *m*/*z* (%): 667.3 $[M+H]^+$; Anal. calcd. for $C_{32}H_{29}Cl_2FN_6O_5$ (%): C, 57.58; H, 4.38; N, 12.59. Found (%): C, 57.63; H, 4.37; N, 12.62.

*5.7.6. N-(3-fluoro-4-((6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy) quinolin-4-yl)oxy)phenyl)-1- phenyl-1H-1,2,3-triazole-4-carboxamide (**31**)*

Yield: 74.8%; M.p.: 151.2–153.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.17 (s, 1H), 8.66 (s, 1H), 8.50 (d, *J* = 5.2 Hz, 1H), 7.97 (dd, *J* = 11.9, 2.3 Hz, 1H), 7.80 (d, *J* = 7.7 Hz, 2H), 7.59 (dd, *J* = 10.0, 4.7 Hz, 3H), 7.53 (t, *J* = 7.3 Hz, 1H), 7.45 (d, *J* = 8.2 Hz, 2H), 7.30 (d, *J* = 8.6 Hz, 1H), 6.44 (d, *J* = 5.2 Hz, 1H), 4.28 (t, *J* = 6.6 Hz, 2H), 4.05 (s, 3H), 2.73 (t, *J* = 7.4 Hz, 2H), 2.60 (s, 4H), 2.25–2.15 (m, 2H), 1.82 (s, 4H); MS (ESI) *m*/*z* (%): 582.8 $[M+H]^+$; Anal. calcd. for $C_{32}H_{31}FN_5O_6$ (%): C, 65.97; H, 5.36; N, 14.42. Found (%): C, 65.91; H, 5.37; N, 14.46.

*5.7.7. 1-(2-chlorophenyl)-N-(3-fluoro-4-((6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy)quinolin-4-yl) oxy) phenyl)-1H-1,2,3-triazole-4-carboxamide (**32**)*

Yield: 75.2%; M.p.: 152.4–154.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.15 (s, 1H), 8.63 (s, 1H), 8.52 (d, *J* = 5.3 Hz, 1H), 7.98 (dd, *J* = 11.9, 2.5 Hz, 1H), 7.70–7.65 (m, 2H), 7.60 (s, 1H), 7.55 (td, *J* = 7.1, 1.9 Hz, 2H), 7.48–7.45 (m, 1H), 7.44 (s, 2H), 7.30 (t, *J* = 8.0 Hz, 1H), 6.46 (d, *J* = 5.3 Hz, 1H), 4.29 (t, *J* = 6.4 Hz, 2H), 4.06 (s, 3H), 3.03–2.84 (m, *J* = 36.3 Hz, 4H), 2.32–2.24 (m, 2H), 1.94–1.88 (m, 4H), 1.31–1.25 (m, 2H); MS (ESI) *m*/*z* (%): 617.1 $[M+H]^+$; Anal. calcd. for $C_{35}H_{34}FN_6O_4$ (%): C, 62.29; H, 4.90; N, 13.62. Found (%): C, 62.33; H, 4.95; N, 13.66.

*5.7.8. N-(3-fluoro-4-((6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy) quinolin-4-yl)oxy)phenyl)-1-(o-tolyl)-1H-1,2,3-triazole-4-carboxamide (**33**)*

Yield: 78.2%; M.p.: 155.4–157.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.26 (s, 1H), 8.54 (d, *J* = 5.2 Hz, 1H), 8.32 (s, 1H), 7.97 (dd, *J* = 10.9, 2.1 Hz, 2H), 7.63 (s, 1H), 7.44 (d, *J* = 10.2 Hz, 2H), 7.38 (t, *J* = 7.5 Hz, 1H), 7.31 (d, *J* = 8.5 Hz, 1H), 7.24 (d, *J* = 7.6 Hz, 2H), 6.45 (d, *J* = 5.1 Hz, 1H), 4.31 (t, *J* = 6.7 Hz, 2H), 4.06 (s, 3H), 2.74–2.69 (m, 2H), 2.58 (s, 4H), 2.24–2.15 (m, 2H), 2.04 (s, 3H), 1.83 (t, *J* = 3.2 Hz, 4H); MS (ESI) *m*/*z* (%): 597.3 $[M+H]^+$; Anal. calcd. for $C_{33}H_{33}FN_6O_4$ (%): C, 66.43; H, 5.57; N, 14.09. Found (%): C, 66.49; H, 5.67; N, 14.16.

*5.7.9. 1-(4-bromophenyl)-N-(3-fluoro-4-((6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy)quinolin-4-yl) oxy)phenyl)-1H-1,2,3-triazole-4-carboxamide (**34**)*

Yield: 77.3%; M.p.: 156.7–158.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.11 (s, 1H), 8.63 (s, 1H), 8.52 (d, *J* = 5.3 Hz, 1H), 7.98 (dd, *J* = 11.9, 2.4 Hz, 1H), 7.76 (d, *J* = 8.9 Hz, 2H), 7.71 (d, *J* = 6.7 Hz, 2H), 7.60 (s, 1H), 7.45 (d, *J* = 5.3 Hz, 2H), 7.32 (d, *J* = 8.6 Hz, 1H), 6.46 (d, *J* = 4.9 Hz, 1H), 4.30 (t, *J* = 6.7 Hz, 2H), 4.07 (s, 3H), 2.75–2.68 (m, 2H), 2.59 (s, 4H), 2.25–2.16 (m, 2H), 1.82 (t, *J* = 3.2 Hz, 4H); MS (ESI) *m*/*z* (%): 660.7 $[M+H]^+$; Anal. calcd. for $C_{32}H_{30}BrFN_6O_4$ (%): C, 58.10; H, 4.57; N, 12.70. Found (%): C, 58.17; H, 4.61; N, 12.76.

*5.7.10. 1-(2,6-dimethylphenyl)-N-(3-fluoro-4-((6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy)quinolin- 4-yl)oxy)phenyl)-1H-1,2,3-triazole-4-carboxamide (**35**)*

Yield: 80.2%; M.p.: 155.2–154.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.24 (s, 1H), 8.52 (d, J = 5.2 Hz, 1H), 8.30 (s, 1H), 7.99 (dd, J = 10.9, 2.1 Hz, 1H), 7.61 (s, 1H), 7.45 (d, J = 10.2 Hz, 2H), 7.40 (t, J = 7.6 Hz, 1H), 7.32 (d, J = 8.6 Hz, 1H), 7.26 (d, J = 7.6 Hz, 2H), 6.48 (d, J = 5.1 Hz, 1H), 4.30 (t, J = 6.7 Hz, 2H), 4.07 (s, 3H), 2.75–2.68 (m, 2H), 2.59 (s, 4H), 2.25–2.16 (m, 2H), 2.05 (s, 6H), 1.82 (t, J = 3.2 Hz, 4H); MS (ESI) m/z (%): 611.0 $[M+H]^+$; Anal. calcd. for $C_{34}H_{35}FN_6O_4$ (%): C, 66.87; H, 5.78; N, 13.76. Found (%): C, 66.91; H, 5.82; N, 13.80.

*5.7.11. N-(3-fluoro-4-((6-methoxy-7-(3-(piperidin-1-yl)propoxy) quinolin-4-yl)oxy)phenyl)-1- phenyl- 1H-1,2,3-triazole-4-carboxamide (**36**)*

Yield: 78.3%; M.p.: 172.1–174.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.14 (s, 1H), 8.65 (s, 1H), 8.51 (d, J = 5.3 Hz, 1H), 7.97 (dd, J = 11.9, 2.4 Hz, 1H), 7.80 (d, J = 7.8 Hz, 2H), 7.63–7.57 (m, 3H), 7.54 (t, J = 7.3 Hz, 1H), 7.47–7.41 (m, 2H), 7.30 (d, J = 8.6 Hz, 1H), 6.44 (d, J = 5.1 Hz, 1H), 4.26 (t, J = 6.5 Hz, 2H), 4.05 (s, 3H), 2.68 (d, J = 4.2 Hz, 2H), 2.57 (d, J = 15.4 Hz, 4H), 2.32–2.11 (m, 2H), 1.69 (d, J = 0.7 Hz, 4H), 1.49 (d, J = 1.4 Hz, 2H); MS (ESI) m/z (%): 596.9 $[M+H]^+$; Anal. calcd. for $C_{33}H_{33}FN_6O_4$ (%): C, 66.43; H, 5.57; N, 14.09. Found (%): C, 66.48; H, 5.61; N, 14.11.

*5.7.12. 1-(2-chlorophenyl)-N-(3-fluoro-4-((6-methoxy-7-(3-(piperidin-1-yl)propoxy)quinolin-4-yl) oxy)phenyl)-1H-1,2,3-triazole-4-carboxamide (**37**)*

Yield: 77.6%; M.p.: 171.4–173.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.14 (s, 1H), 8.63 (s, 1H), 8.52 (d, J = 5.3 Hz, 1H), 7.98 (dd, J = 11.9, 2.4 Hz, 1H), 7.70–7.64 (m, 2H), 7.59 (s, 1H), 7.55 (td, J = 7.1, 1.8 Hz, 2H), 7.49–7.46 (m, 1H), 7.45 (s, 1H), 7.31 (t, J = 8.6 Hz, 1H), 6.46 (d, J = 5.1 Hz, 1H), 4.27 (t, J = 6.7 Hz, 2H), 4.06 (s, 3H), 2.55 (t, J = 7.3 Hz, 2H), 2.50–2.38 (m, 4H), 2.17 (dd, J = 14.3, 7.0 Hz, 2H), 1.64–1.58 (m, 4H), 1.49–1.42 (m, 2H); ^{13}C NMR (600 MHz, $CDCl_3$) δ 159.96, 157.62, 153.29, 152.35, 149.90, 148.78, 146.99, 142.78, 137.72, 137.60, 136.04, 135.94, 131.61, 131.05, 128.84, 128.16, 127.68, 123.97, 116.06, 115.42, 109.62, 109.39, 108.81, 102.23, 67.67, 56.18, 55.81, 54.61 (2C), 26.39, 26.01 (2C), 24.46; MS (ESI) m/z (%): 631.3 $[M+H]^+$; Anal. calcd. for $C_{33}H_{32}ClFN_6O_4$ (%): C, 62.80; H, 5.11; N, 13.32. Found (%): C, 62.83; H, 5.17; N, 13.36.

*5.7.13. N-(3-fluoro-4-((6-methoxy-7-(3-(piperidin-1-yl)propoxy) quinolin-4-yl)oxy)phenyl)-1-(o-tolyl)-1H-1,2,3-triazole-4-carboxamide (**38**)*

Yield: 72.6%; M.p.: 173.7–175.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.17 (s, 1H), 8.52 (d, J = 5.2 Hz, 1H), 8.39 (s, 1H), 7.98 (dd, J = 11.9, 2.4 Hz, 1H), 7.59 (s, 1H), 7.54–7.48 (m, 1H), 7.42–7.39 (m, 2H), 7.31 (d, J = 8.6 Hz, 1H), 6.46 (d, J = 5.2 Hz, 1H), 4.27 (t, J = 6.4 Hz, 2H), 4.05 (s, 3H), 2.89–2.50 (m, 6H), 2.28 (s, 4H), 2.27–2.22 (m, 2H), 1.78–1.68 (m, 4H), 1.56–1.47 (m, 2H); MS (ESI) m/z (%): 645.2 $[M+Cl]^-$; Anal. calcd. for $C_{34}H_{35}FN_6O_4$ (%): C, 66.87; H, 5.78; N, 13.76. Found (%): C, 66.89; H, 5.80; N, 13.79.

*5.7.14. N-(3-fluoro-4-((6-methoxy-7-(3-(piperidin-1-yl)propoxy) quinolin-4-yl)oxy)phenyl)-1-(2- fluorophenyl)-1H-1,2,3-triazole-4-carboxamide (**39**)*

Yield: 75.2%; M.p.: 172.8–174.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.14 (s, 1H), 8.63 (s, 1H), 8.52 (d, J = 5.3 Hz, 1H), 7.98 (dd, J = 11.9, 2.4 Hz, 1H), 7.70–7.64 (m, 2H), 7.59 (s, 1H), 7.55 (td, J = 7.1, 1.8 Hz, 2H), 7.49–7.46 (m, 1H), 7.45 (s, 1H), 7.31 (t, J = 8.6 Hz, 1H), 6.46 (d, J = 5.1 Hz, 1H), 4.27 (t, J = 6.7 Hz, 2H), 4.06 (s, 3H), 2.55 (t, J = 7.3 Hz, 2H), 2.50–2.38 (m, 4H), 2.17 (dd, J = 14.3, 7.0 Hz, 2H), 1.64–1.58 (m, 4H), 1.49–1.42 (m, 2H); MS (ESI) m/z (%): 649.4 $[M+Cl]^-$; Anal. calcd. for $C_{33}H_{32}F_2N_6O_4$ (%): C, 64.49; H, 5.25; N, 13.67. Found (%): C, 64.51; H, 5.28; N, 13.69.

*5.7.15. 1-(4-bromophenyl)-N-(3-fluoro-4-((6-methoxy-7-(3-(piperidin-1-yl)propoxy)quinolin-4-yl) oxy)phenyl)-1H-1,2,3-triazole-4-carboxamide (**40**)*

Yield: 74.8%; M.p.: 175.4–177.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.12 (s, 1H), 8.61 (s, 1H), 8.50 (d, J = 5.3 Hz, 1H), 7.97 (dd, J = 11.7, 2.2 Hz, 1H), 7.68–7.61 (m, 2H), 7.57 (s, 1H), 7.53 (td, J = 7.0, 1.7 Hz, 2H), 7.47–7.44 (m, 1H), 7.42 (s, 1H), 7.30 (t, J = 8.5 Hz, 1H), 6.45 (d, J = 5.0 Hz, 1H), 4.26 (t, J = 6.6 Hz, 2H), 4.05 (s, 3H), 2.53 (t, J = 7.2 Hz, 2H), 2.48–2.42 (m, 4H), 2.16 (dd, J = 14.2, 7.2 Hz, 2H), 1.62–1.59 (m, 4H), 1.48–1.45 (m, 2H); MS (ESI) m/z (%): 674.7 $[M+H]^+$; Anal. calcd. for $C_{33}H_{32}BrFN_6O_4$ (%): C, 58.67; H, 4.77; N, 12.44. Found (%): C, 58.71; H, 4.80; N, 12.46.

*5.7.16. 1-(2,6-dimethylphenyl)-N-(3-fluoro-4-((6-methoxy-7-(3-(piperidin-1-yl)propoxy)quinolin- 4-yl)oxy)phenyl)-1H-1,2,3-triazole-4-carboxamide (**41**)*

Yield: 73.9%; M.p.: 172.5–177.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.17 (s, 1H), 8.51 (d, J = 5.3 Hz, 1H), 8.39 (s, 1H), 7.97 (dd, J = 11.9, 2.5 Hz, 1H), 7.59 (s, 1H), 7.51 (dd, J = 8.2, 5.6 Hz, 1H), 7.46–7.45 (m, 1H), 7.45 (s, 1H), 7.44–7.43 (m, 1H), 7.42–7.38 (m, 1H), 7.30 (t, J = 8.0 Hz, 1H), 6.45 (d, J = 5.2 Hz, 1H), 4.27 (t, J = 6.7 Hz, 2H), 4.06 (s, 3H), 2.95 (d, J = 11.4 Hz, 2H), 2.62–2.54 (m, 2H), 2.20–2.12 (m, 2H), 2.04 (s, 6H), 1.98 (t, J = 10.9 Hz, 2H), 1.64 (d, J = 12.8 Hz, 2H), 1.41–1.33 (m, 1H), 1.30–1.24 (m, 2H), 0.93 (d, J = 8.0 Hz, 3H); MS (ESI) m/z (%): 638.9 $[M+H]^+$; Anal. calcd. for $C_{35}H_{37}FN_6O_4$ (%): C, 67.29; H, 5.97; N, 13.45. Found (%): C, 67.31; H, 5.92; N, 13.48.

*5.7.17. 1-(2,6-dichlorophenyl)-N-(3-fluoro-4-((6-methoxy-7-(3-(piperidin-1-yl)propoxy)quinolin- 4-yl)oxy)phenyl)-1H-1,2,3-triazole-4-carboxamide (**42**)*

Yield: 74.1%; M.p.: 176.3–178.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.19 (s, 1H), 8.52 (d, J = 5.2 Hz, 1H), 8.41 (s, 1H), 7.98 (dd, J = 11.9, 2.4 Hz, 1H), 7.59 (d, J = 7.1 Hz, 2H), 7.56–7.48 (m, 1H), 7.45 (d, J = 4.1 Hz, 2H), 7.32 (d, J = 8.6 Hz, 1H), 7.28 (s, 2H), 6.47 (d, J = 5.2 Hz, 1H), 4.28 (t, J = 6.7 Hz, 2H), 4.07 (s, 3H), 2.62–2.52 (m, 2H), 2.44 (s, 4H), 2.19–2.14 (m, 2H), 1.67–1.55 (m, 4H), 1.46 (d, J = 5.0 Hz, 2H); MS (ESI) m/z (%): 664.2 $[M+H]^+$; Anal. calcd. for $C_{33}H_{31}Cl_2FN_6O_4$ (%): C, 59.55; H, 4.69; N, 12.63. Found (%): C, 59.58; H, 4.72; N, 12.66.

*5.7.18. 1-(3,4-difluorophenyl)-N-(3-fluoro-4-((6-methoxy-7-(3-(piperidin-1-yl)propoxy)quinolin- 4-yl)oxy)phenyl)-1H-1,2,3-triazole-4-carboxamide (**43**)*

Yield: 75.1%; M.p.: 171.8–173.1 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.10 (s, 1H), 8.63 (s, 1H), 8.51 (d, J = 5.3 Hz, 1H), 7.96 (dd, J = 11.9, 2.4 Hz, 1H), 7.79–7.72 (m, 1H), 7.59 (s, 1H), 7.56 (dd, J = 8.8, 3.9 Hz, 1H), 7.45 (s, 1H), 7.44–7.37 (m, 2H), 7.30 (t, J = 8.0 Hz, 1H), 6.44 (d, J = 4.8 Hz, 1H), 4.27 (t, J = 6.7 Hz, 2H), 4.06 (s, 3H), 2.57–2.51 (m, 2H), 2.50–2.38 (m, 4H), 2.19–2.11 (m, 2H), 1.64–1.57 (m, 4H), 1.49–1.42 (m, J = 5.0 Hz, 2H); MS (ESI) m/z (%): 633.2 $[M+H]^+$; Anal. calcd. for $C_{33}H_{31}F_3N_6O_4$ (%): C, 62.65; H, 4.94; N, 13.28. Found (%): C, 62.73; H, 4.99; N, 13.26.

*5.7.19. N-(3-fluoro-4-((6-methoxy-7-(3-(4-methylpiperidin-1-yl) propoxy)quinolin-4-yl)oxy) phenyl)- 1-phenyl-1H-1,2,3-triazole-4-carboxamide (**44**)*

Yield: 76.2%; M.p.: 178.2–179.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.20 (s, 1H), 8.69 (s, 1H), 8.53 (d, J = 5.1 Hz, 1H), 8.00 (dd, J = 11.9, 2.0 Hz, 1H), 7.82 (d, J = 7.7 Hz, 2H), 7.62 (dd, J = 9.9, 5.1 Hz, 3H), 7.56 (t, J = 7.3 Hz, 1H), 7.48 (d, J = 9.0 Hz, 1H), 7.41 (s, 1H), 7.32 (d, J = 8.6 Hz, 1H), 6.48 (d, J = 4.6 Hz, 1H), 4.30 (s, 2H), 4.05 (s, 3H), 3.66 (d, J = 11.4 Hz, 1H), 3.28 (s, 1H), 2.83–2.49 (m, 4H), 1.98 (dd, J = 93.0, 13.3 Hz, 4H), 1.64 (d, J = 12.5 Hz, 2H), 1.08 (d, J = 6.1 Hz, 4H); MS (ESI) m/z (%): 610.9 $[M+H]^+$; Anal. calcd. for $C_{34}H_{35}FN_6O_4$ (%): C,

66.87; H, 5.78; N, 13.76. Found (%): C, 66.90; H, 5.72; N, 13.80.

*5.7.20. 1-(2-chlorophenyl)-N-(3-fluoro-4-((6-methoxy-7-(3-(4-methylpiperidin-1-yl)propoxy) quinolin- 4-yl)oxy)phenyl)-1H-1,2,3-triazole-4-carboxamide (**45**)*

Yield: 75.8%; M.p.: 177.9–178.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.14 (s, 1H), 8.63 (s, 1H), 8.52 (d, J = 5.3 Hz, 1H), 7.98 (dd, J = 11.9, 2.4 Hz, 1H), 7.70–7.65 (m, 2H), 7.59 (s, 1H), 7.55 (td, J = 7.1, 1.8 Hz, 2H), 7.31 (d, J = 8.6 Hz, 1H), 6.46 (d, J = 4.8 Hz, 1H), 4.27 (t, J = 6.7 Hz, 2H), 4.06 (s, 3H), 2.95 (d, J = 11.3 Hz, 2H), 2.58 (t, J = 7.1 Hz, 2H), 2.18 (dd, J = 14.3, 6.9 Hz, 2H), 1.99 (t, J = 10.6 Hz, 2H), 1.65 (d, J = 13.1 Hz, 2H), 1.41–1.34 (m, 1H), 1.28 (d, J = 8.9 Hz, 2H), 0.94 (d, J = 6.2 Hz, 3H); ^{13}C NMR (600 MHz, $CDCl_3$) δ 159.96, 157.63, 153.27, 152.33, 149.90, 148.76, 146.96, 142.78, 137.70, 137.58, 136.06, 135.96, 131.60, 131.03, 128.83, 128.18, 127.67, 123.95, 116.08, 115.43, 109.63, 109.40, 108.79, 102.23, 67.64, 56.17, 55.42, 54.01 (2C), 34.29 (2C), 30.81, 26.49, 21.90; MS (ESI) m/z (%): 645.1 $[M+H]^+$; Anal. calcd. for $C_{34}H_{34}ClFN_6O_4$ (%): C, 63.30; H, 5.31; N, 13.03. Found (%): C, 63.37; H, 5.37; N, 13.06.

*5.7.21. N-(3-fluoro-4-((6-methoxy-7-(3-(4-methylpiperidin-1-yl) propoxy)quinolin-4-yl)oxy) phenyl)-1-(2-fluorophenyl)-1H-1,2,3-triazole-4-carboxamide (**46**)*

Yield: 73.6%; M.p.: 178.2–180.1 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.14 (s, 1H), 8.63 (s, 1H), 8.52 (d, J = 5.3 Hz, 1H), 7.98 (dd, J = 11.9, 2.4 Hz, 1H), 7.70–7.65 (m, 2H), 7.59 (s, 1H), 7.55 (td, J = 7.1, 1.8 Hz, 2H), 7.31 (d, J = 8.6 Hz, 1H), 6.46 (d, J = 4.8 Hz, 1H), 4.27 (t, J = 6.7 Hz, 2H), 4.06 (s, 3H), 2.95 (d, J = 11.3 Hz, 2H), 2.58 (t, J = 7.1 Hz, 2H), 2.18 (dd, J = 14.3, 6.9 Hz, 2H), 1.99 (t, J = 10.6 Hz, 2H), 1.65 (d, J = 13.1 Hz, 2H), 1.41–1.34 (m, 1H), 1.28 (d, J = 8.9 Hz, 2H), 0.94 (d, J = 6.2 Hz, 3H); MS (ESI) m/z (%): 663.4 $[M+Cl]^-$; Anal. calcd. for $C_{34}H_{34}F_2N_6O_4$ (%): C, 64.96; H, 5.45; N, 13.37. Found (%): C, 64.93; H, 5.37; N, 13.41.

*5.7.22. N-(3-fluoro-4-((6-methoxy-7-(3-(4-methylpiperidin-1-yl) propoxy)quinolin-4-yl)oxy) phenyl)-1-(o-tolyl)-1H-1,2,3-triazole-4-carboxamide (**47**)*

Yield: 77.2%; M.p.: 177.7–178.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.17 (s, 1H), 8.51 (d, J = 5.3 Hz, 1H), 8.39 (s, 1H), 7.97 (dd, J = 11.9, 2.5 Hz, 1H), 7.59 (s, 1H), 7.51 (ddd, J = 8.2, 5.6, 2.8 Hz, 1H), 7.46–7.45 (m, 1H), 7.45 (s, 1H), 7.44–7.43 (m, 1H), 7.42–7.38 (m, 2H), 7.30 (t, J = 8.0 Hz, 1H), 6.45 (d, J = 5.2 Hz, 1H), 4.27 (t, J = 6.7 Hz, 2H), 4.06 (s, 3H), 2.95 (d, J = 11.4 Hz, 2H), 2.62–2.54 (m, 2H), 2.28 (s, 3H), 2.20–2.12 (m, 2H), 1.98 (t, J = 10.9 Hz, 2H), 1.64 (d, J = 12.8 Hz, 2H), 1.41–1.33 (m, 1H), 1.30–1.24 (m, 2H), 0.93 (d, J = 8.0 Hz, 3H); MS (ESI) m/z (%): 625.2 $[M+H]^+$; Anal. calcd. for $C_{35}H_{37}FN_6O_4$ (%): C, 67.29; H, 5.97; N, 13.45. Found (%): C, 67.33; H, 5.93; N, 13.46.

*5.7.23. 1-(2,6-dimethylphenyl)-N-(3-fluoro-4-((6-methoxy-7-(3-(4-methylpiperidin-1-yl)propoxy) quinolin-4-yl)oxy)phenyl)-1H-1,2,3-triazole-4-carboxamide (**48**)*

Yield: 76.8%; M.p.: 178.3–180.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.17 (s, 1H), 8.51 (d, J = 5.3 Hz, 1H), 8.39 (s, 1H), 7.97 (dd, J = 11.9, 2.5 Hz, 1H), 7.59 (s, 1H), 7.51 (dd, J = 8.2, 5.6 Hz, 1H), 7.46–7.45 (m, 1H), 7.45 (s, 1H), 7.44–7.43 (m, 1H), 7.42–7.38 (m, 1H), 7.30 (t, J = 8.0 Hz, 1H), 6.45 (d, J = 5.2 Hz, 1H), 4.27 (t, J = 6.7 Hz, 2H), 4.06 (s, 3H), 2.95 (d, J = 11.4 Hz, 2H), 2.62–2.54 (m, 2H), 2.20–2.12 (m, 2H), 2.04 (s, 6H), 1.98 (t, J = 10.9 Hz, 2H), 1.64 (d, J = 12.8 Hz, 2H), 1.41–1.33 (m, 1H), 1.30–1.24 (m, 2H), 0.93 (d, J = 8.0 Hz, 3H); MS (ESI) m/z (%): 639.3 $[M+H]^+$; Anal. calcd. for $C_{36}H_{39}FN_6O_4$ (%): C, 67.69; H, 6.15; N, 13.16. Found (%): C, 67.73; H, 6.17; N, 13.21.

*5.7.24. 1-(2,6-dichlorophenyl)-N-(3-fluoro-4-((6-methoxy-7-(3-(4-methylpiperidin-1-yl)propoxy) quinolin-4-yl)oxy)phenyl)-1H-1,2,3-triazole-4-carboxamide (**49**)*

Yield: 77.4%; M.p.: 179.1–180.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.19 (s, 1H), 8.52 (d, J = 5.2 Hz, 1H), 8.41 (s, 1H), 7.98 (dd, J = 11.9, 2.4 Hz, 1H), 7.59 (d, J = 7.8 Hz, 2H), 7.56–7.51 (m, 1H), 7.46 (d, J = 5.7 Hz, 2H), 7.32 (d, J = 8.6 Hz, 1H), 7.28 (s, 1H), 6.46 (d, J = 5.2 Hz, 1H), 4.27 (t, J = 6.7 Hz, 2H), 4.06 (s, 3H), 2.95 (t, J = 11.8 Hz, 2H), 2.62–2.46 (m, 2H), 2.15 (dd, J = 14.1, 7.1 Hz, 2H), 1.97 (t, J = 11.5 Hz, 2H), 1.64 (d, J = 12.6 Hz, 2H), 1.28 (t, J = 10.4 Hz, 3H), 0.94 (d, J = 6.3 Hz, 3H); MS (ESI) m/z (%): 679.1 $[M+H]^+$; Anal. calcd. for $C_{34}H_{33}Cl_2FN_6O_4$ (%): C, 60.09; H, 4.89; N, 12.37. Found (%): C, 60.13; H, 4.93; N, 12.39.

*5.7.25. 1-(3,4-difluorophenyl)-N-(3-fluoro-4-((6-methoxy-7-(3-(4-methylpiperidin-1-yl)propoxy) quinolin-4-yl)oxy)phenyl)-1H-1,2,3-triazole-4-carboxamide (**50**)*

Yield: 78.3%; M.p.: 179.6–180.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.10 (s, 1H), 8.61 (s, 1H), 8.51 (d, J = 5.3 Hz, 1H), 7.97 (dd, J = 11.9, 2.5 Hz, 1H), 7.79–7.73 (m, 1H), 7.59 (s, 1H), 7.56 (dd, J = 9.1, 3.5 Hz, 1H), 7.45 (s, 1H), 7.44–7.38 (m, 2H), 7.31 (t, J = 8.6 Hz, 1H), 6.44 (d, J = 4.6 Hz, 1H), 4.27 (t, J = 6.7 Hz, 2H), 4.06 (s, 3H), 2.93 (d, J = 11.4 Hz, 2H), 2.59–2.53 (m, 2H), 2.19–2.11 (m, 2H), 1.96 (t, J = 10.5 Hz, 2H), 1.64 (d, J = 12.9 Hz, 2H), 1.40–1.32 (m, 1H), 1.26 (dd, J = 11.9, 3.3 Hz, 2H), 0.94 (d, J = 6.3 Hz, 3H); MS (ESI) m/z (%): 647.2 $[M+H]^+$; Anal. calcd. for $C_{34}H_{33}F_3N_6O_4$ (%): C, 63.15; H, 5.14; N, 13.00. Found (%): C, 63.19; H, 5.17; N, 13.06.

*5.7.26. N-(3-fluoro-4-((6-methoxy-7-(3-(4-methylpiperazin-1-yl) propoxy)quinolin-4-yl)oxy) phenyl)-1-phenyl-1H-1,2,3-triazole-4-carboxamide (**51**)*

Yield: 73.4%; M.p.: 160.2–162.1 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.16 (s, 1H), 8.67 (s, 1H), 8.53 (d, J = 5.2 Hz, 1H), 8.00 (dd, J = 11.9, 2.1 Hz, 1H), 7.83 (d, J = 7.7 Hz, 2H), 7.65 (d, J = 7.2 Hz, 3H), 7.57 (t, J = 7.3 Hz, 1H), 7.47 (d, J = 3.1 Hz, 2H), 7.33 (d, J = 8.6 Hz, 1H), 6.48 (d, J = 5.1 Hz, 1H), 4.31 (t, J = 6.5 Hz, 2H), 4.08 (s, 3H), 3.01–2.52 (m, 10H), 2.44 (s, 3H), 2.24–2.11 (m, 2H); MS (ESI) m/z (%): 611.9 $[M+H]^+$; Anal. calcd. for $C_{35}H_{34}FN_7O_4$ (%): C, 64.80; H, 5.60; N, 16.03. Found (%): C, 64.84; H, 5.67; N, 16.06.

*5.7.27. 1-(2-chlorophenyl)-N-(3-fluoro-4-((6-methoxy-7-(3-(4-methylpiperazin-1-yl)propoxy) quinolin-4-yl)oxy)phenyl)-1H-1,2,3-triazole-4-carboxamide (**52**)*

Yield: 75.1%; M.p.: 161.1–163.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.13 (s, 1H), 8.73 (s, J = 2.4 Hz, 1H), 8.51 (d, J = 5.2 Hz, 1H), 8.02–7.95 (m, 2H), 7.59 (s, 1H), 7.58–7.51 (m, 1H), 7.47 (s, 1H), 7.45 (s, 1H), 7.41 (t, J = 7.7 Hz, 2H), 7.31 (d, J = 8.6 Hz, 1H), 6.45 (d, J = 5.2 Hz, 1H), 4.28 (t, J = 6.6 Hz, 2H), 4.06 (s, 3H), 2.73–2.44 (m, 10H), 2.38 (s, 3H), 2.19–2.11 (m, 2H); MS (ESI) m/z (%): 644.2 $[M-H]^-$; Anal. calcd. for $C_{33}H_{33}ClFN_7O_4$ (%): C, 61.34; H, 5.15; N, 15.17. Found (%): C, 61.38; H, 5.17; N, 15.16.

*5.7.28. N-(3-fluoro-4-((6-methoxy-7-(3-(4-methylpiperazin-1-yl) propoxy)quinolin-4-yl)oxy) phenyl)-1-(2-fluorophenyl)-1H-1,2,3-triazole-4-carboxamide (**53**)*

Yield: 76.2%; M.p.: 162.4–164.1 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.13 (s, 1H), 8.73 (s, J = 2.4 Hz, 1H), 8.51 (d, J = 5.2 Hz, 1H), 8.02–7.95 (m, 2H), 7.59 (s, 1H), 7.58–7.51 (m, 1H), 7.47 (s, 1H), 7.45 (s, 1H), 7.41 (t, J = 7.7 Hz, 2H), 7.31 (d, J = 8.6 Hz, 1H), 6.45 (d, J = 5.2 Hz, 1H), 4.28 (t, J = 6.6 Hz, 2H), 4.06 (s, 3H), 2.73–2.44 (m, 10H), 2.38 (s, 3H), 2.19–2.11 (m, 2H); MS (ESI) m/z (%): 664.4 $[M+Cl]^-$; Anal. calcd. for $C_{35}H_{34}F_2N_7O_4$ (%): C, 62.95; H, 5.28; N, 15.57. Found (%): C, 62.93; H, 5.37; N, 15.56.

*5.7.29. N-(3-fluoro-4-((6-methoxy-7-(3-(4-methylpiperazin-1-yl) propoxy)quinolin-4-yl)oxy) phenyl)-1-(o-tolyl)-1H-1,2,3-triazole-4-carboxamide (**54**)*

Yield: 75.4%; M.p.: 161.7–163.4 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.24 (s, 1H), 8.52 (d, J = 5.2 Hz, 1H), 8.32 (s, 1H), 8.01 (dd, J = 11.8,

2.1 Hz, 1H), 7.63 (s, 1H), 7.46 (d, J = 10.1 Hz, 2H), 7.42 (t, J = 7.5 Hz, 2H), 7.32 (d, J = 8.5 Hz, 1H), 7.26 (d, J = 7.5 Hz, 2H), 6.48 (d, J = 5.1 Hz, 1H), 4.30 (t, J = 6.2 Hz, 2H), 4.05 (s, 3H), 2.91 (dd, J = 13.0, 12.1 Hz, 8H), 2.74 (t, J = 6.1 Hz, 2H), 2.62 (s, 3H), 2.23–2.15 (m, 2H), 2.05 (s, 3H); MS (ESI) m/z (%): 626.3 $[M+H]^+$; Anal. calcd. for $C_{34}H_{36}FN_7O_4$ (%): C, 65.27; H, 5.80; N, 15.67. Found (%): C, 65.33; H, 5.87; N, 15.69.

*5.7.30. 1-(2,6-dimethylphenyl)-N-(3-fluoro-4-((6-methoxy-7-(3-(4-methylpiperazin-1-yl)propoxy) quinolin-4-yl)oxy)phenyl)-1H-1,2,3-triazole-4-carboxamide (**55**)*

Yield: 72.7%; M.p.: 162.5–164.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.25 (s, 1H), 8.53 (d, J = 5.2 Hz, 1H), 8.31 (s, 1H), 8.00 (dd, J = 11.9, 2.2 Hz, 1H), 7.62 (s, 1H), 7.48 (d, J = 10.2 Hz, 2H), 7.41 (t, J = 7.6 Hz, 1H), 7.33 (d, J = 8.6 Hz, 1H), 7.27 (d, J = 7.6 Hz, 2H), 6.49 (d, J = 5.1 Hz, 1H), 4.31 (t, J = 6.3 Hz, 2H), 4.07 (s, 3H), 2.92 (dd, J = 13.1, 12.1 Hz, 8H), 2.75 (t, J = 6.2 Hz, 2H), 2.63 (s, 3H), 2.24–2.14 (m, 2H), 2.07 (s, 6H); MS (ESI) m/z (%): 639.9 $[M+H]^+$; Anal. calcd. for $C_{35}H_{38}FN_7O_4$ (%): C, 65.71; H, 5.99; N, 15.33. Found (%): C, 65.73; H, 5.97; N, 15.36.

*5.7.31. 1-(3,4-difluorophenyl)-N-(3-fluoro-4-((6-methoxy-7-(3-(4-methylpiperazin-1-yl)propoxy) quinolin-4-yl)oxy)phenyl)-1H-1,2,3-triazole-4-carboxamide (**56**)*

Yield: 75.8%; M.p.: 163.1–165.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.10 (s, 1H), 8.62 (s, 1H), 8.51 (d, J = 5.3 Hz, 1H), 7.97 (dd, J = 11.9, 2.4 Hz, 1H), 7.76 (ddd, J = 9.7, 6.7, 2.6 Hz, 1H), 7.59 (s, 1H), 7.56 (dd, J = 8.9, 3.7 Hz, 1H), 7.45 (s, 1H), 7.42 (d, J = 8.3 Hz, 2H), 7.31 (t, J = 8.6 Hz, 1H), 6.44 (d, J = 5.3 Hz, 1H), 4.28 (t, J = 6.7 Hz, 2H), 4.06 (s, 3H), 2.72–2.36 (m, 10H), 2.31 (s, 3H), 2.19–2.11 (m, 2H); MS (ESI) m/z (%): 648.2 $[M+H]^+$; Anal. calcd. for $C_{33}H_{32}F_3N_7O_4$ (%): C, 61.20; H, 4.98; N, 15.14. Found (%): C, 61.33; H, 5.02; N, 15.16.

5.8. Pharmacology

5.8.1. MTT assay in vitro

The anti-proliferative activities of compounds **26**–**56** were evaluated against HT-29, H460, 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) supplement with 10% fetal bovine serum (FBS). Approximate 4 × 10^3 cells, suspended in MEM medium, were plated onto each well of a 96-well plate and incubated in 5% CO_2 at 37 °C for 24 h. The 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 μg/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} were the averages of three determinations and calculated by using the Bacus Laboratories Incorporated Slide Scanner (Bliss) software.

5.8.2. c-Met kinase assay

The c-Met kinase activity was evaluated using homogeneous time-resolved fluorescence (HTRF) assays as previously reported protocol [23,24]. In order to examine the selectivity of the most promising compound **37** on c-Met over other tyrosine kinases, it was screened against VEGFR-2, c-kit, Flt-3, Ron, and EGFR. 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) 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 nm and 615 nm. The inhibition rate (%) was calculated using the following equation: % inhibition = 100 − [(Activity of enzyme with tested compounds − Min)/(Max − Min)] × 100 (Max: the observed enzyme activity measured in the presence of enzyme, substrates, and cofactors; Min: the observed enzyme activity in the presence of substrates, cofactors and in the absence of enzyme). IC_{50} values were calculated from the inhibition curves.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejmech.2016.04.035.

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