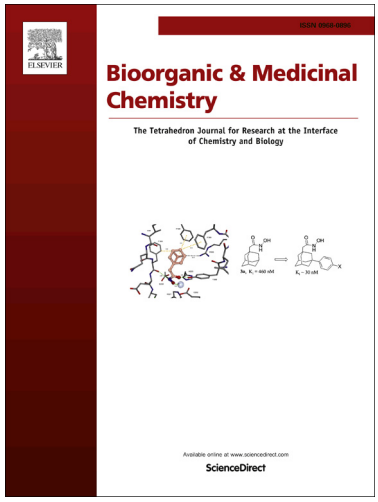

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Design and biological evaluation of novel 4-(2-fluorophenoxy) quinoline derivatives bearing an imidazolone moiety as c-Met kinase inhibitors

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Abstract

A series of 4-(2-fluorophenoxy)quinoline derivatives containing an imidazolone moiety were designed, synthesized and evaluated for their *in vitro* biological activities against c-Met kinase and four cancer cell lines (A549, H460, HT-29 and MKN-45). Most compounds showed moderate to excellent activities in enzyme and cellular assays. The most promising analog, **58** (c-Met IC_{50} = 1.42 nM), displayed 2.1-, 8.6-, fold increase against H460, and MKN-45 cell lines, respectively, compared with foretinib. An analysis of structure-activity relationships revealed that an *ortho* substituted phenyl ring as well as an *N*-unsubstituted imidazolone linker is favorable for antitumor activity.

Keywords: c-Met; antitumor activity; quinoline derivatives; imidazolone-4-carboxamide.

1. Introduction

Mesenchymal–epithelial transition factor (c-Met), a member of a structurally distinct family of receptor tyrosine kinases (RTK), is a proto-oncogene encoding the high affinity receptor for hepatocyte growth factor (HGF).[1,2] The c-Met/HGF signaling pathway plays important roles during normal development, organogenesis, and homeostasis. After activation by HGF, c-Met induces an invasive program consisting of cell proliferation, migration, invasion, and survival that is essential during normal processes, such as morphogenesis and wound healing.[3] Aberrant HGF/c-Met signaling has been identified in a wide range of human malignancies, including breast, gastric, liver, lung cancers and so on.[4-6] Furthermore, overexpression of c-Met and HGF was demonstrated to correlate with poor prognosis or metastatic progression in a number of major human cancers.[7] For these reasons, c-Met and its ligand HGF are emerging as attractive targets for targeted cancer therapies.

Among current approaches for targeting the c-Met signaling pathway, small-molecule inhibitors directed against the ATP binding site of c-Met have been considered the most successful strategy. Over the last decade, a number of c-Met inhibitors have been reported, such as Bristol-Myers Squibb's BMS777607 **1**,[8] Kirin Brewery's acylthiourea **2**,[9] Amgen **3**,[10] AM 7 **4**,[11] cabozantinib **5** [12]and foretinib **6** (**Figure 1**).[13] Among them, 6,7-disubstituted quinoline derivatives have been most extensively investigated. Of these reported quinoline-based inhibitors, principal modification usually occurs at the 7-position of quinoline and the "5 atoms linker" section between moiety A and B. The crystal structure of foretinib (PDB: 3LQ8) and Met kinase complex revealed that the amide linker assumed a pseudocyclic conformation which formed three hydrogen bonds with c-Met.[14] Therefore, on the premise of "**5 atoms regulation**", we postulated various rings can be used to replace the amide linker between moiety A and B via cyclization strategy. Based on this hypothesis, we previously designed a series of 6,7-disubstituted-4-phenoxyquinoline-based c-Met inhibitors exemplified by compounds **7–11** (**Figure 2**),[15] which

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bear 2-arylquinoline-4-carboxamide, 4-oxo-1-phenyl-1,4-dihydrocinnoline-3-carboxamide, 4-arylpyridine-4-carboxamide, 1,2,3-triazole-4-carboxamide and 4-methyl-6-oxo-1-phenyl-1,6-dihydropyridazine-3-carboxamide. However, despite these motivating factors, most of the clinically investigated class II c-Met inhibitors also possess essential activity on other RTK targets. Therefore, novel c-Met inhibitors with improved selectivity profiles, particularly to VEGFR-2, and minimal side effects should be developed.

(**Figure 1.** should be listed here)

(**Figure 2.** should be listed here)

Imidazolone-backbone scaffold-containing molecules are among the vast array of compounds found active as anti-cancer agents presumably because of its ability to form hydrogen-bonding interactions with drug targets (**12–14, Figure 3**).[16] Considering its potency and conformation to **"5 atoms regulation"**, we replaced the cyclopropane-1,1-dicarboxamide fragment of foretinib with 2-oxo-1-phenyl-2,3-dihydro-1*H*-imidazole-4-carboxamide scaffold. We assumed that the carbonyl groups and the *NH* groups of 2-imidazolone ring and carboxamide may function as potential H-bond acceptors or donors to retain interactions with key residues in the binding pocket. In addition, different tertiary amines were introduced at the 7-position of quinolines as polar and hydrophilic fragments. The outcome of this exercise was shown in **Figure 4**, and their structure-activity relationships (SARs) were further explored.

(**Figure 3.** should be listed here)

(**Figure 4.** should be listed here)

All target compounds were evaluated for their inhibition toward c-Met kinase and antiproliferative activities *in vitro* against HT-29 (human colon cancer), H460 (human lung cancer), A549 (human lung adenocarcinoma) and MKN-45 (human gastric cancer), and most of them showed promising inhibition. Furthermore, the inhibitory activities of the most potent compound **58** against five other RTK kinases were also investigated, the results are illustrated in **Table 1** and **Table 2**.

2. Chemistry

The synthesis of the key intermediates of 6,7-disubstituted-4-phenoxyquinolines **22a-e** was achieved in 8 steps from commercially available 1-(4-hydroxy-3-methoxyphenyl)ethanone as shown in **Scheme 1**, which was illustrated in detail in our previous study.[15]

(**Scheme 1.** should be listed here)

The target compounds **28–58** were prepared as illustrated in **Scheme 2**. Condensation of substituted anilines with sodium cyanate in AcOH/H_2O at 50 °C resulted in high yield of intermediates **23a-m**. The rhodium-catalyzed *N*-H insertion reaction of primary ureas with ethyl 2-diazo-3-oxobutanoate gave the corresponding ethyl 3-oxo-2-(3-phenylureido)butanoate, which were converted into the corresponding imidazolones **24a-m** by TFA-catalyzed cyclodehydration.[17] Subsequent methylation with methyl iodide in DMF provided the desired *N*-methylimidazolones **25a-m** in nearly quantitative yield, which were then converted to acids **26a-m** using sodium hydroxide solution at 40 °C for 10 h. The intermediate **26n** was obtained via the *N*-H insertion reaction of primary ureas with *tert*-butyl 2-diazo-3-oxobutanoate and subsequent TFA-induced cyclodehydration as well as deprotection. Finally, intermediates **26a-n** were refluxed in toluene and $SOCl_2$ for 5 h to afford acyl chlorides **27a-n**, which were condensed with intermediates **22a-e** in the presence of sodium carbonate in dichloromethane at room temperature overnight to obtain the target compounds **28–58**, respectively.

(**Scheme 2.** should be listed here)

3. Biology

3.1. HTRF kinase assay

The c-Met kinase activity was evaluated using homogeneous time-resolved fluorescence (HTRF) assays as previously reported.[18,19] In addition, the most promising compound **58** was further evaluated against other five tyrosine kinase (VEGFR-2, c-Kit, Flt-3, EGFR and Ron) using the same screening method. 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-XL 665 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.

3.2. Cell proliferation assay

The anti-proliferative activities of compounds **28–58** were evaluated against four c-Met-dependent cancer cell lines (A549, H460, HT-29 and MKN-45) using the standard MTT assay *in vitro*, with foretinib as the positive control.[20,21] 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 μL 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.

4. Results and discussion

4.1. In vitro assays and SARs

All the target compounds were evaluated for their inhibitory activities against c-Met kinase as well as antitumor activities against A549, H460, HT-29 and MKN-45 cancer cell lines. The results expressed as IC_{50} values are shown in **Table 1** as the mean values of triplicate experiments. As illustrated in **Table 1**, all the tested compounds displayed potent c-Met enzymatic activity with IC_{50} values ranging from 1.42 to 35.68 nM, which validated our hypothesis that the replacement of the cyclopropane-1,1- dicarboxamide framework in foretinib with 2-imidazolone-4-carboxamide moiety maintained the c-Met inhibitory efficacy.

The SARs was commenced by the introduction of a three carbon tether that contains different tertiary amines at the 7-position of the quinoline ring. Of all the amines, the 4-methyl piperidinyl **31** and the 4-methylpiperazinyl **32** afforded greater activities towards morpholinyl **28**, pyrrolidinyl **29** and piperidinyl **30**. Accordingly, 4-methylpiperidinyl and 4-methylpiperazinyl derivatives were further studied in our work.

Comprehensive 4-methylpiperidinyl and 4-methylpiperazinyl analogs with diverse R_2 groups were examined

for potency. The SARs based on IC_{50} values (**Table 1**) revealed that variations in the R_2 groups markedly affect their enzyme activities. Primarily, mono-electron-donating groups (EDGs) such as 4-methyl **34** and 4-methoxy **36** were introduced; a decrease against c-Met enzyme and cellular activities was observed compared to **32**, which had no substituent on the phenyl ring. Incorporation of double-EDGs (3,4-dimethoxy) lowered the efficiency even further (the data not shown). In view of this, the use of EDGs was not pursued.

Halogen groups were subsequently introduced at the *para* position of the phenyl ring with the hope of increased potency. Gratifyingly, the data in **Table 1** showed that halogen made a good contribution to enzyme activity, with following rank order: H<Br<F<Cl. Incorporating a 3,4-dihalogened group in the form of 3,4-difluoro **45** or 3-chloro-4-fluoro **47** afforded compound that, while still potent in the c-Met kinase essay, exhibited somewhat a decreased cellular activity, compared to **38**, which indicates mono-substitution of phenyl is more preferred.

Different electron-withdrawing groups (EWGs) were also investigated, the *para*-substituted trifluoromethyl and trifluoromethoxyl atom allowed us to slightly improve c-Met inhibitory activity (**49**, **51** vs **32**, ranging from 1.2 to 2.3-fold increase). In addition, moving the *para*-trifluoromethyl group **51** to the *ortho* position **55** is advantageous to potency while the *meta* position **53** is not well tolerated, which could be further confirmed by 2-chloro analog **57** vs 4-chloro analog **40**. Our final modification focused on the R_3 group of the imidazolone motif. To our delight, the 2-chloro analog **58**, which is a demethylated version of compound **57**, had the most promising potency towards both cellular and enzyme activities.

(**Table 1.** should be listed here)

4.2. Enzymatic selectivity assays

The inhibitory activity of the most potent compounds **58** against VEGFR-2, c-Kit, Flt-3, EGFR and Ron kinase were also assayed using the homogeneous time resolved fluorescence (HTRF) method (**Table 2**). Compound **58** demonstrated selectivity against VEGFR-2, c-Kit, Flt-3, Ron and EGFR kinase (65-fold, 27-fold, 94-fold, 190-fold and >10000 fold).

(**Table 2.** should be listed here)

5. 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 **58** with c-Met. As shown in **Figure 5**, the protonated nitrogen atom of 4-methylpiperazinyl, nitrogen atom of the quinoline and the 2-imidazolone-4-carboxamide moiety formed five hydrogen-bonding interactions with Asp1222, Met1160 and Tyr1159, respectively.

(**Figure 5.** should be listed here)

6. Conclusions

In summary, we designed and synthesized novel c-Met receptor tyrosine kinase inhibitors based upon 6,7-disubstitued quinoline and imidazolone scaffolds. c-Met kinase and four human cancer cell lines (HT-29, H460, MKN-45 and A549) were used to evaluate the potency of the synthesized compounds. The results revealed that

most of the tested compounds were potent c-Met inhibitors (c-Met IC_{50}=1.42 to 35.68 nM). Compared with foretinib, one compound showed higher c-Met kinase inhibitory activity, and 12 were more potent against one or more cell lines. The analysis of SARs indicated that the replacement of the cyclopropane-1,1-dicarboxamide framework in foretinib with the 2-imidazole-4-carboxamide scaffold maintained the potent efficiency. The preference for a 2-chloro substituted phenyl ring in moiety **B** as well as an *N*-unsubstituted imidazolone linker was observed. Moreover, the three-carbon tether containing 4-methylpiperazinyl (R_1) in the 7-position of quinolines is advantageous. To our delight, the most promising compound **58**, showed excellent inhibition of c-Met kinase (IC_{50} = 1.42 nM) compared to five other kinases screened in this report, as well as 2.1- and 8.6-fold increase against H460 and MKN-45 cell lines compared to foretinib, respectively. The druggability of **58** is currently evaluated and this compound is also optimized. Research progress will be reported in due course.

7. Experimental

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; or Bruker ARX-600, 600 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.).

7.1. General procedure for preparation of 3-fluoro-4-(6,7-disubstituted quinolin-4-yloxy)anilines (22a–e)

The preparation of the key intermediates **22a–e** has been illustrated in detail in our laboratory previous study, so the synthesis method would not be listed here.[15]

7.1.1. 3-Fluoro-4-(6-methoxy-7-(3-morpholinopropoxy)quinolin-4-yloxy)aniline (22a)

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 $[M+Na]^+$.

7.1.2. 3-Fluoro-4-(6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy)quinolin-4-yloxy)aniline (22b)

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, *J* = 12.8, 7.1 Hz, 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 $[M+H]^+$.

7.1.3. 3-Fluoro-4-(6-methoxy-7-(3-(piperdine-1-yl)propoxy)quinolin-4-yloxy)aniline (22c)

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 $[M+H]^+$.

7.1.4. 3-Fluoro-4-(6-methoxy-7-(3-(4-methylpiperdine-1-yl)propoxy)quinolin-4-yl-oxy)aniline (22d)

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 $[M+H]^+$.

7.1.5. 3-Fluoro-4-(6-methoxy-7-(3-(4-methylpiperazine-1-yl)propoxy)quinolin-4-yl-oxy)aniline (22e)

White solid; yield: 77%; M.p.:201–202 °C ^{1}H NMR (300 MHz,$CDCl_3$) 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 $[M+Na]^+$.

7.2.General procedure for preparation of ureas (23a–m)

To a solution of substituted aniline (0.1 mol) dissolved in 48 mL glacial acetic acid and 96 mL H_2O, sodium cyanate (13 g, 0.2 mol) in warm water (90 mL) was added with continuous stirring. The mixture was warmed to 50 °C for 2 h and then cooled in ice, The crude solid, thus obtained was filtered, dried, and recrystallized with boiling water.

7.2.1. phenylurea (23a).

White solid, yield: 90.2%; M.p.:145–147 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.47 (s, 1H), 7.38 (dd, *J* = 8.4 Hz, 0.9 Hz, 2H), 7.2 (t, *J* = 7.6 Hz, 2H), 6.88 (t, *J* = 7.6 Hz, 1H), 5.81 (brs, 2H). MS (ESI) m/z (%): 137.1 $[M+H]^+$.

7.2.2. 4-methylphenylurea (23b).

White solid, yield: 81.1%; M.p.:178–179 °C. MS (ESI) m/z (%): 173.1 $[M+Na]^+$.

7.2.3. 4-methoxyphenylurea (23c).

White solid, yield: 76.5%; M.p.:165–166 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.31 (s, 1H), 7.28 (d, *J* = 6.8 Hz, 2H), 6.80 (d, *J* = 6.8 Hz, 2H), 5.73 (s, 2H), 3.68 (s, 3H). MS (ESI) m/z (%): 189.1 $[M+Na]^+$.

7.2.4. 4-fluorophenylurea (23d).

White solid, yield: 80.6%; M.p.:178–180 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.54 (s, 1H), 7.39 (dd, *J* = 9.1, 5.0 Hz, 2H), 7.04 (t, *J* = 8.9 Hz, 2H), 5.83 (s, 2H). MS (ESI) m/z (%): 177.2 $[M+Na]^+$.

7.2.5. 4-chlorophenylurea (23e).

White solid, yield: 84.8%; M.p.:206–208 °C. MS (ESI) m/z (%): 193.2 $[M+Na]^+$.

7.2.6. 4-bromophenylurea (23f).

White solid, yield: 78.8%; M.p.:224–226 °C. MS (ESI) m/z (%): 215.1 $[M+H]^+$.

7.2.7. 3,4-difluorophenylurea (23g).

White solid, yield: 76.8%; M.p.:182–184 °C. MS (ESI) m/z (%): 172.9 $[M+H]^+$.

7.2.8. 3-chloro-4-fluorophenylurea (23h).

White solid, yield: 75.4%; M.p.:186–188 °C. MS (ESI) m/z (%): 189.1 $[M+H]^+$.

7.2.9. 4-(trifluoromethoxy)phenyl)urea (23i).

White solid, yield: 74.2%; M.p.:135–139 °C. MS (ESI) m/z (%): 221.2 $[M+H]^+$.

7.2.10. 4-(trifluoromethyl)phenylurea (23j).

White solid, yield: 79.6%; M.p.:140–142 °C. MS (ESI) m/z (%): 205.1 $[M+H]^+$.

7.2.11. 3-(trifluoromethyl)phenylurea (23k).

White solid, yield: 75.4%; M.p.:102–105 °C. MS (ESI) m/z (%): 205.2 $[M+H]^+$.

7.2.12. 2-(trifluoromethyl)phenylurea (23l).

White solid, yield: 80.6%; M.p.:154–158 °C. MS (ESI) m/z (%): 205.0 $[M+H]^+$.

7.2.13. 2-chlorophenylurea (23m).

White solid, yield: 84.8%; M.p.:152–153 °C. MS (ESI) m/z (%): 193.1 $[M+Na]^+$.

7.3. General procedure for the synthesis of 2-imidazolones (24a–m)

To a vigorously stirred suspension of ethyl 2-diazo-3-oxobutanoate (14 mmol) and finely powdered urea **23** (408 mg, 18 mmol) in toluene-1,2-dichloroethane (1:1, 140 mL) was heated to 80 °C and a suspension of Rh_2Oct_4 (217 mg, 0.28 mmol) in toluene (28 mL) was added over 60 min. The mixture was then stirred for an additional 30 min. After cooling to room temperature, TFA (16.8 mL) was added dropwisely, the solution was then stirred for 30 min, after removal of solvent under reduced pressure, the residue was dissolved in 150 mL CH_2Cl_2, washed with 6N HCl (3 × 30 mL), and then brine before being dried. The organic layer was concentrated, triturated with ether to obtain the imidazolone as a white solid.

7.3.1. ethyl 5-methyl-2-oxo-1-phenyl-2,3-dihydro-1*H*-imidazole-4-carboxylate (24a)

White solid, yield: 80.7%; M.p.:173–175 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (brs, 1H), 7.54 – 7.39 (m, 3H), 7.33 – 7.27 (m, 2H), 4.32 (q, *J* = 7.4 Hz, 2H), 2.26 (s, 3H), 1.34 (t, *J* = 7.4 Hz, 3H). MS (ESI) m/z (%): 246.9 $[M+H]^+$, 514.8 $[2M+Na]^+$.

7.3.2. ethyl 5-methyl-2-oxo-1-(p-tolyl)-2,3-dihydro-1*H*-imidazole-4-carboxylate (24b)

White solid, yield: 71.0%; M.p.:211–212 °C. MS (ESI) m/z (%): 261.1 $[M+H]^+$, 521.2 $[2M+H]^+$.

7.3.3. ethyl 1-(4-methoxyphenyl)-5-methyl-2-oxo-2,3-dihydro-1*H*-imidazole-4-carboxylate (24c)

White solid, yield: 73.8%; M.p.:201–203 °C. MS (ESI) m/z (%): 277.2 $[M+H]^+$, 575.4 $[2M+Na]^+$.

7.3.4. ethyl 1-(4-fluorophenyl)-5-methyl-2-oxo-2,3-dihydro-1*H*-imidazole-4-carboxylate (24d)

White solid, yield: 78.6%; M.p.:202–204 °C. MS (ESI) m/z (%): 264.8 $[M+H]^+$, 550.6 $[2M+Na]^+$.

7.3.5. ethyl 1-(4-chlorophenyl)-5-methyl-2-oxo-2,3-dihydro-1*H*-imidazole-4-carboxylate (24e)

White solid, yield: 81.8%; M.p.:219–220 °C. MS (ESI) m/z (%): 281.0 $[M+H]^+$, 560.9 $[2M+H]^+$.

7.3.6. ethyl 1-(4-bromophenyl)-5-methyl-2-oxo-2,3-dihydro-1*H*-imidazole-4-carboxylate (24f)

White solid, yield: 75.2%; M.p.:232–233 °C. MS (ESI) m/z (%): 324.9 $[M+H]^+$, 672.9 $[2M+Na]^+$.

7.3.7. ethyl 1-(3,4-difluorophenyl)-5-methyl-2-oxo-2,3-dihydro-1*H*-imidazole-4-carboxylate (24g)

White solid, yield: 83.2%; M.p.:213–215 °C. MS (ESI) m/z (%): 304.9 $[M+Na]^+$, 586.4 $[2M+Na]^+$.

7.3.8. ethyl 1-(3-chloro-4-fluorophenyl)-5-methyl-2-oxo-2,3-dihydro-1*H*-imidazole-4-carboxylate (24h)

White solid, yield: 72.4%; M.p.:217–219 °C. MS (ESI) m/z (%): 299.0 $[M+H]^+$, 597.2 $[2M+H]^+$.

7.3.9. ethyl 5-methyl-2-oxo-1-(4-(trifluoromethoxy)phenyl)-2,3-dihydro-1*H*-imidazole-4-carboxylate(24i)

White solid, yield: 84.3%; M.p.:146–147 °C. MS (ESI) m/z (%): 331.0 $[M+H]^+$, 683.0 $[2M+Na]^+$.

7.3.10. ethyl 5-methyl-2-oxo-1-(4-(trifluoromethyl)phenyl)-2,3-dihydro-1*H*-imidazole-4-carboxylate (24j)

White solid, yield: 81.7%; M.p.:170–173 °C. MS (ESI) m/z (%): 337.1 $[M+Na]^+$, 651.2 $[2M+Na]^+$.

7.3.11. ethyl 5-methyl-2-oxo-1-(3-(trifluoromethyl)phenyl)-2,3-dihydro-1*H*-imidazole-4-carboxylate (24k)

White solid, yield: 79.5%; M.p.:158–161 °C. MS (ESI) m/z (%): 314.2 $[M+H]^+$, 626.7 $[2M+H]^+$.

7.3.12. ethyl 5-methyl-2-oxo-1-(2-(trifluoromethyl)phenyl)-2,3-dihydro-1H-imidazole-4-carboxylate (24l)

White solid, yield: 78.9%; M.p.:196–198 °C. MS (ESI) m/z (%): 336.9 $[M+Na]^+$, 628.8 $[2M+H]^+$.

7.3.13. ethyl 1-(2-chlorophenyl)-5-methyl-2-oxo-2,3-dihydro-1*H*-imidazole-4-carboxylate (24m)

White solid, yield: 74.9%; M.p.:205–207 °C. MS (ESI) m/z (%): 280.9 $[M+H]^+$.

7.4. General procedure for the synthesis of *N*-methyl-2-imidazolones (25a–m)

To a vigorously stirred mixture of 2-imidazolones **24** (3 mmol) and K_2CO_3 (828 mg, 6 mmol) in DMF (10 mL) was added methyl iodide (6 mmol) at room temperature, and the resulting suspension was stirred for 3 h. After completion of the reaction, the mixture was poured into ice-water, the precipitate was filtered and dried under vacuum to obtain the compound as a white solid.

7.4.1. ethyl 3,5-dimethyl-2-oxo-1-phenyl-2,3-dihydro-1*H*-imidazole-4-carboxylate (25a)

White solid, yield: 89.5%; M.p.:89–92 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 – 7.38 (m, 3H), 7.32 – 7.21 (m, 2H), 4.32 (q, *J* = 7.0 Hz, 2H), 3.54 (s, 3H), 2.26 (s, 3H), 1.34 (t, *J* = 7.0 Hz, 3H). MS (ESI) m/z (%): 261.1 $[M+H]^+$.

7.4.2. ethyl 3,5-dimethyl-2-oxo-1-(p-tolyl)-2,3-dihydro-1*H*-imidazole-4-carboxylate (25b)

White solid, yield: 88.1%; M.p.:112–113 °C. MS (ESI) m/z (%): 313.3 $[M+K]^+$.

7.4.3. ethyl 1-(4-methoxyphenyl)-3,5-dimethyl-2-oxo-2,3-dihydro-1*H*-imidazole-4-carboxylate (25c)

White solid, yield: 86.3%; M.p.:108–109 °C. MS (ESI) m/z (%): 290.9 $[M+H]^+$, 602.8 $[2M+Na]^+$.

7.4.4. ethyl 1-(4-fluorophenyl)-3,5-dimethyl-2-oxo-2,3-dihydro-1*H*-imidazole-4-carboxylate (25d)

White solid, yield: 92.4%; M.p.:162–163 °C. MS (ESI) m/z (%): 300.9 $[M+Na]^+$.

7.4.5. ethyl 1-(4-chlorophenyl)-3,5-dimethyl-2-oxo-2,3-dihydro-1*H*-imidazole-4-carboxylate (25e)

White solid, yield: 88.8%; M.p.:116–117 °C. MS (ESI) m/z (%): 295.1 $[M+H]^+$.

7.4.6. ethyl 1-(4-bromophenyl)-3,5-dimethyl-2-oxo-2,3-dihydro-1*H*-imidazole-4-carboxylate (25f)

White solid, yield: 90.3%; M.p.:119–122 °C. MS (ESI) m/z (%): 377.1 $[M+K]^+$.

7.4.7. ethyl 1-(3,4-difluorophenyl)-3,5-dimethyl-2-oxo-2,3-dihydro-1*H*-imidazole-4-carboxylate (25g)

White solid, yield: 93.0%; M.p.:111–112 °C. MS (ESI) m/z (%): 297.1 $[M+H]^+$, 318.4 $[M+Na]^+$.

7.4.8. ethyl 1-(3-chloro-4-fluorophenyl)-3,5-dimethyl-2-oxo-2,3-dihydro-1*H*-imidazole-4-carboxylate (25h)

White solid, yield: 90.7%; M.p.:114–116 °C. MS (ESI) m/z (%): 312.6 $[M+H]^+$, 645.6 $[2M+H]^+$.

7.4.9. ethyl 3,5-dimethyl-2-oxo-1-(4-(trifluoromethoxy)phenyl)-2,3-dihydro-1*H*-imidazole-4-carboxylate (25i)

White solid, yield: 91.7%; M.p.:86–88 °C. MS (ESI) m/z (%): 383.1 $[M+K]^+$.

7.4.10. ethyl 3,5-dimethyl-2-oxo-1-(4-(trifluoromethyl)phenyl)-2,3-dihydro-1*H*-imidazole-4-carboxylate (25j)

White solid, yield: 86.6%; M.p.:93–95 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.4 Hz, 2H), 7.56 (d, *J* = 8.3 Hz, 2H), 4.30 (q, *J* = 7.0 Hz, 2H), 3.52 (s, 3H), 2.24 (s, 3H), 1.30 (t, *J* = 7.0 Hz, 3H). MS (ESI) m/z (%): 351.1 $[M+Na]^+$.

7.4.11. ethyl 3,5-dimethyl-2-oxo-1-(3-(trifluoromethyl)phenyl)-2,3-dihydro-1*H*-imidazole-4-carboxylate (25k)

White solid, yield: 89.2%; M.p.:88–89 °C. MS (ESI) m/z (%): 328.9 $[M+H]^+$.

7.4.12. ethyl 3,5-dimethyl-2-oxo-1-(2-(trifluoromethyl)phenyl)-2,3-dihydro-1*H*-imidazole-4-carboxylate (25l)

White solid, yield: 85.1%; M.p.:103–105 °C. MS (ESI) m/z (%): 329.1 $[M+H]^+$.

7.4.13. ethyl 1-(2-chlorophenyl)-3,5-dimethyl-2-oxo-2,3-dihydro-1*H*-imidazole-4-carboxylate (25m)

White solid, yield: 81.5%; M.p.:102–103 °C. MS (ESI) m/z (%): 294.8 $[M+H]^+$.

7.5. General procedure for the synthesis of 2-imidazolone acid (26a–n)

To a stirred mixture of 2-imidazolone ester (1 mmol) in dioxane/EtOH (9 mL, 7:2) is added 5 eq of NaOH in 1 mL water at room temperature, and the resulting suspension was stirred for 10 h at 40 °C. After removal of solvent under reduced pressure, the residue was dissolved in water, acidified with glacial acetic acid to provide the 2-imidazolone acid as a white solid.

7.5.1. 3,5-dimethyl-2-oxo-1-phenyl-2,3-dihydro-*1H*-imidazole-4-carboxylic acid (26a)

White solid, yield: 80.5%; M.p.:182–185 °C. MS (ESI) m/z (%): 232.9 $[M+H]^+$.

7.5.2. 3,5-dimethyl-2-oxo-1-(p-tolyl)-2,3-dihydro-*1H*-imidazole-4-carboxylic acid (26b)

White solid, yield: 74.0%; M.p.:212–215 °C. MS (ESI) m/z (%): 246.9 $[M+H]^+$.

7.5.3. 1-(4-methoxyphenyl)-3,5-dimethyl-2-oxo-2,3-dihydro-*1H*-imidazole-4-carboxylic acid (26c)

White solid, yield: 72.5%; M.p.:197–199 °C. MS (ESI) m/z (%): 262.9 $[M+H]^+$.

7.5.4. 1-(4-fluorophenyl)-3,5-dimethyl-2-oxo-2,3-dihydro-*1H*-imidazole-4-carboxylic acid (26d)

White solid, yield: 79.7%; M.p.:219–223 °C. MS (ESI) m/z (%): 250.9 $[M+H]^+$.

7.5.5. 1-(4-chlorophenyl)-3,5-dimethyl-2-oxo-2,3-dihydro-*1H*-imidazole-4-carboxylic acid (26e)

White solid, yield: 76.6%; M.p.:224–225 °C. MS (ESI) m/z (%): 266.9 $[M+H]^+$.

7.5.6. 1-(4-bromophenyl)-3,5-dimethyl-2-oxo-2,3-dihydro-*1H*-imidazole-4-carboxylic acid (26f)

White solid, yield: 72.9%; M.p.:225–227 °C. MS (ESI) m/z (%): 310.9 $[M+H]^+$.

7.5.7. 1-(3,4-difluorophenyl)-3,5-dimethyl-2-oxo-2,3-dihydro-*1H*-imidazole-4-carboxylic acid (26g)

White solid, yield: 82.5%; M.p.:191–193 °C. MS (ESI) m/z (%): 268.9 $[M+H]^+$.

7.5.8. 1-(3-chloro-4-fluorophenyl)-3,5-dimethyl-2-oxo-2,3-dihydro-*1H*-imidazole-4-carboxylic acid (26h)

White solid, yield: 76.9%; M.p.:196–198 °C. MS (ESI) m/z (%): 285.0 $[M+H]^+$.

7.5.9. 3,5-dimethyl-2-oxo-1-(4-(trifluoromethoxy)phenyl)-2,3-dihydro-*1H*-imidazole-4-carboxylic acid (26i)

White solid, yield: 78.8%; M.p.:190–192 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.80 (d, J = 8.1 Hz, 2H), 7.56 (d, J = 8.4 Hz, 2H), 3.40 (s, 3H), 2.21 (s, 3H). MS (ESI) m/z (%): 317.0 $[M+H]^+$.

7.5.10. 3,5-dimethyl-2-oxo-1-(4-(trifluoromethyl)phenyl)-2,3-dihydro-*1H*-imidazole-4-carboxylic acid (26j)

White solid, yield: 83.5%; M.p.:187–188 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.84 (d, J = 8.4 Hz, 2H), 7.58 (d, J = 8.4 Hz, 2H), 3.41 (s, 3H), 2.25 (s, 3H). MS (ESI) m/z (%): 322.8 $[M+Na]^+$.

7.5.11. 3,5-dimethyl-2-oxo-1-(3-(trifluoromethyl)phenyl)-2,3-dihydro-*1H*-imidazole-4-carboxylic acid (26k)

White solid, yield: 77.1%; M.p.:157–158 °C. MS (ESI) m/z (%): 300.8 $[M+H]^+$, 323.0 $[M+Na]^+$.

7.5.12. 3,5-dimethyl-2-oxo-1-(2-(trifluoromethyl)phenyl)-2,3-dihydro-*1H*-imidazole-4-carboxylic acid (26l)

White solid, yield: 78.9%; M.p.:195–197 °C. MS (ESI) m/z (%): 300.9 $[M+H]^+$.

7.5.13. 1-(2-chlorophenyl)-3,5-dimethyl-2-oxo-2,3-dihydro-*1H*-imidazole-4-carboxylic acid (26m)

White solid, yield: 74.5%; M.p.:231–132 °C. MS (ESI) m/z (%): 301.0 $[M+H]^+$.

7.5.14. 1-(2-chlorophenyl)-5-methyl-2-oxo-2,3-dihydro-*1H*-imidazole-4-carboxylic acid (26n)

To a vigorously stirred suspension of *tert*-butyl 2-diazo-3-oxobutanoate **1** (14 mmol) and finely powdered urea **23m** (408 mg, 18 mmol) in toluene-1,2-dichloroethane (1:1, 140 mL) was heated to 80 °C and a suspension of Rh_2Oct_4 (217 mg, 0.28 mmol) in toluene (28 mL) was added over 60 min. The mixture was then stirred for an additional 30 min. After cooling to room temperature, TFA (16.8 mL) was added dropwisely, the solution was then stirred for 3 h, after removal of solvent under reduced pressure, the residue was dissolved in 150 mL CH_2Cl_2, washed with 6N HCl (3 × 30 mL), and then brine before being dried. The organic layer was concentrated, triturated with ether to obtain the imidazolone-4-carboxylic acid **26n** as a white solid. Yield: 88.2%; M.p.:207–209 °C. MS (ESI) m/z (%): 252.9 $[M+H]^+$.

7.6. General procedure for Preparation of the target Compounds (28–58)

A mixture of the corresponding acid **26a-n** (0.486 mmol), toluene (5 mL), and $SOCl_2$ (2.5 mL) was heated at reflux for 5 h. Upon cooling to room temperature, the solvent was evaporated in vacuum. The residue was redissolved in dried CH_2Cl_2 (5 mL) and drop-wise added to a mixture of the corresponding aniline **22a-e** (0.243 mmol), Na_2CO_3 (0.486 mmol) and CH_2Cl_2 (5 mL) in an ice bath, which was then removed to raise the temperature to room temperature and stirred overnight. The resulting mixture was sequentially washed with 20% K_2CO_3 (10 mL × 2) and then brine (20 mL × 2), 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 to afford **28-58** as white solids.

7.6.1. N-(3-fluoro-4-((6-methoxy-7-(3-morpholinopropoxy)quinolin-4-yl)oxy)phenyl)-3,5-dimethyl-2-oxo-1-phenyl-2,3-dihydro-1*H*-imidazole-4-carboxamide (28)

Yield: 74.4%; M.p.:151–153 °C; IR (KBr) cm^{-1}: 3427.7, 2955.1, 2853.7, 1698.0, 1668.3, 1597.3, 1507.2, 1480.6, 1431.3, 1350.2, 1305.5, 1251.2, 1211.3, 1155.3, 1143.2, 1012.2, 854.9; ^{1}H NMR (600 MHz, DMSO-d_6) δ

10.86 (s, 1H), 8.47 (d, *J* = 5.2 Hz, 1H), 7.98 (dd, *J* = 13.0, 2.3 Hz, 1H), 7.66 (dd, *J* = 8.8 Hz,1.2 Hz, 1H), 7.56 (t, *J* = 7.7 Hz, 2H), 7.54 (s, 1H), 7.50 – 7.44 (m, 2H), 7.41 (s, 1H), 7.38 – 7.34 (m, 2H), 6.46 (d, *J* = 5.2 Hz, 1H), 4.21 (t, *J* = 6.4 Hz, 2H), 3.96 (s, 3H), 3.59 (t, *J* = 4.4 Hz, 3H), 3.36 (s, 3H), 2.47 (t, *J* = 7.1 Hz, 3H), 2.44 – 2.34 (m, 4H), 2.14 (s, 3H), 2.02 – 1.94 (m, 2H). MS (ESI) m/z (%): 663.8 $[M+Na]^+$; Anal. calcd. for $C_{35}H_{36}FN_5O_6$ (%): C, 65.51; H, 5.65; N, 10.91; Found (%): C, 65.54; H, 5.69; N, 10. 96.

7.6.2. N-(3-fluoro-4-((6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl)-3,5-dimethyl-2-oxo-1-phenyl-2,3-dihydro-1*H*-imidazole-4-carboxamide (29)

Yield: 67.6%; M.p.:120–121 °C; IR (KBr) cm^{-1}: 3425.0, 2929.8, 2795.5, 1690.1, 1669.1, 1597.4, 1506.8, 1480.0, 1431.3, 1349.5, 1305.5, 1249.8, 1210.9, 1166.5, 1138.1, 971.4, 853.2; ^1H NMR (600 MHz, $CDCl_3$) δ 8.48 (d, *J* = 5.2 Hz, 1H), 8.14 (s, 1H), 7.72 (dd, *J* = 11.6, 1.6 Hz, 1H), 7.57 (s, 1H), 7.49 (t, *J* = 7.6 Hz, 2H), 7.44 (t, *J* = 7.4 Hz, 2H), 7.30 (dd, *J* = 9.0, 2.1 Hz, 1H), 7.28 – 7.23 (m, 2H), 7.24 – 7.19 (t, *J* = 8.6 Hz, 1H), 6.39 (d, *J* = 5.1 Hz, 1H), 4.27 (t, *J* = 6.6 Hz, 2H), 4.05 (s, 3H), 3.51 (s, 3H), 2.69 (t, *J* = 7.3 Hz, 2H), 2.59 – 2.51 (m, 4H), 2.25 (s, 3H), 2.21 – 2.13 (m, 2H), 1.84 – 1.76 (m, 4H). MS (ESI) m/z (%): 626.1 $[M+H]^+$; Anal. calcd. for $C_{35}H_{36}FN_5O_5$ (%): C, 67.19; H, 5.80; N, 11.19; Found (%): C, 67.24; H, 5.89; N, 11. 23.

7.6.3. N-(3-fluoro-4-((6-methoxy-7-(3-(piperidin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl)-3,5-dimethyl-2-oxo-1-phenyl-2,3-dihydro-1*H*-imidazole-4-carboxamide (30)

Yield: 64.9%; M.p.:126–128 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 10.66 (s, 1H), 8.48 (d, *J* = 5.3 Hz, 1H), 7.95 (dd, *J* = 12.3, 2.3 Hz, 1H), 7.66 – 7.56 (m, 2H), 7.55 (s, 1H), 7.53 – 7.43 (m, 3H), 7.42 (s, 1H), 7.40 – 7.29 (m, 2H), 6.47 (d, *J* = 5.2 Hz, 1H), 4.21 (t, *J* = 6.7 Hz, 2H), 3.97 (s, 3H), 3.33 (s, 3H), 2.79 – 2.55 (m, 6H), 2.14 (s, 3H), 2.13 – 2.02 (m, 2H), 1.63 – 1.53 (m, 4H), 1.44 (m, 2H). MS (ESI) m/z (%): 640.0 $[M+H]^+$; Anal. calcd. for $C_{36}H_{38}FN_5O_5$ (%): C, 67.59; H, 5.99; N, 10.95; Found (%): C, 67.64; H, 6.09; N, 10. 98.

7.6.4. N-(3-fluoro-4-((6-methoxy-7-(3-(4-methylpiperidin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl)-3,5-dimethyl-2-oxo-1-phenyl-2,3-dihydro-1*H*-imidazole-4-carboxamide (31)

Yield: 73.6%; M.p.:113–114 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.50 (s, 1H), 8.48 (d, *J* = 5.3 Hz, 1H), 7.71 (dd, *J* = 11.9, 2.4 Hz, 1H), 7.57 (s, 1H), 7.47 (t, *J* = 7.4 Hz, 2H), 7.44 – 7.38 (m, 2H), 7.32 (dd, *J* = 8.6, 1.2 Hz, 1H), 7.25 – 7.22 (m, 2H), 7.19 (t, *J* = 8.7 Hz, 1H), 6.39 (d, *J* = 5.2 Hz, 1H), 4.24 (t, *J* = 6.6 Hz, 2H), 4.04 (s, 3H), 3.49 (s, 3H), 2.94 (d, *J* = 10.9 Hz, 2H), 2.57 (t, *J* = 7.3 Hz, 2H), 2.23 (s, 3H), 2.20 – 2.09 (m, 2H), 1.98 (t, *J* = 10.7 Hz, 2H), 1.63 (d, *J* = 12.2 Hz, 2H), 1.42 – 1.32 (m, 1H), 1.32 – 1.22 (m, 2H), 0.93 (d, *J* = 6.3 Hz, 3H). MS (ESI) m/z (%): 653.9$[M+H]^+$; Anal. calcd. for $C_{37}H_{40}FN_5O_5$ (%): C, 67.98; H, 6.17; N, 10.71; Found (%): C, 67.99; H, 6.02; N, 10. 99.

7.6.5. N-(3-fluoro-4-((6-methoxy-7-(3-(4-methylpiperazin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl)-3,5-dimethyl-2-oxo-1-phenyl-2,3-dihydro-1*H*-imidazole-4-carboxamide (32)

Yield: 71.2%; M.p.:115–118 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.50 (d, *J* = 5.3 Hz, 1H), 7.91 (s, 1H), 7.74 (dd, *J* = 11.8, 2.3 Hz, 1H), 7.58 (s, 1H), 7.55 – 7.48 (m, *J* = 7.5 Hz, 3H), 7.47 – 7.41 (m, 1H), 7.32 – 7.28 (m, 3H), 7.26 – 7.21 (m, 1H), 6.41 (d, *J* = 5.3 Hz, 1H), 4.27 (t, *J* = 6.7 Hz, 2H), 4.05 (s, 3H), 3.52 (s, 3H), 2.70 – 2.35 (m, 10H), 2.31 (s, 3H), 2.27 (s, 3H), 2.20 – 2.10 (m, 2H). ^{13}C NMR (101 MHz, DMSO) δ 159.77, 159.03, 155.13, 152.69, 152.41, 152.35, 150.04, 149.32, 146.84, 138.34, 136.30, 136.18, 134.66, 129.85 (2C), 128.81, 128.31 (2C), 124.65, 124.25, 116.97, 116.41, 114.88, 108.89, 102.46, 99.46, 67.20, 56.26, 55.26 (2C), 54.83, 53.22 (2C), 46.24, 29.37, 26.52. MS (ESI) m/z (%): 654.8 $[M+H]^+$; Anal. calcd. for $C_{36}H_{39}FN_6O_5$ (%): C, 66.04; H, 6.00; N, 12.84; Found (%): C, 66.19; H, 6.06; N, 12. 79.

7.6.6. N-(3-fluoro-4-((6-methoxy-7-(3-(4-methylpiperidin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl)-3,5-dimethyl-2-oxo-1-(p-tolyl)-2,3-dihydro-1*H*-imidazole-4-carboxamide (33)

Yield: 65.8%; M.p.:131–132 °C; ^1H NMR (600 MHz, $CDCl_3$) δ 8.48 (d, *J* = 5.3 Hz, 1H), 8.07 (s, 1H), 7.69 (dd, *J* = 11.8, 2.4 Hz, 1H), 7.57 (s, 1H), 7.43 (d, *J* = 7.1 Hz, 1H), 7.30 – 7.27 (m, 3H), 7.21 (t, *J* = 8.6 Hz, 1H), 7.13

(d, *J* = 8.2 Hz, 2H), 6.39 (d, *J* = 5.1 Hz, 1H), 4.25 (t, *J* = 6.7 Hz, 2H), 4.05 (s, 3H), 3.50 (s, 3H), 2.95 (d, *J* = 10.2 Hz, 2H), 2.58 (t, *J* = 7.2 Hz, 2H), 2.39 (s, 3H), 2.24 (s, 3H), 2.16 (dt, *J* = 13.8, 6.8 Hz, 2H), 2.02 – 1.96 (m, 2H), 1.63 (d, *J* = 12.7 Hz, 2H), 1.37 (s, 1H), 1.32 – 1.23 (m, 2H), 0.93 (d, *J* = 6.4 Hz, 3H). MS (ESI) m/z (%): 667.9 $[M+H]^+$; Anal. calcd. for $C_{38}H_{42}FN_5O_5$ (%): C, 68.35; H, 6.34; N, 10.49; Found (%): C, 68.28; H, 6.32; N, 10.51.

7.6.7. N-(3-fluoro-4-((6-methoxy-7-(3-(4-methylpiperazin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl)-3,5-dimethyl-2-oxo-1-(p-tolyl)-2,3-dihydro-1*H*-imidazole-4-carboxamide (34)

Yield: 66.2%; M.p.:114–116 °C; IR (KBr) cm^{-1}: 3419.0, 3250.6, 2935.3, 2796.7, 1694.1, 1620.6, 1580.0, 1511.2, 1479.5, 1431.1, 1348.5, 1249.6, 1210.1, 1164.0, 1096.4, 1011.4, 840.7; ^1H NMR (400 MHz, $CDCl_3$) δ 8.49 (d, *J* = 5.1 Hz, 1H), 8.22 (s, 1H), 7.68 (dd, *J* = 12.0, 2.1 Hz, 1H), 7.58 (s, 1H), 7.44 (s, 1H), 7.36 – 7.27 (m, 3H), 7.22 (t, *J* = 8.0 Hz, 1H), 7.13 (d, *J* = 5.5 Hz, 2H), 6.40 (d, *J* = 5.1 Hz, 1H), 4.27 (t, *J* = 6.5 Hz, 2H), 4.06 (s, 3H), 3.50 (s, 3H), 2.86 – 2.42 (m, 10H), 2.39 (s, 3H), 2.31 (s, 3H), 2.25 (s, 3H), 2.20 – 2.05 (m, 2H). MS (ESI) m/z (%): 668.9 $[M+H]^+$; Anal. calcd. for $C_{37}H_{41}FN_6O_5$ (%): C, 66.45; H, 6.18; N, 12.57; Found (%): C, 66.28; H, 6.32; N, 12.51.

7.6.8. N-(3-fluoro-4-((6-methoxy-7-(3-(4-methylpiperidin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl)-1-(4-methoxyphenyl)-3,5-dimethyl-2-oxo-2,3-dihydro-1*H*-imidazole-4-carboxamide (35)

Yield: 67.3%; M.p.:121–124 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.49 (d, *J* = 5.2 Hz, 1H), 8.10 (s, 1H), 7.70 (dd, *J* = 12.0, 2.2 Hz, 1H), 7.58 (s, 1H), 7.44 (s, 1H), 7.30 (m, 1H), 7.23 (m, 1H), 7.17 (d, *J* = 8.1 Hz, 2H), 6.99 (d, *J* = 7.9 Hz, 2H), 6.40 (d, *J* = 5.2 Hz, 1H), 4.26 (t, *J* = 6.7 Hz, 2H), 4.06 (s, 3H), 3.83 (s, 3H), 3.51 (s, 3H), 2.93 (d, *J* = 9.9 Hz, 2H), 2.60 – 2.45 (m, 2H), 2.25 (s, 3H), 2.22 – 2.08 (m, 2H), 1.96 (t, *J* = 10.9 Hz, 2H), 1.64 (d, *J* = 12.1 Hz, 2H), 1.32 – 1.18 (m, 1H), 1.27 (t, *J* = 11.1 Hz, 2H), 0.94 (d, *J* = 4.7 Hz, 3H). MS (ESI) m/z (%): 683.9 $[M+H]^+$; Anal. calcd. for $C_{38}H_{42}FN_5O_6$ (%): C, 66.75; H, 6.19; N, 10.24; Found (%): C, 66.78; H, 6.22; N, 10.31.

7.6.9. N-(3-fluoro-4-((6-methoxy-7-(3-(4-methylpiperazin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl)-1-(4-methoxyphenyl)-3,5-dimethyl-2-oxo-2,3-dihydro-1H-imidazole-4-carboxamide (36)

Yield: 65.8%; M.p.:131–133 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 10.69 (s, 1H), 8.47 (s, *J* = 5.3 Hz, 1H), 7.96 (dd, *J* = 12.9, 2.1 Hz, 1H), 7.69 – 7.59 (m, 1H), 7.54 (s, 1H), 7.46 (t, *J* = 7.8 Hz 1H), 7.39 (s, 1H), 7.27 (d, *J* = 6.7 Hz, 2H), 7.09 (d, *J* = 6.5 Hz, 2H), 6.46 (d, *J* = 5.2 Hz, 1H), 4.19 (t, *J* = 6.5 Hz, 2H), 3.96 (s, 3H), 3.82 (s, 3H), 3.37 (s, 3H), 2.48 – 2.23 (m, 10H), 2.15 (s, 3H), 2.11 (s, 3H), 2.04 – 1.85 (m, 2H). MS (ESI) m/z (%): 684.8 $[M+H]^+$; Anal. calcd. for $C_{37}H_{41}FN_6O_6$ (%): C, 64.90; H, 6.04; N, 12.27; Found (%): C, 64.88; H, 6.02; N, 12.34.

7.6.10. N-(3-fluoro-4-((6-methoxy-7-(3-(4-methylpiperidin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl)-1-(4-fluorophenyl)-3,5-dimethyl-2-oxo-2,3-dihydro-1*H*-imidazole-4-carboxamide (37)

Yield: 62.9%; M.p.:101–103 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.47 (d, *J* = 5.3 Hz, 1H), 8.44 (s, 1H), 7.72 (dd, *J* = 11.9, 2.4 Hz, 1H), 7.57 (s, 1H), 7.41 (s, 1H), 7.34 (d, *J* = 7.7 Hz, 1H), 7.22 (d, *J* = 8.1 Hz, 2H), 7.20 (t, *J* = 2.5 Hz, 1H), 7.17 (d, *J* = 8.0 Hz, 2H), 6.39 (d, *J* = 5.2 Hz, 1H), 4.24 (t, *J* = 6.6 Hz, 2H), 4.04 (s, 3H), 3.48 (s, 3H), 2.95 (d, *J* = 11.0 Hz, 2H), 2.58 (t, *J* = 7.2 Hz, 2H), 2.21 (s, 3H), 2.19 – 2.10 (m, 2H), 1.99 (t, *J* = 10.7 Hz, 2H), 1.63 (d, *J* = 11.3 Hz, 2H), 1.44 – 1.34 (m, 1H), 1.32 – 1.28 (m, 2H), 0.92 (d, *J* = 6.2 Hz, 3H). MS (ESI) m/z (%): 671.9 $[M+H]^+$; Anal. calcd. for $C_{37}H_{39}F_2N_5O_5$ (%): C, 66.16; H, 5.85; N, 10.43; Found (%): C, 66.29; H, 5.66; N, 10.69.

7.6.11. N-(3-fluoro-4-((6-methoxy-7-(3-(4-methylpiperazin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl)-1-(4-fluorophenyl)-3,5-dimethyl-2-oxo-2,3-dihydro-1*H*-imidazole-4-carboxamide (38)

Yield: 69.1%; M.p.:108–110 °C; IR (KBr) cm^{-1}: 3421.7, 3251.7, 2935.3, 2879.4, 2796.3, 1694.2, 1620.6, 1580.0, 1511.3, 1479.5, 1431.1, 1348.1, 1348.5, 1249.6, 1210.2, 1164.0, 1096.4, 1011.4，951.6，892.8，840.6; ^1H NMR (400 MHz, $CDCl_3$) δ 8.42 (d, *J* = 5.3 Hz, 1H), 7.99 (s, 1H), 7.67 (dd, *J* = 11.8, 2.3 Hz, 1H), 7.51 (s, 1H), 7.37 (s, 1H), 7.25 (dd, *J* = 8.8, 1.6 Hz, 1H), 7.20 – 7.16 (m, 3H), 7.13 (d, *J* = 8.1, 2H), 6.34 (d, *J* = 5.1 Hz, 1H), 4.20 (t, *J* = 6.7 Hz, 2H), 3.99 (s, 3H), 3.46 (s, 3H), 2.73 – 2.31 (m, 10H), 2.25 (s, 3H), 2.18 (s, 3H), 2.13 – 2.00 (m, 2H). MS (ESI) m/z (%): 672.9 $[M+H]^+$; Anal. calcd. for $C_{36}H_{38}F_2N_6O_5$ (%): C, 64.27; H, 5.69; N, 12.49; Found (%): C,

64.36; H, 5.66; N, 12.35.

7.6.12. 1-(4-chlorophenyl)-N-(3-fluoro-4-((6-methoxy-7-(3-(4-methylpiperidin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl)-3,5-dimethyl-2-oxo-2,3-dihydro-1*H*-imidazole-4-carboxamide (39)

Yield: 69.2%; M.p.:115–117 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (d, *J* = 5.3 Hz, 1H), 7.95 (s, 1H), 7.74 (dd, *J* = 11.8, 2.3 Hz, 1H), 7.57 (s, 1H), 7.47 (d, *J* = 8.6 Hz, 2H), 7.43 (s, 1H), 7.30 (dd, *J* = 9.0, 2.1 Hz, 1H), 7.25 (t, *J* = 8.4 Hz, 1H), 7.21 (d, *J* = 8.6 Hz, 1H), 7.23 – 7.20 (m, 1H), 6.41 (d, *J* = 5.2 Hz, 1H), 4.25 (t, *J* = 6.7 Hz, 2H), 4.05 (s, 3H), 3.50 (s, 3H), 2.92 (d, *J* = 11.4 Hz, 2H), 2.55 (t, *J* = 7.5 Hz, 2H), 2.25 (s, 3H), 2.19 – 2.10 (m, 2H), 1.96 (t, *J* = 10.9 Hz, 2H), 1.63 (d, *J* = 12.0 Hz, 2H), 1.40 – 1.33 (m, 1H), 1.30 – 1.21 (m, 2H), 0.93 (d, *J* = 6.3 Hz, 3H). MS (ESI) m/z (%): 687.8 $[M+H]^+$; Anal. calcd. for $C_{37}H_{39}ClFN_5O_5$ (%): C, 64.58; H, 5.71; N, 10.18; Found (%): C, 64.39; H, 5.66; N, 10.33.

7.6.13. 1-(4-chlorophenyl)-N-(3-fluoro-4-((6-methoxy-7-(3-(4-methylpiperazin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl)-3,5-dimethyl-2-oxo-2,3-dihydro-1*H*-imidazole-4-carboxamide (40)

Yield: 70.4%; M.p.:121–123 °C; IR (KBr) cm^{-1}: 3420.8, 2935.2, 2796.4, 1695.0, 1668.8, 1579.5, 1508.3, 1479.4, 1431.0, 1348.7, 1249.8, 1164.9, 1091.2, 1011.3, 833.4; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (d, *J* = 5.2 Hz, 1H), 7.86 (s, 1H), 7.75 (dd, *J* = 11.8, 2.2 Hz, 1H), 7.58 (s, 1H), 7.48 (d, *J* = 8.6 Hz, 2H), 7.44 (s, 1H), 7.30 (dd, *J* = 8.9, 2.2 Hz, 1H), 7.25 (d, *J* = 4.5 Hz, 1H), 7.23 (d, *J* = 8.6 Hz, 2H), 6.42 (d, *J* = 5.2 Hz, 1H), 4.27 (t, *J* = 6.6 Hz, 2H), 4.05 (s, 3H), 3.51 (s, 3H), 2.75 – 2.35 (m, 10H), 2.31 (s, 3H), 2.27 (s, 3H), 2.15 (dt, *J* = 13.7, 6.7 Hz, 2H). ^{13}C NMR (101 MHz, DMSO) δ159.76, 158.94, 152.69, 152.41, 152.19, 150.03, 149.31, 146.85, 138.35, 136.34, 136.17, 133.55, 133.28, 130.06 (2C), 129.87 (2C), 124.63, 124.00, 116.98, 116.63, 114.88, 108.96, 108.85, 99.45, 67.19, 56.25, 55.26 (2C), 54.83, 53.22 (2C), 46.23, 29.38, 26.53, 11.61. MS (ESI) m/z (%): 711.0 $[M+Na]^+$; Anal. calcd. for $C_{36}H_{38}ClFN_6O_5$ (%): C, 62.74; H, 5.56; N, 12.19; Found (%): C, 62.59; H, 5.46; N, 12.35.

7.6.14. 1-(4-bromophenyl)-N-(3-fluoro-4-((6-methoxy-7-(3-(4-methylpiperidin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl)-3,5-dimethyl-2-oxo-2,3-dihydro-1*H*-imidazole-4-carboxamide (41)

Yield: 71.5%; M.p.:131–132 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (d, *J* = 5.3 Hz, 1H), 7.81 (s, 1H), 7.74 (dd, *J* = 11.8, 2.1 Hz, 1H), 7.63 (d, *J* = 8.6 Hz, 2H), 7.57 (s, 1H), 7.43 (s, 1H), 7.31 – 7.27 (m, 1H), 7.26 – 7.22 (m, 1H), 7.16 (d, *J* = 8.6 Hz, 2H), 6.41 (d, *J* = 5.2 Hz, 1H), 4.25 (t, *J* = 6.7 Hz, 2H), 4.05 (s, 3H), 3.50 (s, 3H), 2.95 – 2.87 (m, 2H), 2.58 – 2.50 (m, 2H), 2.26 (s, 3H), 2.19 – 2.07 (m, 2H), 1.95 (t, *J* = 10.7 Hz, 2H), 1.63 (d, *J* = 12.2 Hz, 2H), 1.42 – 1.29 (m, 1H), 1.30 – 1.17 (m, 2H), 0.92 (d, *J* = 6.3 Hz, 3H). ^{13}C NMR (101 MHz, DMSO) δ159.79, 159.03, 152.68, 152.43, 152.15, 150.03, 149.30, 146.84, 136.22, 136.11, 133.99, 132.81 (2C), 130.35(2C), 124.58, 123.81, 121.72, 117.09, 116.80, 114.87, 108.94, 108.90, 102.43, 99.46, 67.29, 56.25, 55.21, 54.00 (2C), 34.52 (2C), 30.92, 29.41, 26.72, 22.33, 11.59. MS (ESI) m/z (%): 731.9 $[M+H]^+$; Anal. calcd. for $C_{37}H_{39}BrFN_5O_5$ (%):C, 60.66; H, 5.37; N, 9.56; Found (%): C, 60.69; H, 5.28; N, 9.63.

7.6.15. 1-(4-bromophenyl)-N-(3-fluoro-4-((6-methoxy-7-(3-(4-methylpiperazin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl)-3,5-dimethyl-2-oxo-2,3-dihydro-1*H*-imidazole-4-carboxamide (42)

Yield: 66.7%; M.p.:133–135 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (d, *J* = 5.2 Hz, 1H), 8.07 (s, 1H), 7.77 (dd, *J* = 11.9, 2.3 Hz, 1H), 7.62 (d, *J* = 8.6 Hz, 2H), 7.57 (s, 1H), 7.43 (s, 1H), 7.37 – 7.30 (m, 1H), 7.23 (t, *J* = 8.6 Hz, 1H), 7.15 (d, *J* = 8.6 Hz, 2H), 6.42 (d, *J* = 5.2 Hz, 1H), 4.26 (t, *J* = 6.5 Hz, 2H), 4.04 (s, 3H), 3.50 (s, 3H), 2.86 – 2.45 (m, 10H), 2.42 (s, 3H), 2.26 (s, 3H), 2.19 – 2.09 (m, 2H). MS (ESI) m/z (%): 734.7 $[M+H]^+$; Anal. calcd. for $C_{36}H_{38}BrFN_5O_5$ (%): C, 58.94; H, 5.22; N, 11.46; Found (%): C, 58.99; H, 5.28; N, 11.61.

7.6.16. 1-(3,4-difluorophenyl)-N-(3-fluoro-4-((6-methoxy-7-(3-morpholinopropoxy)quinolin-4-yl)oxy)phenyl)-3,5-dimethyl-2-oxo-2,3-dihydro-1*H*-imidazole-4-carboxamide (43)

Yield: 64.5%; M.p.:118–122 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.82 (s, 1H), 8.47 (d, *J* = 5.1 Hz, 1H), 7.96 (dd, *J* = 12.3, 2.5 Hz, 1H), 7.70 – 7.56 (m, 3H), 7.53 (s, 1H), 7.46 (t, *J* = 9.0 Hz, 1H), 7.40 (s, 1H), 7.27 (m, 1H), 6.46 (d, *J* = 5.0 Hz, 1H), 4.20 (t, *J* = 5.8 Hz, 2H), 3.96 (s, 3H), 3.59 (m, 4H), 3.34 (s, 3H), 2.47 (t, *J* = 7.0 Hz,

2H), 2.39 (m, 4H), 2.16 (s, 3H), 2.04 – 1.93 (m, 2H). MS (ESI) m/z (%): 678.0 $[M+H]^+$; Anal. calcd. for $C_{35}H_{34}F_3N_5O_6$ (%):C, 62.03; H, 5.06; N, 10.33; Found (%): C, 62.35; H, 5.08; N, 10.11.

7.6.17. 1-(3,4-difluorophenyl)-N-(3-fluoro-4-((6-methoxy-7-(3-(4-methylpiperidin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl)-3,5-dimethyl-2-oxo-2,3-dihydro-1*H*-imidazole-4-carboxamide (44)

Yield: 64.9%; M.p.:109–111 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.47 (d, *J* = 5.1 Hz, 1H), 7.94 (s, 1H), 7.75 (dd, *J* = 10.5, 2.1 Hz, 1H), 7.56 (s, 1H), 7.42 (s, 1H), 7.30 (t, *J* = 9.0 Hz, 2H), 7.25 (m, 1H), 7.17 – 7.08 (m, 1H), 7.03 (d, *J* = 8.1 Hz, 1H), 6.40 (d, *J* = 5.0 Hz, 1H), 4.24 (t, *J* = 6.5 Hz, 2H), 4.04 (s, 3H), 3.49 (s, 3H), 2.91 (d, *J* = 10.7 Hz, 2H), 2.54 (t, *J* = 7.2 Hz, 2H), 2.25 (s, 3H), 2.18 – 2.08 (m, 2H), 1.94 (t, *J* = 11.3 Hz, 2H), 1.62 (d, *J* = 12.1 Hz, 2H), 1.40 – 1.31 (m, 1H), 1.24 (d, *J* = 10.2 Hz, 2H), 0.92 (d, *J* = 6.3 Hz, 3H). MS (ESI) m/z (%): 690.0 $[M+H]^+$; Anal. calcd. for $C_{37}H_{38}F_3N_5O_5$ (%): C, 64.43; H, 5.55; N, 10.15; Found (%): C, 64.49; H, 5.45; N, 10.21.

7.6.18. 1-(3,4-difluorophenyl)-N-(3-fluoro-4-((6-methoxy-7-(3-(4-methylpiperazin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl)-3,5-dimethyl-2-oxo-2,3-dihydro-1*H*-imidazole-4-carboxamide (45)

Yield: 68.8%; M.p.:118–120 °C; IR (KBr) cm^{-1}: 3418.6, 2935.0, 2801.7, 2320.3, 1698.2, 1670.3, 1580.6, 1508.6, 1480.0, 1431.7, 1349.3, 1304.8, 1249.8, 1211.2, 1164.6, 1120.6, 1096.1，949.9, 853.6，779.7; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.45 (d, *J* = 5.0 Hz, 1H), 7.92 (s, 1H), 7.73 (dd, *J* = 11.8, 2.2 Hz, 1H), 7.54 (s, 1H), 7.43 (s, 1H), 7.29 (t, *J* = 9.0 Hz, 2H), 7.24 (m, 1H), 7.15 – 7.07 (m, 1H), 7.03 (d, *J* = 8.1 Hz, 1H), 6.41 (d, *J* = 5.1 Hz, 1H), 4.23 (t, *J* = 6.5 Hz, 2H), 4.02 (s, 3H), 3.49 (s, 3H), 2.78 – 2.35 (m, 10H), 2.38 (s, 3H), 2.26 (s, 3H), 2.19 – 2.08 (m, 2H). MS (ESI) m/z (%): 690.8 $[M+H]^+$; Anal. calcd. for $C_{36}H_{37}F_3N_6O_5$ (%): C, 62.60; H, 5.40; N, 12.17; Found (%): C, 62.49; H, 5.45; N, 12.21.

7.6.19. 1-(3-chloro-4-fluorophenyl)-N-(3-fluoro-4-((6-methoxy-7-(3-(4-methylpiperidin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl)-3,5-dimethyl-2-oxo-2,3-dihydro-1*H*-imidazole-4-carboxamide (46)

Yield: 65.9%; M.p.:117–119 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (d, *J* = 5.3 Hz, 1H), 7.78 (dd, *J* = 10.5, 2.0 Hz, 1H), 7.71 (s, 1H), 7.58 (s, 1H), 7.45 (s, 1H), 7.40 (dd, *J* = 6.5, 2.3 Hz, 1H), 7.34 – 7.28 (m, 2H), 7.26 – 7.24 (m, 1H), 7.23 – 7.17 (m, 1H), 6.42 (d, *J* = 5.2 Hz, 1H), 4.27 (t, *J* = 6.7 Hz, 2H), 4.07 (s, 3H), 3.53 (s, 3H), 2.94 (d, *J* = 11.2 Hz, 2H), 2.56 (t, *J* = 7.3 Hz, 2H), 2.29 (s, 3H), 2.22 – 2.10 (m, 2H), 1.97 (t, *J* = 10.8 Hz, 2H), 1.65 (d, *J* = 12.6 Hz, 2H), 1.43 – 1.31 (m, 1H), 1.30 – 1.19 (m, 2H), 0.94 (d, *J* = 6.3 Hz, 3H). MS (ESI) m/z (%): 705.8 $[M+H]^+$; Anal. calcd. for $C_{37}H_{38}ClF_2N_5O_5$ (%): C, 62.93; H, 5.42; N, 9.92; Found (%): C, 62.98; H, 5.35; N, 10.01.

7.6.20. 1-(3-chloro-4-fluorophenyl)-N-(3-fluoro-4-((6-methoxy-7-(3-(4-methylpiperazin-1-yl)propoxy)quinlin-4-yl)oxy)phenyl)-3,5-dimethyl-2-oxo-2,3-dihydro-1*H*-imidazole-4-carboxamide (47)

Yield: 66.4%; M.p.:131–133 °C; IR (KBr) cm^{-1}: 3422.0, 2936.3, 2879.6, 2797.7, 1698.2, 1669.8, 1620.2, 1504.5, 1479.4, 1431.1, 1348.6, 1283.2, 1250.0, 1210.7, 1164.4, 1122.1, 1097.8, 871.8; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (d, *J* = 5.3 Hz, 1H), 7.83 (s, 1H), 7.75 (dd, *J* = 11.8, 2.2 Hz, 1H), 7.57 (s, 1H), 7.43 (s, 1H), 7.36 (dd, *J* = 6.3, 2.5 Hz, 1H), 7.32 – 7.28 (m, 2H), 7.24 (d, *J* = 8.8 Hz, 1H), 7.20 – 7.14 (m, 1H), 6.41 (d, *J* = 4.8 Hz, 1H), 4.26 (t, *J* = 6.7 Hz, 2H), 4.05 (s, 3H), 3.51 (s, 3H), 2.70 – 2.31 (m, 10H), 2.30 (s, 3H), 2.27 (s, 3H), 2.19 – 2.08 (m, 2H). ^{13}C NMR (101 MHz, DMSO) δ 159.78, 158.99, 158.53, 156.07, 155.12, 152.68, 152.41, 152.23, 150.03, 149.31, 146.85, 131.72, 129.34, 124.59, 123.92, 120.61, 120.43, 118.11, 117.90, 117.11, 116.77, 114.88, 109.16, 108.96, 99.46, 67.19, 56.25, 55.26 (2C), 54.83, 53.22 (2C), 46.23, 29.45, 26.53, 11.51. MS (ESI) m/z (%): 707.0 $[M+H]^+$; Anal. calcd. for $C_{36}H_{37}ClF_2N_6O_5$ (%): C, 61.14; H, 5.27; N, 11.88; Found (%): C, 61.18; H, 5.32; N, 12.01.

7.6.21. N-(3-fluoro-4-((6-methoxy-7-(3-(4-methylpiperidin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl)-3,5-dimethyl-2-oxo-1-(4-(trifluoromethoxy)phenyl)-2,3-dihydro-1*H*-imidazole-4-carboxamide (48)

Yield: 72.8%; M.p.:134–135 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (d, *J* = 5.1 Hz, 1H), 7.77 (dd, *J* = 11.4, 2.1 Hz, 1H), 7.62 (s, 1H), 7.57 (s, 1H), 7.43 (s, 1H), 7.40 – 7.31 (m, 4H), 7.29 (dd, *J* = 8.7, 2.1 Hz, 1H), 7.26(m, 1H), 6.41 (d, *J* = 5.2 Hz, 1H), δ 4.25 (t, *J* = 6.8 Hz, 2H), 4.05 (s, 3H), 3.53 (s, 3H), 3.03 (d, *J* = 9.8 Hz, 2H), 2.75 – 2.61 (m, 2H), 2.29 (s, 3H), 2.26 – 2.15 (m, 2H), 2.12 – 1.98 (m, 2H), 1.65 (d, *J* = 11.2 Hz 2H), 1.48 – 1.29 (m, 3H),

0.92 (d, *J* = 5.3 Hz, 3H). MS (ESI) m/z (%): 637.8 $[M+H]^+$; Anal. calcd. for $C_{38}H_{39}F_4N_5O_6$ (%): C, 61.87; H, 5.33; N, 9.49; Found (%): C, 61.92; H, 5.27; N, 9.42.

7.6.22. N-(3-fluoro-4-((6-methoxy-7-(3-(4-methylpiperazin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl)-3,5-dimethyl-2-oxo-1-(4-(trifluoromethoxy)phenyl)-2,3-dihydro-1*H*-imidazole-4-carboxamide (49)

Yield: 74.2%; M.p.:138–140 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.48 (d, *J* = 5.2 Hz, 1H), 7.75 (dd, *J* = 11.7, 2.2 Hz, 1H), 7.65 (s, 1H), 7.57 (s, 1H), 7.43 (s, 1H), 7.38 – 7.32 (m, 4H), 7.29 (dd, *J* = 8.8, 2.2 Hz, 1H), 7.24 (m, 1H), 6.40 (d, *J* = 5.1 Hz, 1H), 4.26 (t, *J* = 6.7 Hz, 2H), 4.05 (s, 3H), 3.52 (s, 3H), 2.84 – 2.36 (m, 10H), 2.29 (s, 3H), 2.28 (s, 3H), 2.17 – 2.10 (m, 2H). MS (ESI) m/z (%): 738.8 $[M+H]^+$; Anal. calcd. for $C_{37}H_{38}F_4N_6O_6$ (%): C, 60.16; H, 5.19; N, 11.38; Found (%): C, 60.22; H, 5.27; N, 9.42.

7.6.23. N-(3-fluoro-4-((6-methoxy-7-(3-(4-methylpiperidin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl)-3,5-dimethyl-2-oxo-1-(4-(trifluoromethyl)phenyl)-2,3-dihydro-1*H*-imidazole-4-carboxamide (50)

Yield: 72.0%; M.p.:124–126 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.73 (s, 1H), 8.47 (d, *J* = 5.1 Hz, 1H), 8.04 – 7.85 (m, 3H), 7.64 (d, *J* = 7.5 Hz, 2H), 7.59 (m, 1H), 7.53 (s, 1H), 7.46 (t, *J* = 8.9 Hz, 1H), 7.39 (s, 1H), 6.46 (d, *J* = 5.1 Hz, 1H), 4.18 (t, *J* = 6.7 Hz, 2H), 3.96 (s, 3H), 3.34 (s, 3H), 2.85 (d, *J* = 9.8 Hz, 2H), 2.48 – 2.36 (m, 2H), 2.19 (s, 3H), 2.05 – 1.92 (m, 2H), 1.57 (d, *J* = 11.0 Hz, 2H), 1.36 – 1.08 (m, 5H), 0.89 (d, *J* = 5.3 Hz, 3H). MS (ESI) m/z (%): 722.4 $[M+H]^+$; Anal. calcd. for $C_{38}H_{39}F_4N_5O_5$ (%): C, 63.24; H, 5.45; N, 9.70; Found (%): C, 63.32; H, 5.47; N, 9.76.

7.6.24. N-(3-fluoro-4-((6-methoxy-7-(3-(4-methylpiperazin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl)-3,5-dimethyl-2-oxo-1-(4-(trifluoromethyl)phenyl)-2,3-dihydro-1*H*-imidazole-4-carboxamide (51)

Yield: 73.8%; M.p.:128–129 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.48 (d, *J* = 5.2 Hz, 1H), 7.80 – 7.73 (m, 4H), 7.57 (s, 1H), 7.44 (d, *J* = 8.3 Hz, 2H), 7.43 (s, 1H), 7.30 (dd, *J* = 8.8, 1.9 Hz, 1H), 7.25 (t, *J* = 8.7 Hz, 1H), 6.41 (d, *J* = 5.1 Hz, 1H), 4.26 (t, *J* = 6.7 Hz, 2H), 4.05 (s, 3H), 3.52 (s, 3H), 2.75 – 2.33 (m, 10H), 2.30 (s, 6H), 2.17 – 2.09 (m, 2H). MS (ESI) m/z (%): 722.9 $[M+H]^+$; Anal. calcd. for $C_{37}H_{38}F_4N_6O_5$ (%): C, 61.49; H, 5.30; N, 11.63; Found (%): C, 61.32; H, 5.45; N, 11.56.

7.6.25. N-(3-fluoro-4-((6-methoxy-7-(3-(4-methylpiperidin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl)-3,5-dimethyl-2-oxo-1-(3-(trifluoromethyl)phenyl)-2,3-dihydro-1*H*-imidazole-4-carboxamide (52)

Yield: 65.9%; M.p.:116–118 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (d, *J* = 5.3 Hz, 1H), 7.81 (s, 1H), 7.77 (dd, *J* = 11.6, 2.0 Hz, 1H), 7.73 (d, *J* = 7.6 Hz, 1H), 7.67 (t, *J* = 7.7 Hz, 1H), 7.58 (s, 1H), 7.58 – 7.51 (m, 2H), 7.45 (s, 1H), 7.33 – 7.28 (m, 1H), 7.26 – 7.23 (m, 1H), 6.42 (d, *J* = 5.2 Hz, 1H), 4.27 (t, *J* = 6.7 Hz, 2H), 4.07 (s, 3H), 3.54 (s, 3H), 2.94 (d, *J* = 11.3 Hz, 2H), 2.56 (t, *J* = 7.3 Hz, 2H), 2.32 (s, 3H), 2.23 – 2.07 (m, 2H), 1.97 (t, *J* = 10.9 Hz, 2H), 1.64 (d, *J* = 12.4 Hz, 2H), 1.43 – 1.32 (m, 1H), 1.32 – 1.22 (m, 2H), 0.94 (d, *J* = 6.3 Hz, 3H). MS (ESI) m/z (%): 721.8 $[M+H]^+$; Anal. calcd. for $C_{38}H_{39}F_4N_5O_5$ (%): C, 63.24; H, 5.45; N, 9.70; Found (%): C, 63.34; H, 5.53; N, 9.56.

7.6.26. N-(3-fluoro-4-((6-methoxy-7-(3-(4-methylpiperazin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl)-3,5-dimethyl-2-oxo-1-(3-(trifluoromethyl)phenyl)-2,3-dihydro-1*H*-imidazole-4-carboxamide (53)

Yield: 66.5%; M.p.:117–120 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.41 (d, *J* = 5.3 Hz, 1H), 7.69 (dd, *J* = 11.8, 2.4 Hz, 1H), 7.67 (s, 1H), 7.64 (d, *J* = 7.9 Hz, 1H), 7.59 (t, *J* = 7.8 Hz, 1H), 7.50 (s, 1H), 7.49 – 7.48 (m, 1H), 7.45 (d, *J* = 7.9 Hz, 1H), 7.36 (s, 1H), 7.23 – 7.21 (m, 1H), 7.21 – 7.20 (m, *J* = 2.9 Hz, 1H), 6.34 (d, *J* = 4.9 Hz, 1H), 4.19 (t, *J* = 6.7 Hz, 2H), 3.98 (s, 3H), 3.45 (s, 3H), 2.63 – 2.28 (m, 10H), 2.23 (s, 3H), 2.22 (s, 3H), 2.10 – 2.02 (m, 2H). MS (ESI) m/z (%): 723.0 $[M+H]^+$; Anal. calcd. for $C_{37}H_{38}F_4N_6O_5$ (%): C, 61.49; H, 5.30; N, 11.63; Found (%): C, 61.64; H, 5.33; N, 11.51.

7.6.27. N-(3-fluoro-4-((6-methoxy-7-(3-(4-methylpiperidin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl)-3,5-dimethyl-2-oxo-1-(2-(trifluoromethyl)phenyl)-2,3-dihydro-1*H*-imidazole-4-carboxamide (54)

Yield: 67.1%; M.p.:109–111 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (d, *J* = 5.3 Hz, 1H), 7.93 (s, 1H), 7.86 (dd,

J = 7.5, 2.1 Hz, 1H), 7.80 – 7.69 (m, 2H), 7.65 (t, *J* = 7.7 Hz, 1H), 7.57 (s, *J* = 4.1 Hz, 1H), 7.42 (s, *J* = 6.7 Hz, 1H), 7.36 – 7.29 (m, 2H), 7.24 (t, *J* = 8.5 Hz, 1H), 6.41 (d, *J* = 5.2 Hz, 1H), 4.25 (t, *J* = 6.7 Hz, 2H), 4.05 (s, 3H), 3.53 (s, 3H), 2.93 (d, *J* = 11.3 Hz, 2H), 2.56 (t, *J* = 7.2 Hz, 2H), 2.25 – 2.14 (m, 2H), 2.14 (s, 3H), 1.97 (t, *J* = 10.9 Hz, 2H), 1.64 (d, *J* = 12.6 Hz, 2H), 1.44 – 1.32 (m, 1H), 1.31 – 1.19 (m, 2H), 0.93 (d, *J* = 6.3 Hz, 3H). MS (ESI) m/z (%): 721.8 $[M+H]^+$; Anal. calcd. for $C_{38}H_{39}F_4N_5O_5$ (%): C, 63.24; H, 5.45; N, 9.70; Found (%): C, 63.34; H, 5.37; N, 9.74.

7.6.28. N-(3-fluoro-4-((6-methoxy-7-(3-(4-methylpiperazin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl)-3,5-dimethyl-2-oxo-1-(2-(trifluoromethyl)phenyl)-2,3-dihydro-1*H*-imidazole-4-carboxamide (55)

Yield: 67.6%; M.p.:118–120 °C; IR (KBr) cm^{-1}: 3426.2, 2935.7, 2879.4, 2797.2, 1699.7, 1669.6, 1607.6, 1508.3, 1480.0, 1431.7, 1349.2, 1304.7, 1210.9, 1164.6, 1132.8, 1011.7, 852.4, 739.2; ^1H NMR (400 MHz, $CDCl_3$) δ 8.42 (d, *J* = 5.3 Hz, 1H), 7.85 (s, 1H), 7.79 (d, *J* = 7.2 Hz, 1H), 7.70 – 7.63 (m, 2H), 7.59 (t, *J* = 7.6 Hz, 1H), 7.51 (s, 1H), 7.37 (s, 1H), 7.29 – 7.23 (m, 2H), 7.17 (t, *J* = 8.6 Hz, 1H), 6.34 (d, *J* = 5.2 Hz, 1H), 4.20 (t, *J* = 6.7 Hz, 2H), 3.99 (s, 3H), 3.46 (s, 3H), 2.67 – 2.27 (m, 10H), 2.23 (s, 3H), 2.13 – 2.07 (m, 2H), 2.07 (s, 3H). MS (ESI) m/z (%): 722.9 $[M+H]^+$; Anal. calcd. for $C_{37}H_{38}F_4N_6O_5$ (%): C, 61.49; H, 5.30; N, 11.63; Found (%): C, 61.58; H, 5.35; N, 11.42.

7.6.29. 1-(2-chlorophenyl)-N-(3-fluoro-4-((6-methoxy-7-(3-(4-methylpiperidin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl)-3,5-dimethyl-2-oxo-2,3-dihydro-1*H*-imidazole-4-carboxamide (56)

Yield: 69.2%; M.p.:125–128 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.50 (d, *J* = 5.3 Hz, 1H), 7.89 (s, 1H), 7.75 (dd, *J* = 11.8, 2.4 Hz, 1H), 7.61 – 7.56 (m, 2H), 7.49 – 7.41 (m, 3H), 7.39 – 7.34 (m, 1H), 7.34 (dd, *J* = 9.1, 1.7 Hz , 1H), 7.25 (t, *J* = 8.5 Hz, 1H), 6.42 (d, *J* = 5.2 Hz, 1H), 4.27 (t, *J* = 6.7 Hz, 2H), 4.06 (s, 3H), 3.56 (s, 3H), 2.99 (d, *J* = 11.4 Hz, 2H), 2.66 – 2.57 (m, 2H), 2.20 (s, 3H), 2.16 (m, 2H), 2.03 (t, *J* = 10.9 Hz, 2H), 1.66 (d, *J* = 12.1 Hz, 2H), 1.46 – 1.36 (m, 1H), 1.35 – 1.26 (m, 2H), 0.95 (d, *J* = 6.2 Hz, 3H). MS (ESI) m/z (%): 688.1 $[M+H]^+$; Anal. calcd. for $C_{37}H_{39}ClFN_5O_5$ (%): C, 64.58; H, 5.71; N, 10.18; Found (%): C, 64.45; H, 5.56; N, 10.37.

7.6.30. 1-(2-chlorophenyl)-N-(3-fluoro-4-((6-methoxy-7-(3-(4-methylpiperazin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl)-3,5-dimethyl-2-oxo-2,3-dihydro-1*H*-imidazole-4-carboxamide (57)

Yield: 70.4%; M.p.:135–136 °C; IR (KBr) cm^{-1}: 3424.1, 3252.1, 2946.6, 2921.9, 2769.8, 1695.5, 1669.5, 1578.8, 1507.9, 1479.8, 1430.4, 1348.2, 1248.7, 1209.9, 1164.8, 1098.6, 1011.2, 852.9; ^1H NMR (400 MHz, $CDCl_3$) δ 8.50 (d, *J* = 5.3 Hz, 1H), 7.88 (s, 1H), 7.74 (dd, *J* = 11.8, 2.4 Hz, 1H), 7.60 – 7.55 (m, 2H), 7.48 – 7.39 (m, 3H), 7.35 (dt, *J* = 7.6, 3.2 Hz, 1H), 7.31 (dd, *J* = 9.0, 1.5 Hz, 1H), 7.24 (t, *J* = 8.6 Hz, 1H), 6.41 (d, *J* = 5.2 Hz, 1H), 4.27 (t, *J* = 6.7 Hz, 2H), 4.06 (s, 3H), 3.55 (s, 3H), 2.77 – 2.35 (m, 10H), 2.31 (s, 3H), 2.19 (s, 3H), 2.17 – 2.08 (m, 2H). ^{13}C NMR (101 MHz, DMSO) δ 159.80, 158.95, 155.13, 152.69, 152.45, 151.89, 150.07, 149.33, 146.89, 138.44, 136.38, 133.23, 132.29, 131.97, 131.65, 130.76, 129.02, 124.61, 117.15, 116.56, 114.93, 109.25, 109.01, 102.50, 99.51, 67.23, 56.28, 55.07 (2C), 54.86, 53.25 (2C), 46.26, 29.52, 26.56, 11.12. MS (ESI) m/z (%): 710.8 $[M+Na]^+$; Anal. calcd. for $C_{36}H_{38}ClFN_6O_5$ (%): C, 62.74; H, 5.56; N, 12.19; Found (%): C, 62.59; H, 5.46; N, 12.33.

7.6.31. 1-(2-chlorophenyl)-N-(3-fluoro-4-((6-methoxy-7-(3-(4-methylpiperazin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl)-5-methyl-2-oxo-2,3-dihydro-1*H*-imidazole-4-carboxamide (58)

Yield: 62.1%; M.p.:121–122 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 9.02 (s, 1H), 8.49 (d, *J* = 5.2 Hz, 1H), 7.60 (dd, *J* = 12.9, 2.0 Hz, 2H), 7.58 (s, 1H), 7.45 (m, 4H), 7.38 (d, *J* = 8.6 Hz, 1H), 7.07 (t, *J* = 8.7 Hz, 1H), 6.38 (d, *J* = 5.2 Hz, 1H), 4.27 (t, *J* = 6.5 Hz, 2H), 4.04 (s, 3H), 2.78 – 2.47 (m, 10H), 2.44 (s, 3H), 2.32 (s, 3H), 2.19 – 2.08 (m, 2H). MS (ESI) m/z (%): 675.3 $[M+H]^+$; Anal. calcd. for $C_{35}H_{36}ClFN_6O_5$ (%): C, 62.26; H, 5.37; N, 12.45; Found (%): C, 62.29; H, 5.46; N, 12.20.

References and notes

1. Bottaro, D. P.; Rubin, J. S.; Faletto, D. L.; Chan, A. M.; Kmiecik, T. E.; Vande Woude, G. F.; Aaronson, S. A. *Science*. **1991**, *251*, 802.
2. Naldini, L.; Vigna, E.; Narsimhan, R. P.; Gaudino, G.; Zarnegar, R.; Michalopoulos, G. K.; Comoglio, P. M. *Oncogene*. **1991**, *6*, 501−504.
3. Comoglio, P. M.; Tamagnone, L.; Boccaccio, C. *Exp. Cell Res.* **1999**, *253*, 88−99.
4. Aguirre Ghiso, J. A.; Alonso, D. F.; Farías, E. F.; Gomez, D. E.; deKier Joffe, E. B. *Eur.J. Biochem*. **1999**, *263*, 295–304.
5. Parr, C.; Watkins, G.; Mansel, R. E.; Jiang, W. G. *Clin. Cancer Res*. **2004**, *10*, 202–211.
6. Bellusci, S.; Moens, G.; Gaudino, G.; Comoglio, P.; Nakamura, T.; Thiery, J. P.; Jouanneau, J. *Oncogene*. **1994**, *9*, 1091–1099.
7. Jeffers, M.; Rong, S.; Anver, M.; Vande Woude, G. F. *Oncogene* **1996**, *13*, 853–861.
8. Takayama, H.; LaRochelle, W. J.; Sharp, R.; Otsuka, T.; Kriebel, P.; Anver, M.; Aaronson, S. A.; Merlino, G. *Natl Acad. Sci. U.S.A*. **1997**, *94*, 701–706.
9. Otsuka, T.; Takayama, H.; Sharp, R.; Celli, G.; LaRochelle, W. J.; Bottaro, D. P.; Ellmore, N.; Vieira, W.; Owens, J. W.; Anver, M.; Merlino, G. *Cancer Res*. **1998**, *58*, 5157–5167.
10. Cheng, H.L.; Trink, B.; Tzai, T.-S.; Liu, H.-S.; Chan, S.H.; Ho, C.L.; Sidransky, D.; Chow, N.-H. *J. Clin. Oncol*. **2002**, *20*, 1544−1550.
11. Lengyel, E.; Prechtel, D.; Resau, J. H.; Gauger, K.; Welk, A.; Lindemann, K.; Alanti, G.; Richter, T.; Knudsen, B.; Vande Woude, G. F.; Harneck, N. *Int. J. Cancer*. **2005**, *113*, 678−682.
12. Sawada, K.; Radjabi, A. E.; Shinomiya, N.; Kistner, E.; Kenny, H.; Becker, A. R.; Turkyilmaz, M. A.; Salgia, R.; Yamada, S. D.; Vande Woude, G. F.; Tretiakova, M. S.; Lengyel, E. *Cancer Res*. **2007**, *67*, 1670−1679.
13. Lo Muzio, L.; Farina, A.; Rubini, C.; Coccia, E.; Capogreco, M.; Colella,G.; Leonardi, R.; Campisi, G.; Carinci, F. *Tumor Biol*. **2006**, *27*, 116−121.
14. Qian, F.; Engst, S.; Yamaguchi, K.; Yu, P. W.; Won, K. A.; Mock, L.; Lou, T.; Tan, J.; Li, C.; Tam, D.; Lougheed, J.; Yakes, F. M.; Bentzien, F.; Xu, W.; Wooster, R.; Greshock, J.; Joly, A. H. *Cancer Res*. **2009**, *69*, 8009–8016.
15. (a) Tang, Q. D.; Zhao, Y. F.; Du, X. M.; Chong, L. E.; Gong, P.; Guo, C. *Eur. J. Med. Chem.* **2013**, *69*, 77; (b) Li, S.; Huang, Q.; Liu, Y. J.; Zhang, X. L.; Liu, S.; He, C.; Gong, P. *Eur. J. Med. Chem.* **2013**, *64*, 62; (c) Li, S.; Zhao, Y. F.; Wang, K. W.; Gao, Y. L.; Han, J. M.; Cui, B. B.; Gong, P. Bioorg.Med. Chem. 2013, 21, 2843; (d) Zhou, S. G.; Liao, H. M.; He, C.; Dou, Y. N.; Jiang, M. Y.; Zhao, Y. F.; Gong, P. *Eur. J. Med. Chem*., **2014**, *83*, 581; (e) Zhou, S. G.; Liao, H. M.; Liu, M.M.; Feng, G. B.; Fu, B. L.; Li, R. J.; Cheng, M. S.; Zhao, Y. F.; Gong, P. *Bioorg. Med. Chem*., **2014**, *22*, 6438.
16. (a) Huang; He, K.; Philip, H.; Wei, M.; Andy, O.; Angela, W.; James, V.; Thomas, B. WO2008024970; (b) Ahearn, S. P.; M.; Jung, J.; Pu, Q. L.; Rivkin, A.; Scott, M. E.; Witter, D. J.; Guerin, D. WO2013085802; (c) Guckian, K.; Lee, W. C.; Lin, E.; WO2008094556.
17. Lee, S. H.; Clapham, B.; Koch, G.; Zimmermann, J.; Janda, K. D. *Org. Lett*. **2003**, *5*, 511–514.
18. Liu, L. B.; Siegmund, A.; Xi, N.; Kaplan-Lefko, P.; Rex, K.; Chen, A.; Lin, J.; Moriguchi, J.; Berry, L.; Huang, L. Y.; Teffera, Y.; Yang, Y. J.; Zhang, Y. H.; Bellon, S. F.; Lee, M.; Shimanovich, R.; Bak, A.; Dominguez, C.; Norman, M. H.; Harmange, J. C.; Dussault, I.; Kim, T. S. *J. Med. Chem.* **2008**, *51*, 3688.
19. Peach, M. L.; Tan, N.; Tan, N.; Choyke, S. J.; Giubellino, A.; Athauda, G.; Burke, T. R.; Nicklaus, M. C.; Bottaro, D. P. *J. Med. Chem*. **2009**, *52*, 943.
20. Takayuki, N.; Osamu, T.; Atsumi, Y.; Tomohiro, M.; Keiko, T.; Setsuo, F.; Shuji, S.; Makoto, A.; Hiroshi, O. *Cancer Sci.* **2010**, *101*, 210.
21. Tiedt, R.; Degenkolbe, E.; Furet, P.; Appleton, B. A.; Wagner, S.; Schoepfer, J.; Buck, E.; Ruddy, D. A.; Monahan, J. E.; Jones, M. D.; Blank, J.; Haasen, D.; Drueckes, P.; Wartmann, M.; McCarthy, C.; Sellers, W. R.; Hofmann, F. *Cancer Res*. **2011**, *71*, 5255.

Legends

Figure 1. Structures of small-molecule c-Met inhibitors

Figure 2. Our previous work on small-molecule c-Met kinase inhibitors

Figure 3. Anticancer agents bearing imidazolone moiety

Figure 4. General structure of the target compounds

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.

Scheme 2. Reagents and conditions: (i) NaOCN, AcOH/H_2O, 50 °C, 2 h; (ii) (a) Rh_2Oct_4 (2 mol %), ethyl 2-diazo-3-oxobutanoate, 1:1 toluene/DCE, 80 °C, 30 min. (b) 10% TFA, rt, 30 min; (iii) CH_3I (3 equiv), K_2CO_3 (3 equiv) DMF, 3 h; (iv) NaOH (5 equiv), 1,4-dioxane/EtOH, 40 °C, 10 h; (v) (a) Rh_2Oct_4 (2 mol %), *tert*-butyl 2-diazo-3-oxobutanoate, 1:1 toluene/DCE, 80 °C, 30 min. (b) 10% TFA, rt, 3 h; (vi) PhMe, $SOCl_2$, reflux, 5 h; (vii) appropriate aniline, Na_2CO_3, CH_2Cl_2.

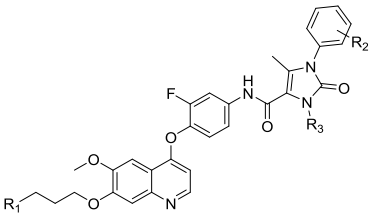
Table 1
SARs of quinoline derivatives.

Table 2
kinase selectivity profile of compound **58** and foretinib

Figure 5. The c-Met active site in complex with compound **58**, Compound **58** was shown in colored sticks (green: carbon atom, blue: nitrogen atom, red: oxygen atom, yellow: chlorine atom, cyan: fluorine atom). The conventional H-bond interaction was shown in green dotted line.

Table 1

SAR of quinoline derivatives.



Compd.	R_1	R_2	R_3	IC_{50} (μM)[a]				c-Met IC_{50}(nM)
				A549	H460	HT-29	MKN-45	
28	morpholinyl	H	CH_3	0.98 ±0.14	0.79 ±0.09	0.74 ±0.08	0.32 ±0.03	35.68 ±2.54
29	pyrrolidinyl	H	CH_3	1.46 ±0.18	1.03 ±0.19	0.94 ±0.09	0.51 ±0.07	ND
30	piperidinyl	H	CH_3	0.79 ±0.09	0.65 ±0.06	0.56 ±0.03	0.24 ±0.04	31.20 ±2.32
31	4-methylpiperidinyl	H	CH_3	0.66 ±0.08	0.59 ±0.05	0.36 ±0.03	0.21 ±0.04	28.54 ±2.86
32	4-methylpiperazinyl	H	CH_3	0.60 ±0.08	0.42 ±0.04	0.30 ±0.02	0.19 ±0.02	23.86 ±2.11
33	4-methylpiperidinyl	4-CH_3	CH_3	1.12 ±0.14	0.94 ±0.10	0.79 ±0.09	0.43 ±0.07	ND
34	4-methylpiperazinyl	4-CH_3	CH_3	0.83 ±0.08	0.51 ±0.04	0.49 ±0.03	0.36 ±0.03	24.25 ±2.10
35	4-methylpiperidinyl	4-OCH_3	CH_3	1.04 ±0.20	0.94 ±0.08	0.79 ±0.08	0.49 ±0.06	ND
36	4-methylpiperazinyl	4-OCH_3	CH_3	0.96 ±0.12	0.69 ±0.06	0.56 ±0.02	0.44 ±0.05	27.30 ±2.14
37	4-methylpiperidinyl	4-F	CH_3	0.52 ±0.04	0.25 ±0.04	0.24 ±0.03	**0.084 ±0.007**	6.26 ±0.41
38	4-methylpiperazinyl	4-F	CH_3	0.43 ±0.06	0.26 ±0.03	0.19 ±0.04	**0.067 ±0.005**	5.41 ±0.32
39	4-methylpiperidinyl	4-Cl	CH_3	0.42 ±0.04	**0.20 ±0.02**	0.17 ±0.03	**0.062 ±0.006**	5.64 ±0.36
40	4-methylpiperazinyl	4-Cl	CH_3	0.36 ±0.03	**0.17 ±0.02**	0.14 ±0.02	**0.058 ±0.003**	4.36 ±0.38
41	4-methylpiperidinyl	4-Br	CH_3	0.68 ±0.07	0.55 ±0.06	0.28 ±0.02	0.16 ±0.04	18.44 ±2.46
42	4-methylpiperazinyl	4-Br	CH_3	0.48 ±0.06	0.36 ±0.04	0.29 ±0.05	0.12 ±0.03	13.3 ±0.96
43	morpholinyl	3,4-2F	CH_3	0.62 ±0.09	0.54 ±0.05	0.39 ±0.06	0.17 ±0.04	18.6 ±1.40
44	4-methylpiperidinyl	3,4-2F	CH_3	0.53 ±0.08	0.23 ±0.02	0.23 ±0.04	**0.095 ±0.006**	7.43 ±0.46
45	4-methylpiperazinyl	3,4-2F	CH_3	0.40 ±0.05	0.24 ±0.03	0.18 ±0.02	**0.086 ±0.005**	5.80 ±0.24
46	4-methylpiperidinyl	3-Cl-4-F	CH_3	0.43 ±0.04	0.25 ±0.04	0.20 ±0.03	**0.089 ±0.007**	6.67 ±0.32
47	4-methylpiperazinyl	3-Cl-4-F	CH_3	0.38 ±0.03	0.21 ±0.02	0.14 ±0.02	**0.073 ±0.008**	5.16 ±0.20
48	4-methylpiperidinyl	4-OCF_3	CH_3	0.62 ±0.09	0.59 ±0.05	0.40 ±0.04	0.14 ±0.04	25.49 ±2.69
49	4-methylpiperazinyl	4-OCF_3	CH_3	0.44 ±0.04	0.34 ±0.02	0.27 ±0.02	0.12 ±0.04	20.54 ±2.81
50	4-methylpiperidinyl	4-CF_3	CH_3	0.54 ±0.06	0.41 ±0.04	0.36 ±0.01	0.13 ±0.02	14.68 ±2.36
51	4-methylpiperazinyl	4-CF_3	CH_3	0.50 ±0.05	0.36 ±0.02	0.26 ±0.03	**0.098 ±0.008**	10.64 ±2.23
52	4-methylpiperidinyl	3-CF_3	CH_3	0.88 ±0.10	0.58 ±0.04	0.52 ±0.06	0.32 ±0.03	26.18 ±2.52
53	4-methylpiperazinyl	3-CF_3	CH_3	0.77 ±0.06	0.57 ±0.03	0.43 ±0.07	0.20 ±0.01	19.22±1.24
54	4-methylpiperidinyl	2-CF_3	CH_3	0.45 ±0.03	0.22 ±0.02	0.14 ±0.01	**0.081 ±0.004**	10.86 ±1.50
55	4-methylpiperazinyl	2-CF_3	CH_3	0.37 ±0.03	**0.19 ±0.01**	0.13 ±0.02	**0.069 ±0.007**	8.10 ±1.32
56	4-methylpiperidinyl	2-Cl	CH_3	0.32 ±0.05	**0.18 ±0.02**	0.15 ±0.01	**0.043 ±0.005**	4.16 ±0.28
57	4-methylpiperazinyl	2-Cl	CH_3	0.31 ±0.04	**0.13 ±0.01**	0.12 ±0.01	**0.037 ±0.006**	2.90 ±0.23
58	4-methylpiperazinyl	2-Cl	H	0.25 ±0.02	**0.10 ±0.008**	0.086 ±0.005	**0.014 ±0.004**	**1.42 ±0.14**
Foretinib[b]		-	-	0.19 ± 0.02	0.21 ± 0.03	0.032 ± 0.005	0.12 ±0.03	1.64 ±0.10

Bold values show the IC_{50} values of the target compounds lower than the values of the positive control. ND: Not determined.

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

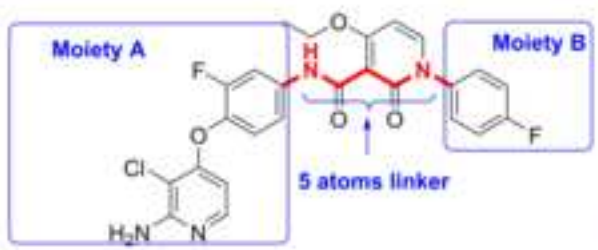
[b] Used as a positive control.

Table 2

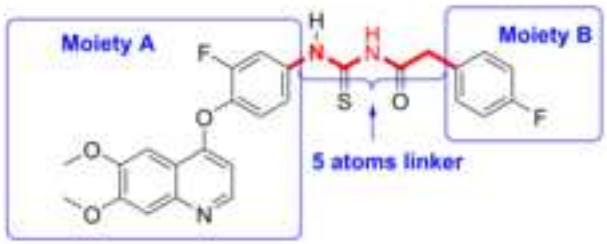
kinase selectivity profile of compound **58** and foretinib

Enzyme	Enzyme IC_{50} (nM)	
	58	foretinib
VEGFR-2	92.6	4.86
c-kit	38.2	6.72
Flt-3	134	5.58
Ron	270	3.43
EGFR	>100,000	2990

Figure(1)

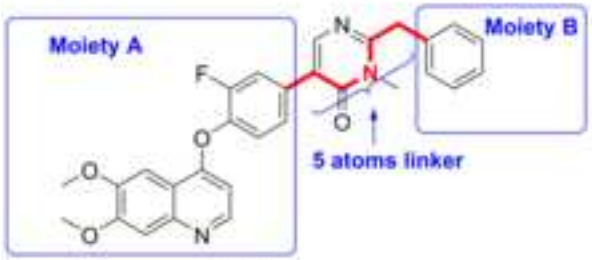


1 BMS777607
c-Met (3.9nM)
Phase II

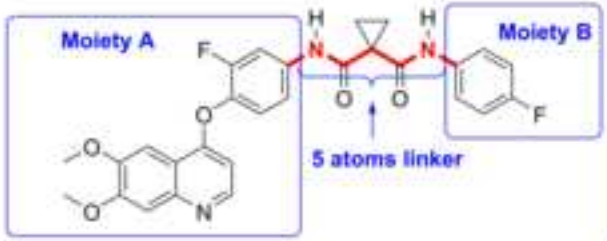


2 Kirin
c-Met (80 nM)
VEGFR2 (32 nM)
Preclinical

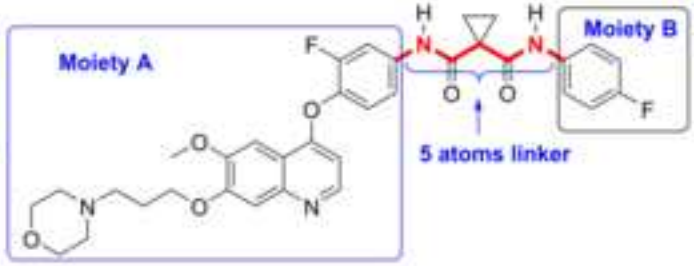
3 Amgen
c-Met (1 nM)
VEGFR2 (7.8 nM)
Preclinical



4 AM7
c-Met (8.9 nM)
Preclinical

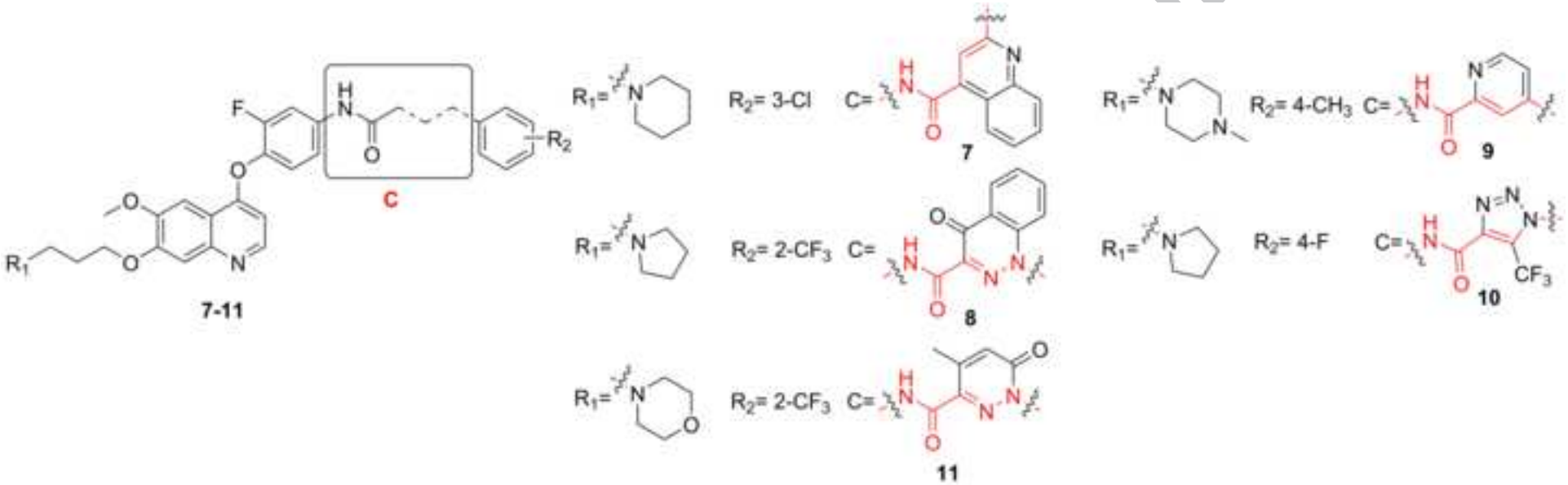


5 Cabozantinib, XL184
c-Met (21 nM)
VEGFR2 (7 nM)
Launched



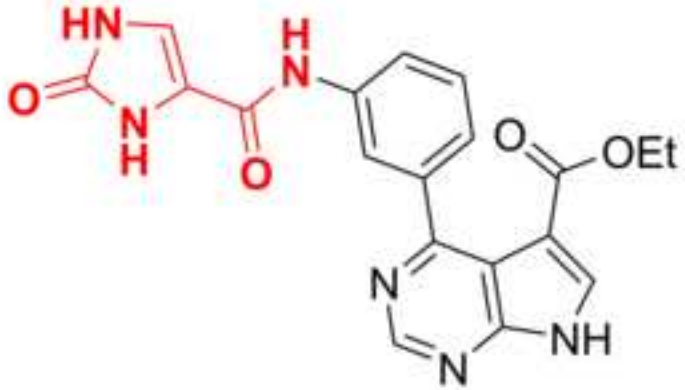
6 Foretinib, XL880
c-Met (0.4 nM)
VEGFR2 (0.8nM)
PhaseIII

Figure(2)

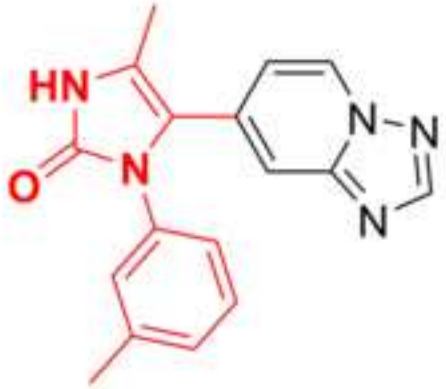


Figure(3)

12 HSP-90 inhibitor

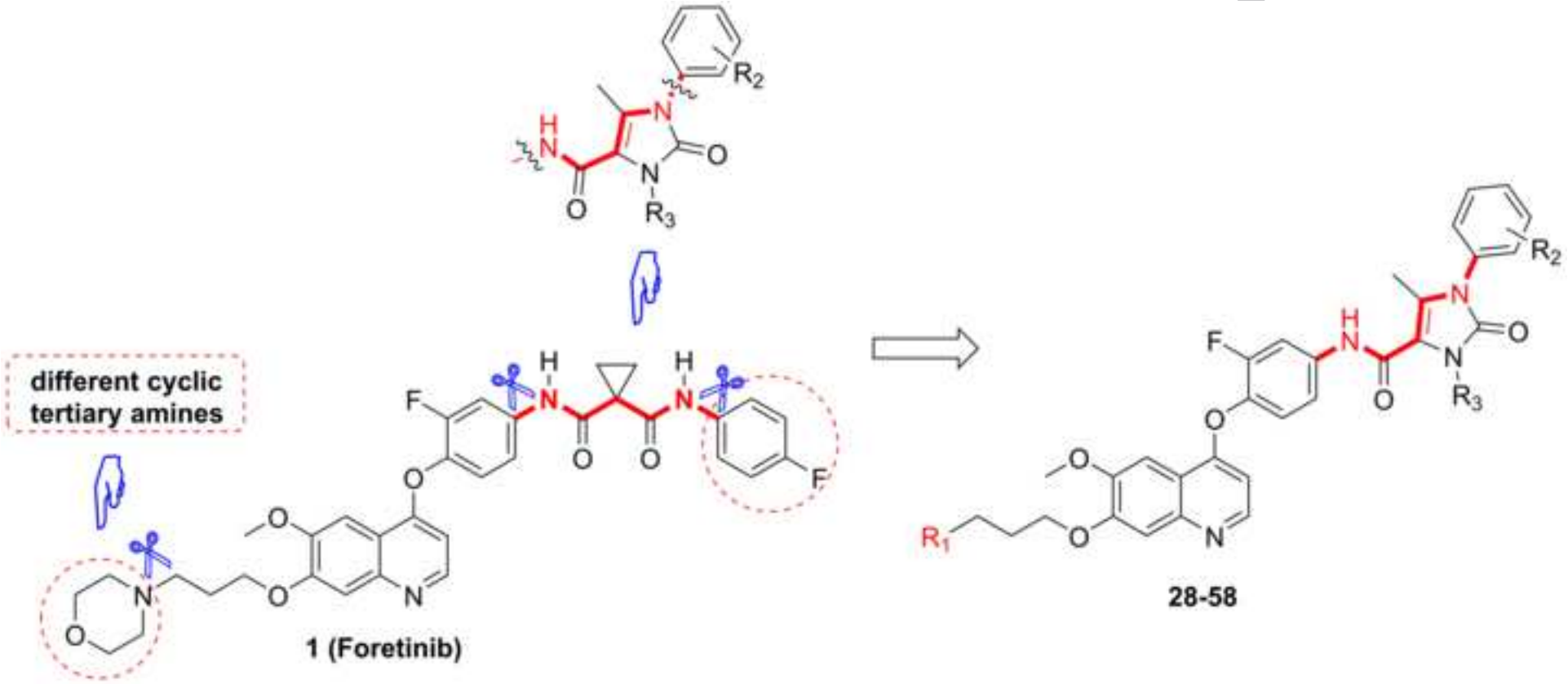


13 JAK inhibitor

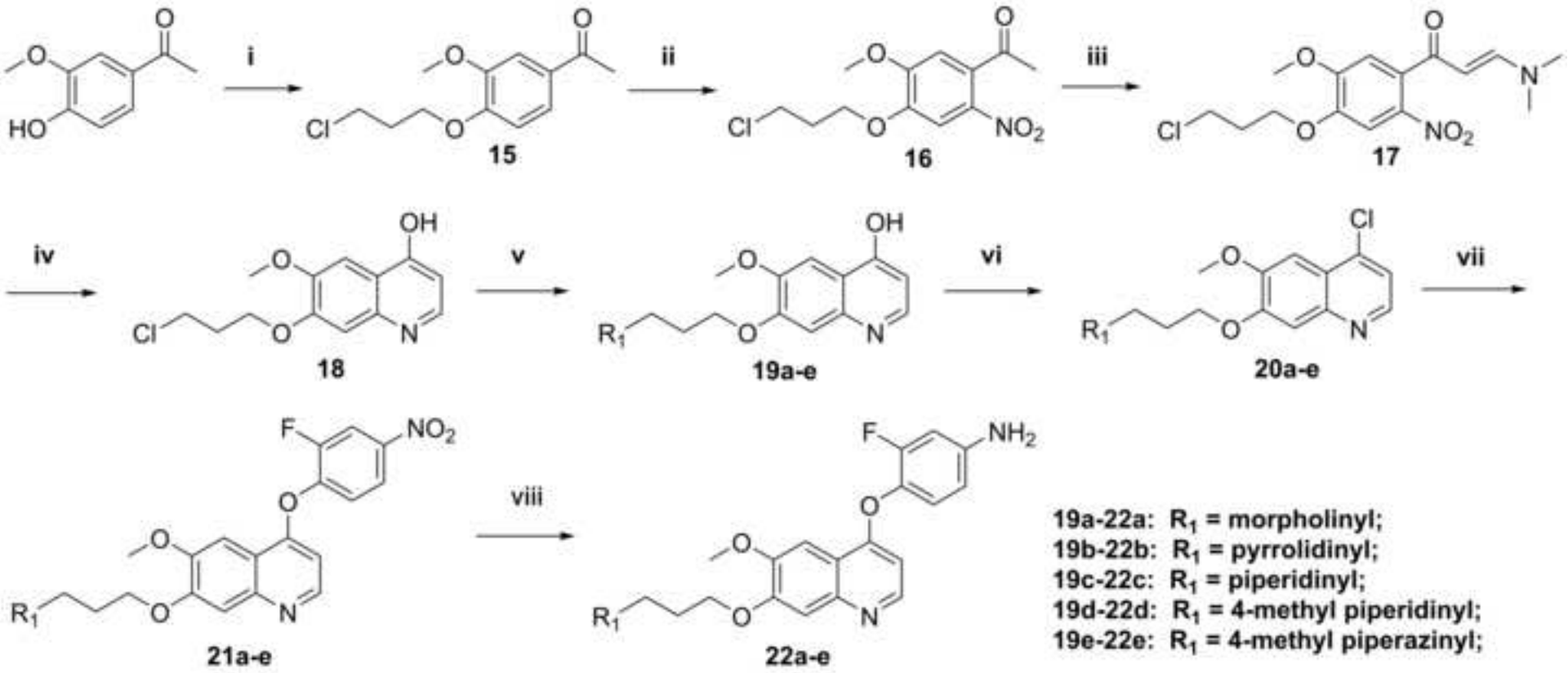


14 ALK5/ALK4 antagonist

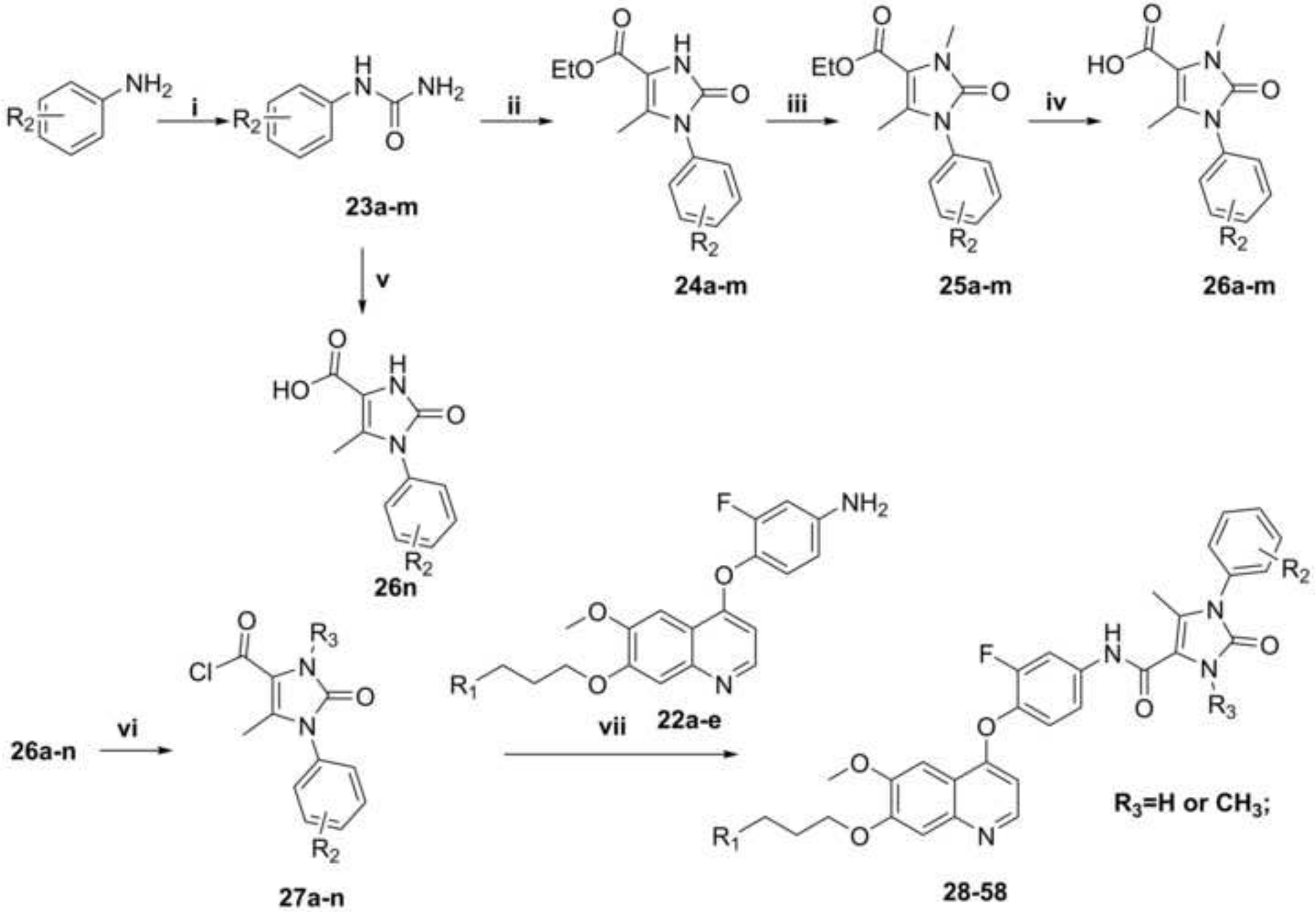
Figure(4)



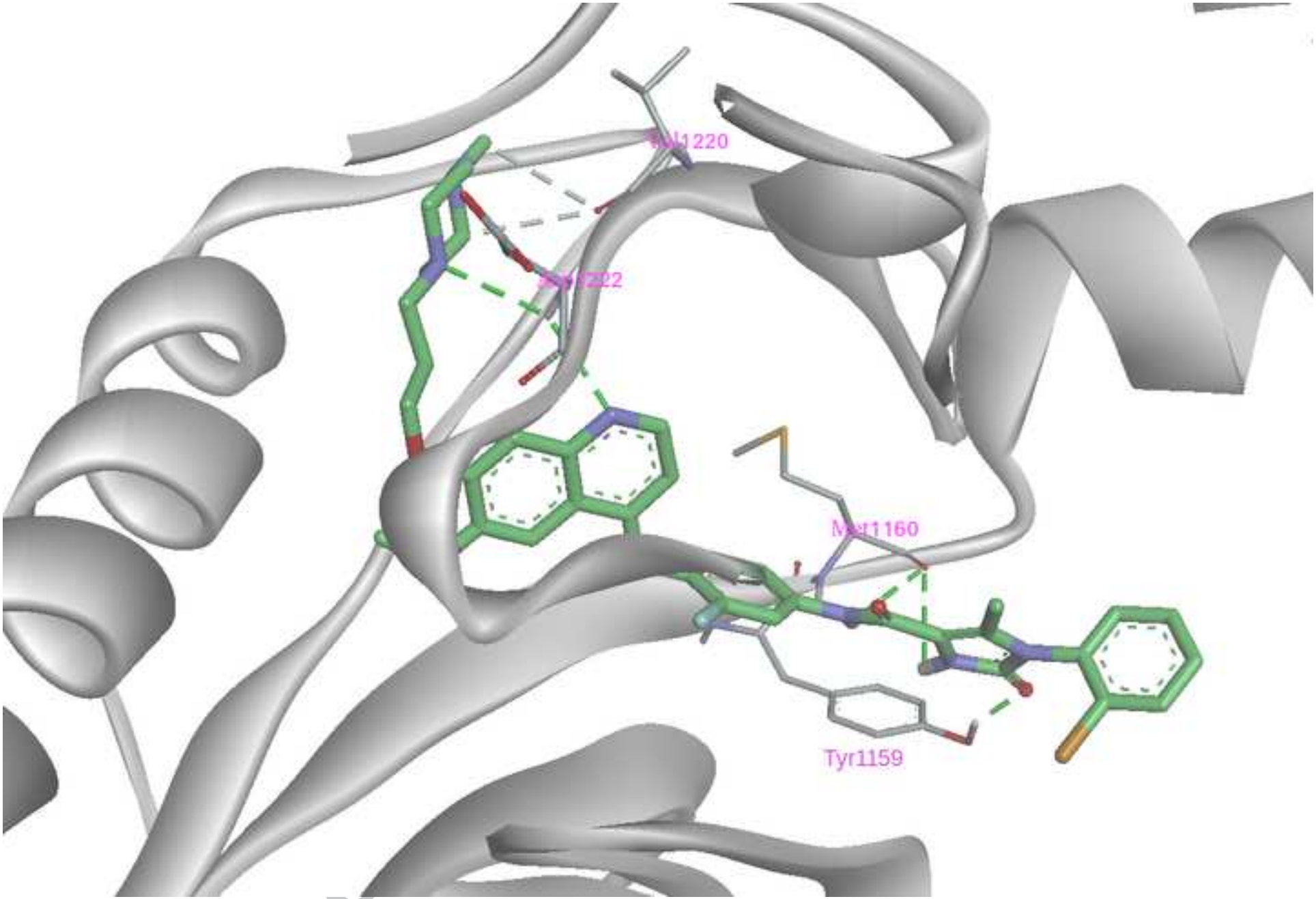
Scheme 1



Scheme 2



Figure(5)



Graphical abstract

A series of novel 4-(2-fluorophenoxy)quinoline derivatives containing imidazolone moiety designed, synthesized and evaluated for their enzymatic assays, cytotoxicity and docking analysis.