Bioorganic Chemistry 57 (2014) 30–42

Contents lists available at ScienceDirect

Bioorganic Chemistry

journal homepage: www.elsevier.com/locate/bioorg

Design, synthesis and pharmacological evaluation of 6,7-disubstituted-4-phenoxyquinoline derivatives as potential antitumor agents

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ARTICLE INFO

Article history:
Received 3 June 2014
Available online 12 August 2014

Keywords:
c-Met
4-Phenoxyquinoline derivatives
Anticancer activity
2,4-Imidazolinedione/pyrazolone

ABSTRACT

Two series of 6,7-disubstituted-4-phenoxyquinoline derivatives bearing 2,4-imidazolinedione/pyrazolone scaffold were designed, synthesized and evaluated for their c-Met kinase inhibition and cytotoxicity against HT-29, H460, A549, MKN-45, and U87MG cancer cell lines *in vitro*. The pharmacological data indicated that most of the tested compounds showed moderate to significant cytotoxicity and high selectivity against HT-29, H460 and A549 cancer cell lines as compared with foretinib. The SAR analyses indicated that compounds with halogen groups, especially trifluoromethyl groups at 2-position on the phenyl ring (moiety B) were more effective. In this study, a promising compound **17** (c-Met IC_{50} = 2.20 nM, a multi-target tyrosine kinase inhibitor) showed the most potent antitumor activities with IC_{50} values of 0.14 μM, 0.18 μM, 0.09 μM, 0.03 μM, and 1.06 μM against HT-29, H460, A549, MKN-45, and U87MG cell lines, respectively.

1. Introduction

c-Met kinase inhibitors have recently become an attractive therapeutic target for cancer therapy and it normally activated by binding its natural ligand hepatocyte growth factor (HGF), also known as scatter factor (SF). The binding of HGF to c-Met induces several complex signaling pathways and results in cell proliferation, motility, migration, and survival [1–3]. Moreover, c-Met has been found to be overexpressed or mutated in human cancers, especially correlated with advanced disease stage and poor prognosis. As a result, c-Met has attracted considerable attention as a potential target for cancer treatment [4–6].

Recently, a number of new 6,7-disubstituted-4-phenoxyquinoline derivatives with excellent antitumor activity have been reported. Many of these derivatives are being marketed or under clinical/preclinical studies, such as cabozantinib (**1**), Foretinib (**2**) and AM 7 (**3**) (Fig. 1) [7,8]. Cabozantinib (**XL-184, 1**), a typical multikinase inhibitor (c-Met included) bearing quinoline pharmacophore, was approved by U.S. FDA in November 2012 for the treatment of patients with progressive metastatic medullary thyroid cancer (MTC) [9]. Foretinib (**XL880, 2**), which is currently undergoing phase III studies for different cancer types, is a novel oral multikinase inhibitor targeting c-Met, VEGFR, RON, KDR and Flt-1. As shown in **Figure 1**, the main modification of these quinoline derivatives was focused on the 5-atom linker containing hydrogen-bond donors or acceptors between moiety A and B, which is known as **"5 atoms regulation"** in our previous study [10]. In addition, the modifications of the A moiety usually occurred at 7-position of quinoline, while the methoxy group was replaced by a water-soluble fragment, such as 3-morpholinopropoxy group. These structural features indicated that exploring a satisfactory linker was a practicable way of designing new quinoline derivatives. In our previous study, we had introduced 1,4-dihydroquinoline, *N*-arylidene semicarbazide and quinoline scaffolds as part of the 5-atom linkers, and the resulting derivatives (**4**–**6,** Fig. 1) showed excellent antitumor activity [11–13].

Compounds containing *N*-Aryl-pyrazolone-4-imino and 2,4-imidazolinedione framework displayed a multitude of biological activities, including antitumor, antibacterial, antihypertensive, antiplatelet and anti-inflammatory activities [14–17]. Remarkably, this framework was widely used as a building block in the design of anticancer agents because of its ability to form hydrogen-bonding interactions with drug targets. For example, compound **7** and **8** (Fig. 2), as a potent catalytic inhibitor of human telomerase, was reported as large ribonucleoprotein complex of reverse transcriptase enzyme [18,19]. It was interested that the *N*-Aryl-pyrazolone-4-imino and 2,4-imidazolinedione framework conformed to the rule of **"5 atoms regulation"** and contained both hydrogen-bond donor and acceptor, which indicated that it was a satisfactory linker.

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http://dx.doi.org/10.1016/j.bioorg.2014.07.011
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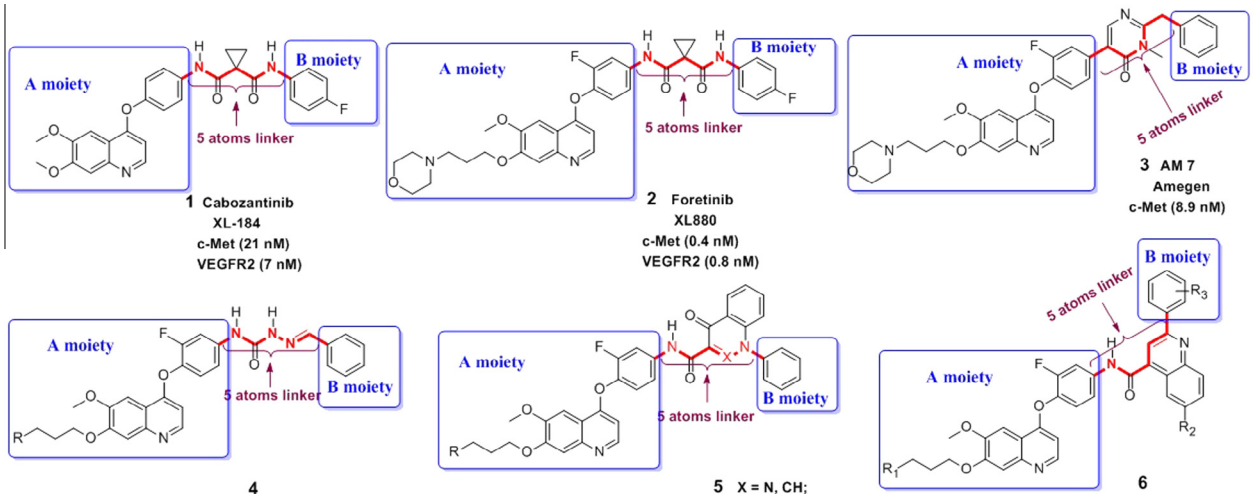


Fig. 1. Structures of small-molecule c-Met inhibitors based on the 6,7-disubstituted-4-phenoxyquinoline scaffold.

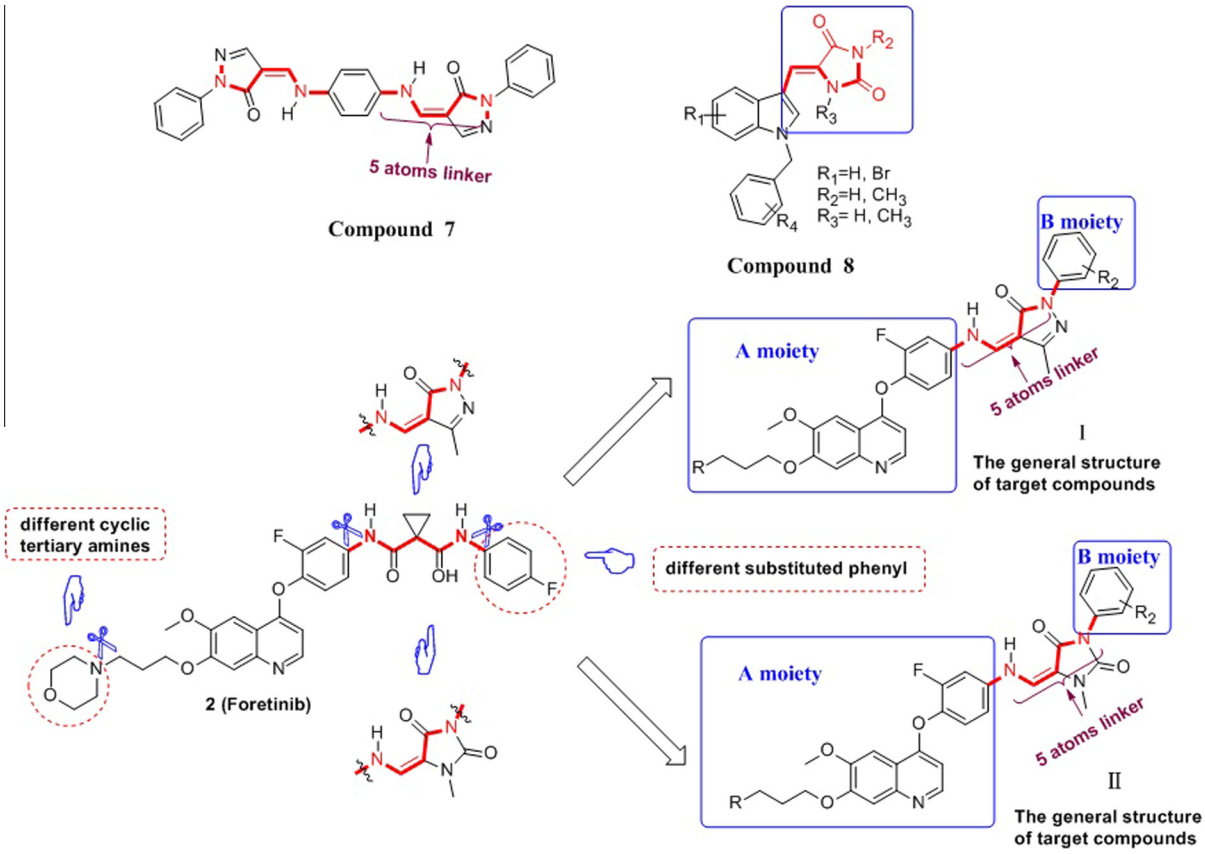


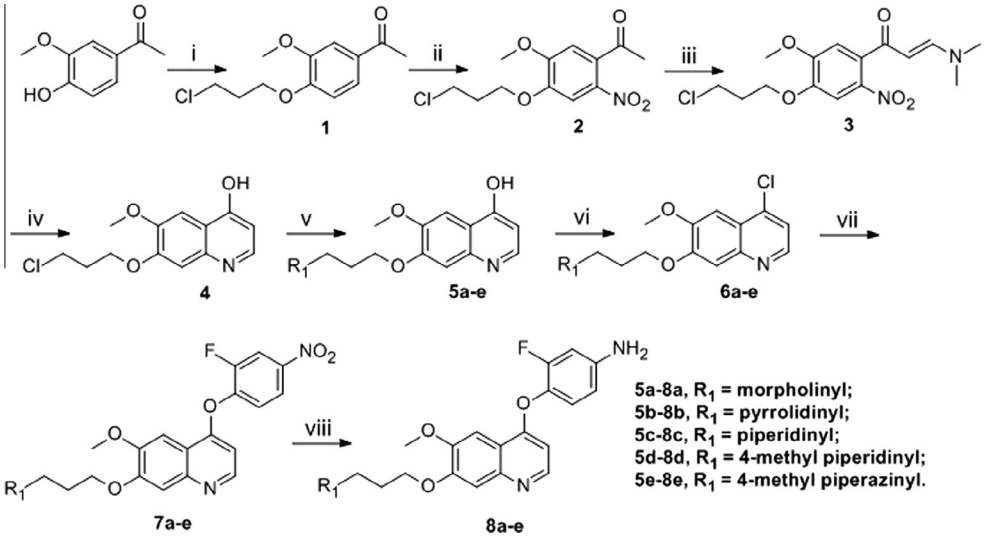
Fig. 2. The structure of compound **7**, **8** and the target compounds.

Therefore, we selected *N*-Aryl-pyrazolone-4-imino and 2,4-imidazolinedione framework as the 5-atom linker to obtains two series of novel 6,7-disubstituted-4-phenoxyquinoline derivatives (**I, II** Fig. 2). Meanwhile, at the 7-position of quinolines, a three-carbon tether which contained different cyclic tertiary amines were introduced, such as 4-methyl piperidinyl, piperidinyl, 4-methyl piperazinyl and pyrrolidinyl group. Additionally, various substituents (R_2) were introduced into the phenyl ring (B moiety) to investigate their effect on activity. In this paper, the synthesis of these quinoline derivatives was reported and their *in vitro* anticancer activities against five human cancer cell lines included the A549 (human lung adenocarcinoma), H460 (human lung cancer), HT-29 (human colon cancer), MKN-45 (human gastric cancer) and U87MG (human glioblastoma), and c-Met kinase were evaluated, respectively.

2. Chemistry

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

The key intermediates 6,7-disubstituted-4-phenoxyquinolines **8a–e** were synthesized using a convenient eight-step procedure



Scheme 1. Reagents and conditions: (i) $Br(CH_2)_3Cl$, acetone, 0 °C, 30 min, r.t., 12 h; (ii) 98%HNO_3, CH_2Cl_2, 0 °C, 4 h; (iii) DMF-DMA, toluene, 110 °C, 10 h; (iv) Fe powder, AcOH, r.t., 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.

starting from 1-(4-hydroxy-3-methoxyphenyl)ethanone (Scheme 1), which was illustrated in detail in our previous study [11,20].

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

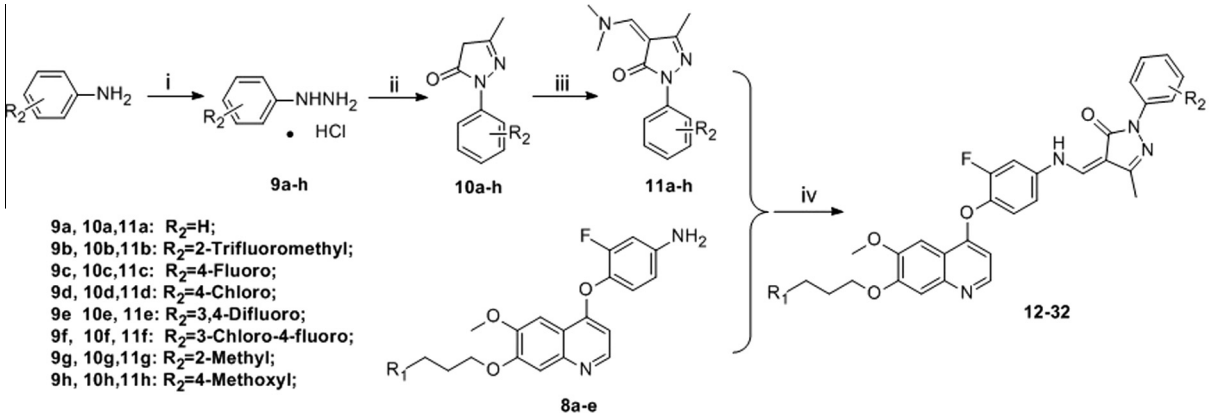
The target compounds **12–32** were synthesized according to the routes outlined in Scheme 2. The side chains **11a–h** were prepared from substituted aniline, which was diazotized and subsequent $NaHSO_3$ provide to **9a–h**. Cyclization of **9a–h** with ethyl acetoacetate in refluxing acetic acid under basic conditions yielded **10a–h**, which were further treated with *N*,*N*-dimethyl formamide dimethyl acetal (DMF-DMA) to provide **11a–h** in high yield. Finally, condensation of intermediates **8a–e** with **11a–h** in the presence of acetic acid at reflux for 12 h provided compounds **12–32**.

2.3. Synthesis of the target compounds of 2,4-imidazolinedione-based quinolones

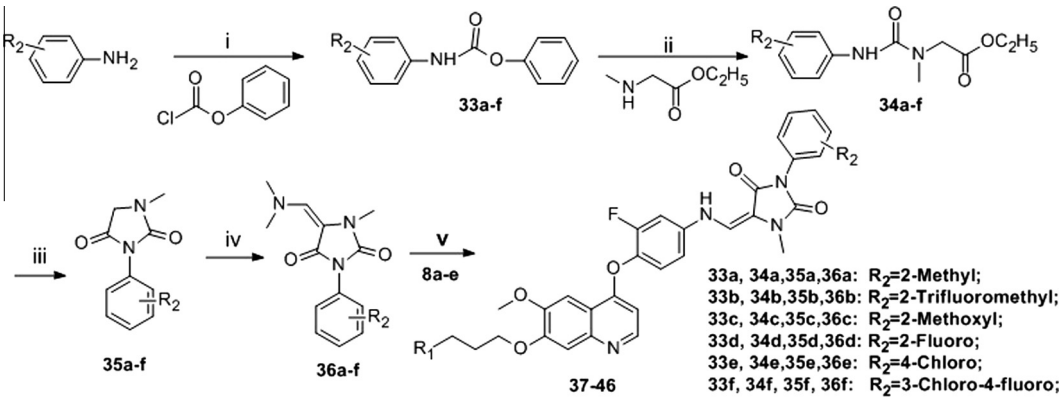
The synthesis of the target compounds **37–46** were described in Scheme 3. The commercially available substituted aniline was condensed phenyl chloroformate at room temperature to afford intermediates **33a–f** as white solids. Subsequently, the intermediates **33a–f** with sarcosine ethyl ester hydrochloride in the presence of potassium carbonate in DMF solution obtained urea **34a–f**. Cyclization of **34a–f** with ethanol in refluxing concentrated hydrochloric acid under basic conditions yielded **35a–f** [21]. Subsequent aminomethylenation using modified Vilsmeier–Haack reagent *N*,*N*-dimethyl formamide dimethyl acetal (DMF-DMA) at 50 °C afforded intermediates **36a–f** as yellow solids [22].

The structures and relative stereochemistry of the target compounds were confirmed by MS spectra, ^1H NMR, ^{13}C NMR, 2D nuclear Overhauser effect spectroscopy (NOESY) NMR and IR. The experimental procedure shown in Scheme 2 led selectively to the *Z* isomer, which was confirmed by 2D NOESY NMR spectroscopic approach [23–24].

For the representative compound **17**, the NOESY effect was observed between the protons of CH_3 (2.30, s) and CH=C (7.88, s) in *Z* isomer (Fig. 3) (see Supplementary Information), which should not be observed in the putative *E* isomer due to the larger intramolecular H–H distances. Moreover, the *Z* isomers were relatively stable at room temperature because of intramolecular hydrogen bond. Experimental data showed that they were not easily converted to the corresponding *E* isomers. On the basis of the above analysis, the relative stereochemistry of target compounds was established unambiguously.



Scheme 2. Reagents and conditions: (i) $NaNO_2$, HCl, H_2O, $NaHSO_3$, H_2O, reflux; (ii) Ethyl acetoacetate, AcOH, reflux; (iii) DMF-DMA, 50 °C. (iv) Appropriate aniline, AcOH, reflux.



Scheme 3. Reagents and conditions: (i) Py, DCM, 0 °C, r.t.; (ii) K_2CO_3, DMF, 60 °C; (iii) EtOH, 10 M HCl, reflux; (iv) DMF-DMA, CH_3CN, reflux; (v) appropriate aniline, AcOH, reflux.

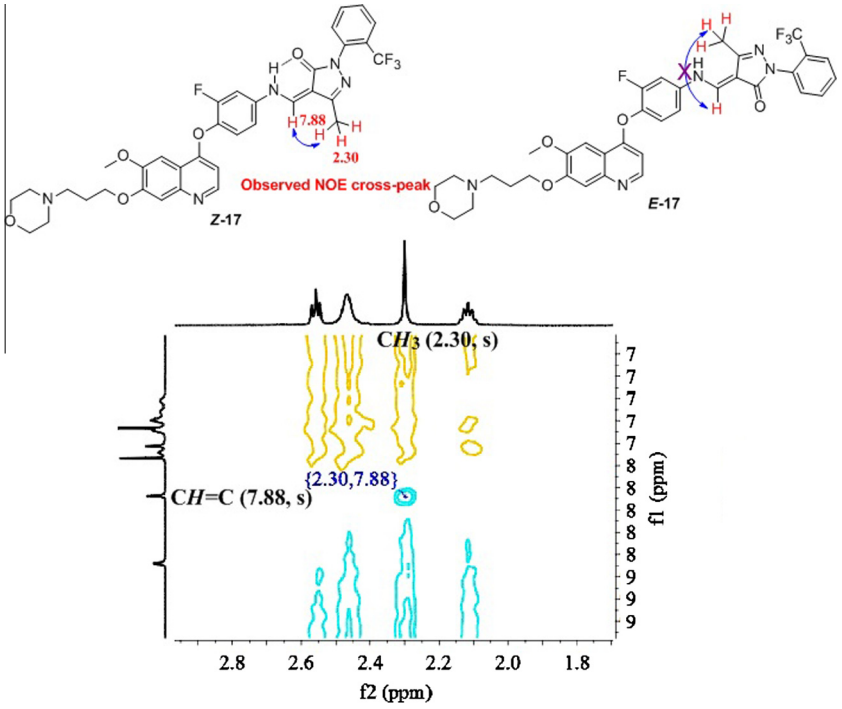


Fig. 3. Key NOESY of representative compound **17.**

3. Pharmacology

3.1. Cytotoxic activities against tumor cells assay

The antiproliferative activities of compounds **12–32** and **37–46** were evaluated against HT-29, H460, A549, MKN-45, and U87MG cell lines by 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} (inhibitory concentration 50%) were the averages of three determinations and calculated by using the Bacus Laboratories Incorporated Slide Scanner (Bliss) software.

3.2. HTRF kinase assay

The c-Met kinase activity was evaluated by the use of homogeneous time-resolved fluorescence (HTRF) assays, as previously reported protocol [25,26]. 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.

4. Results and discussion

4.1. In vitro cytotoxic activities and structure activity relationships

All the target compounds **12–32** and **37–46** were evaluated for their antitumor activities against non-small cell lung cancer cell line (A549), human lung cancer (H460), human colorectal cancer cell line (HT-29), human gastric cancer (MKN-45), and human glioblastoma cell line (U87MG) by using MTT assay with foretinib as the positive control. The results 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 activities against the different cancer cells with potencies in the single-digit μM range, which suggested that introduction of *N*-Aryl-pyrazolone-4-imino and 2,4-imidazolinedione moiety as the 5-atom linker maintained the potent cytotoxicity. In general, most of them displayed high selectivity toward HT-29, H460 and MKN-45 cancer cells. Notably, compounds **17** and **38** exhibited more potent antitumor activities against all tested cell lines than foretinib with IC_{50} values ranging from 0.02 to 1.06 μM.

In addition, it was worth noting that compounds with the same R_2 groups but different R_1 groups showed minor differences in cytostatic activity, such as compounds **13**, **17**, **21** and **44**, showing comparable potency with IC_{50} values ranging from 0.18 to 0.37 μM against H460 cells. In contrast, the activities of compounds with the same R_1 groups but different R_2 groups were markedly different. Introduction of mono-EWGs and double-electron-withdrawing groups (double-EWGs) had a positive effect on the cytotoxic activity, but the electron-donating groups (EDGs) had a negative effect. For example, compound **16**, with no substituent on the phenyl ring, displayed strong cytotoxicity with an IC_{50} of 0.20 μM against HT-29 cells. The introduction of EWGs (**17**, R_2 = 2-trifluoromethyl, IC_{50} = 0.14 μM; **14**, R_2 = 4-fluoro, IC_{50} = 0.16 μM) led to an obvious improvement in antitumor activity, which could be further confirmed by compounds **13**, **21**, **32**, and **40**. On the contrary, the addition of EDGs (**29, 31, 39** and **45** $R_2 = CH_3$ or OCH_3, IC_{50} = 0.98 to 2.61 μM) caused the potency reduce by 5.58- to 14.2-fold against H460 cells, and the same trend was observed for compounds **30** (IC_{50} = 1.10 μM [A549]), **37** (IC_{50} = 1.20 μM [A549]), and **43** (IC_{50} = 1.32 μM [A549]), which compared with (**16**, R_2 = H, IC_{50} = 0.20 μM). However, incorporation of double-EWGs (**19**, R_2 = 3-chloro-4-fluoro, IC_{50} = 0.16 μM; **22**, R_2 = 3,4-difluoro, IC_{50} = 0.19 μM) showed minor discrepancy in cytostatic activity compared with mono-EWGs (**40**, R_2 = 4-fluoro, IC_{50} = 0.17 μM). The pharmacological data suggested that a proper degree of electron density on pyrazolone-4-imino and 2,4-imidazolinedione moiety was probably necessary to improve the antitumor activity.

4.2. In vitro enzymatic assays

As shown in Table 2, the five tested compounds all exhibited excellent c-Met enzymatic potency, suggesting that the inhibition of c-Met is a candidate underlying mechanism for the antitumor effect. Compound **17** showed the most potent activity with an IC_{50} value of 2.20 nM, which was comparable to that of the positive control, foretinib (IC_{50} = 1.89 nM), indicating that this compound deserves further study with regard to its application in the treatment of cancer.

4.3. Enzymatic selectivity assays

To examine the selectivity of compound **17** on c-Met over other kinases, it was screened against 7 other tyrosine kinases (Table 3). Compared with its high potency against c-Met (IC_{50} = 2.20 nM), **17** also exhibited inhibitory effects against c-Kit, Flt-3, Ron, Flt-1 and PDGFRα, although the potency was 1.1- to 15.9-fold lower than that against c-Met. However, compound **17** showed weak kinase inhibition activity against VEGFR-2 (IC_{50} = 325.51 nM) with compared to foretinib. Moreover, this compound showed little or no kinase inhibition activity against EGFR kinase (IC_{50} > 10 μM). These data suggested that compound **17** is a promising selective multi-target kinase inhibitor.

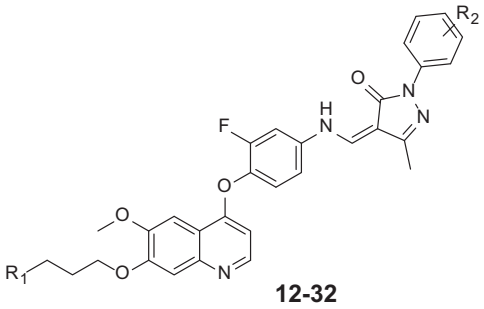
5. Conclusion

In summary, two series of 6,7-disubstituted-4-phenoxyquinoline derivatives bearing 2,4-imidazolinedione/pyrazolone scaffold were designed, synthesized and their chemical structures as well as the relative stereochemistry were confirmed. The synthesized compounds were evaluated for their biological activity, and most of them showed moderate to significant cytotoxicity and high selectivity against HT-29, H460 and A549 cancer cell lines. In particular, the most promising compound **17** (c-Met IC_{50} = 2.20 nM, a multi-target tyrosine kinase inhibitor) showed the most potent antitumor activities with IC_{50} values of 0.14 μM, 0.18 μM, 0.09 μM, 0.03 μM, and 1.06 μM against HT-29, H460, A549, MKN-45, and U87MG cell lines, respectively. The structure-activity relationships (SARs) analyses indicated that the replacement of the cyclopropane-1,1-dicarboxamide framework of foretinib with the *N*-Aryl-pyrazolone-4-imino and 2,4-imidazolinedione moiety maintained the potent cytotoxicity. Moreover, compounds with mono/double-EWGs on the phenyl ring (moiety B) were more active than those without substituents or EDGs, especially trifluoromethyl groups at 2-position on the phenyl ring (moiety B) were more active than those with methyl groups or methoxy groups. Further studies on structural optimization and biological activities about these derivatives are still underway in our laboratory and will be reported in the future.

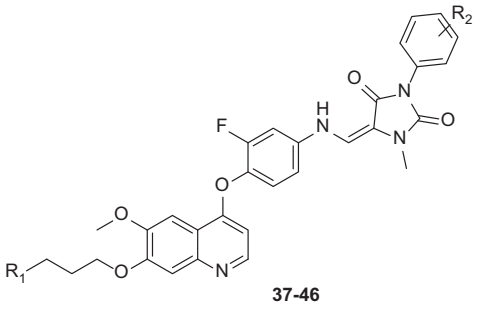
6. Experimental

Reagent and General Procedures Unless otherwise specified, all melting points were obtained on a Büchi Melting Point B-540 apparatus (Büchi Labortechnik, Flawil, Switzerland) and were uncorrected. 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. Mass spectra (MS) were taken in ESI mode on Agilent 1100 LC-MS (Agilent, Palo Alto, CA, U.S.A.). ^1H 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. All materials were obtained from commercial suppliers and were used without further purification. The IR spectra were recorded by means of the KBr pellet technique on a Bruker FTS 135 spectrometer. Column chromatography was run on silica gel (200–300 mesh) from Qingdao Ocean Chemicals (Qingdao, Shandong, China).

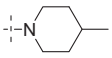
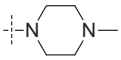
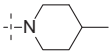
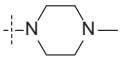
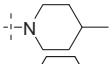
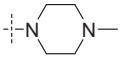
Table 1
Structures and cytotoxic activities of compound **12**–**32** and **37**–**46** against HT-29, H460, A549, MKN-45, and U87MG cell lines *in vitro*.



12-32



37-46

Compd.	R_1	R_2	IC_{50} (μMol/L) ± SD[a]				
			HT-29	H460	A549	MKN-45	U87MG
12		H	0.25 ± 0.02	0.28 ± 0.02	0.25 ± 0.05	0.13 ± 0.01	**1.05 ± 0.05**
13		2-CF_3	**0.15 ± 0.01**	**0.18 ± 0.01**	0.13 ± 0.01	0.09 ± 0.02	1.12 ± 0.02
14		4-F	**0.16 ± 0.02**	**0.20 ± 0.03**	0.14 ± 0.04	0.33 ± 0.01	1.90 ± 0.21
15		3,4-$(F)_2$	0.20 ± 0.01	0.27 ± 0.02	0.63 ± 0.05	0.12 ± 0.01	1.97 ± 0.12
16		H	0.20 ± 0.03	0.39 ± 0.06	0.53 ± 0.05	0.32 ± 0.08	ND
17		2-CF_3	**0.14 ± 0.02**	**0.18 ± 0.03**	**0.09 ± 0.02**	**0.03 ± 0.001**	**1.06 ± 0.05**
18		4-Cl	0.20 ± 0.01	0.27 ± 0.03	**0.06 ± 0.02**	0.15 ± 0.002	1.21 ± 0.07
19		3-Cl,4-F	**0.16 ± 0.01**	0.24 ± 0.03	0.47 ± 0.01	0.15 ± 0.004	1.70 ± 0.22
20		H	0.35 ± 0.03	0.48 ± 0.02	0.77 ± 0.02	0.15 ± 0.007	ND
21		2-CF_3	**0.15 ± 0.02**	**0.19 ± 0.02**	0.33 ± 0.03	0.08 ± 0.003	1.23 ± 0.01
22		3,4-$(F)_2$	**0.19 ± 0.04**	0.28 ± 0.03	0.32 ± 0.03	0.23 ± 0.02	2.50 ± 0.02
23		H	0.25 ± 0.02	0.36 ± 0.07	0.34 ± 0.03	0.19 ± 0.02	**0.52 ± 0.02**
24		3-Cl,4-F	0.29 ± 0.02	0.40 ± 0.05	0.12 ± 0.05	0.12 ± 0.01	1.20 ± 0.02
25		H	0.23 ± 0.03	0.38 ± 0.07	0.62 ± 0.05	0.29 ± 0.08	ND
26		4-F	0.22 ± 0.02	0.27 ± 0.08	0.46 ± 0.07	0.16 ± 0.03	2.24 ± 0.03
27		3-Cl,4-F	0.32 ± 0.02	0.36 ± 0.07	0.21 ± 0.03	0.10 ± 0.02	2.20 ± 0.03
28		2-CH_3	1.12 ± 0.04	1.59 ± 0.15	1.02 ± 0.08	0.66 ± 0.05	2.56 ± 0.25
29		2-CH_3	1.17 ± 0.05	1.53 ± 0.11	1.03 ± 0.10	0.62 ± 0.06	2.62 ± 0.22
30		4-OCH_3	1.32 ± 0.07	1.64 ± 0.10	1.10 ± 0.06	0.76 ± 0.08	2.89 ± 0.35
31		4-OCH_3	1.35 ± 0.06	1.68 ± 0.08	1.12 ± 0.09	0.86 ± 0.09	2.88 ± 0.32
32		2-CH_3	1.26 ± 0.05	1.61 ± 0.07	1.06 ± 0.11	0.64 ± 0.04	2.66 ± 0.36
37		2-CH_3	1.30 ± 0.04	1.69 ± 0.05	1.20 ± 0.06	0.66 ± 0.05	2.86 ± 0.05
38		2-CF_3	**0.14 ± 0.03**	**0.20 ± 0.03**	**0.10 ± 0.002**	**0.02 ± 0.001**	**1.01 ± 0.07**
39		2-CH_3	1.11 ± 0.09	1.40 ± 0.01	0.83 ± 0.01	0.77 ± 0.03	2.23 ± 0.31
40		2-F	**0.17 ± 0.04**	**0.19 ± 0.03**	0.12 ± 0.02	0.09 ± 0.01	1.30 ± 0.02
41		2-OCH_3	1.13 ± 0.11	1.47 ± 0.12	1.20 ± 0.13	0.56 ± 0.15	ND
42		4-Cl	0.26 ± 0.02	0.36 ± 0.01	0.23 ± 0.07	0.15 ± 0.11	1.43 ± 0.01
43		2-CH_3	1.81 ± 0.14	2.22 ± 0.12	1.32 ± 0.13	1.01 ± 0.18	2.50 ± 0.12
44		2-CF_3	**0.18 ± 0.01**	0.37 ± 0.03	0.21 ± 0.02	0.15 ± 0.02	1.35 ± 0.08
45		2-CH_3	2.30 ± 0.13	2.61 ± 0.17	1.77 ± 0.12	1.02 ± 0.02	2.36 ± 0.17
46		3-Cl,4-F	0.25 ± 0.05	0.26 ± 0.02	0.15 ± 0.03	0.12 ± 0.01	1.59 ± 0.22
Foretinib[b]			0.19 ± 0.01	0.21 ± 0.03	0.11 ± 0.01	0.032 ± 0.02	1.08 ± 0.12

Bold values show the IC_{50} 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.

*6.1. Preparation of 3-fluoro-4-(6,7-disubstituted quinolin-4-yloxy)anilines **(8a–e)***

The preparation of the key intermediates (**8a**–**e**) has been illustrated in detail in our laboratory previous study, so the synthesis method would not be listed here.

*6.1.1. 3-Fluoro-4-(6-methoxy-7-(3-(piperdine-1-yl)propoxy)quinolin-4-yloxy)aniline **(8a)***

This compound was obtained as gray solid in 85.5% yield. mp 196–197 °C. ESI-MS *m/z*: 426.3 $[M + H]^+$. 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; ^1H 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).

*6.1.2. 3-Fluoro-4-(6-methoxy-7-(3-(4-methylpiperdine-1-yl)propoxy) quinolin-4-yl-oxy)aniline **(8b)***

This compound was obtained as white solid in 77.4% yield. mp 193–194 °C. ESI-MS *m/z*: 440.3 $[M + H]^+$. ^1H NMR (300 MHz, $CDCl_3$)

Table 2
c-Met kinase activity of selected compounds **13, 17, 21, 38, 40,** and **Foretinib** *in vitro*.

Compd.	IC_{50} on c-Met (nM)[a]
13	5.04
17	2.20
21	6.63
38	2.75
40	8.78
Foretinib[b]	1.89

[a] The values are an average of triplicate separate determinations.
[b] Used as a positive control.

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).

6.1.3. 3-Fluoro-4-(6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy)quinolin-4-yloxy)aniline ***(8c)***

This compound was obtained as light yellow solid in 72.3% yield. mp 208–209 °C. ESI-MS *m/z*: 412.5 $[M+H]^+$. ^1H 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).

6.1.4. 3-Fluoro-4-(6-methoxy-7-(3-morpholinopropoxy)quinolin-4-yloxy)aniline ***(8d)***

This compound was obtained as white solid in 81.8% yield. mp 217–218 °C. ESI-MS *m/z*: 428.2 $[M+H]^+$, 450.1 $[M+Na]^+$. ^1H 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).

6.1.5. 3-Fluoro-4-(6-methoxy-7-(3-(4-methylpiperazine-1-yl)propoxy)quinolin-4-yl-oxy)aniline ***(8e)***

This compound was obtained as white solid in 77% yield. mp 201–202 °C. ESI-MS *m/z*: 441.4 $[M+H]^+$, 463.3 $[M+Na]^+$. ^1H 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).

6.2. Preparation of pyrazolone-based quinoline derivatives

6.2.1. General procedure for preparation intermediates of Phenylhydrazine hydrochloride ***(9a–h)***

To a mixture of substituted phenyl amine (0.06 mol) and 15% HCl (60 mL), $NaNO_2$ (5 g, 0.072 mol) in H_2O (200 mL) was added drop-wise at 0 °C. After the completion of addition, the reaction mixture was stirred at this temperature for 30 min. and then was dropped into the mixture of saturated solution of sodium hydrogen sulfite (22.5 g, 0.216 mol), keeping the reaction below 20 °C. Upon completing the addition, the reaction was heated under refluxed for 3 h and cooled to room temperature. The solid is filtered and washed with ethyl acetate and the cake was dried to give white solid **9a–h** yielded 90%.

Table 3
Inhibition of tyrosine kinases by compound **17** and Foretinib.

Compd.	Enzyme IC_{50}[a] in nM						
	c-Kit	Flt-3	PDGFRα	VEGFR-2	EGFR	Ron	Flt-1
17	2.30	8.38	32.23	325.51	>10,000	4.24	8.56
Foretinib[b]	6.72	5.61	6.78	4.86	2990	3.52	6.89

[a] Data presented is the mean ± SD value of three independent determinations.
[b] Used as a positive control.

6.2.2. General procedure for preparation of 3-methyl-1-(substituted phenyl)-1H-pyrazol-5(4H)-one ***(10a–h)***

To a solution of an appropriate intermediate **9a–h** (0.028 mol) and ethyl acetoacetate (0.034 mol) dissolved in acetic acid (10 mL), the reaction mixture was heated under refluxed with stirring until the starting materials could no longer be detected by TLC. The solvent was evaporated under reduced pressure and the residue was dissolved in ethyl acetate and saturated sodium bicarbonate solution, the mixture was washed with saturated sodium bicarbonate solution (20 mL × 3), brine (20 mL × 3) in sequence, and the organic phase was separated, dried, and evaporated. The crude product was crystallized from THF and Hexane to afford brown solids **10a–h**.

*6.2.2.1. 3-methyl-1-phenyl-1H-pyrazol-5(4H)-one (**10a**).* Yield 74.8%. mp 124–126 °C. ESI-MS *m/z*: 175.20 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, *J* = 8.0 Hz, 2H), 7.39 (t, *J* = 7.4 Hz, 2H), 7.18 (t, *J* = 7.2 Hz, 1H), 3.42 (s, 2H), 2.19 (s, 3H).

*6.2.2.2. 3-methyl1-(2-(trifluoromethyl)phenyl)-1H-pyrazol-5(4H)-one (**10b**).* Yield 74.5%. mp 122–123 °C. ESI-MS *m/z*: 243.20 $[M+H]^+$.

*6.2.2.3. 1-(4-fluorophenyl)-3-methyl-1H-pyrazol-5(4H)-one (**10c**).* Yield 74.2%. mp 125–127 °C. ESI-MS *m/z*: 193.19 $[M+H]^+$.

*6.2.2.4. 1-(4-chlorophenyl)-3-methyl-1H-pyrazol-5(4H)-one (**10d**).* Yield 7.5%. mp 123–124 °C. ESI-MS *m/z*: 210.14 $[M+H]^+$.

*6.2.2.5. 1-(3,4-difluorophenyl)-3-methyl-1H-pyrazol-5(4H)-one (**10e**).* Yield 74.2%. mp 122.2–123.3 °C. ESI-MS *m/z*: 211.18 $[M+H]^+$.

*6.2.2.6. 1-(3-chloro-4-fluorophenyl)-3-methyl-1H-pyrazol-5(4H)-one (**10f**).* Yield 74.3%. mp 125–127 °C. ESI-MS *m/z*: 227.63 $[M+H]^+$.

*6.2.2.7. 3-methyl-1-(o-tolyl)-1H-pyrazol-5(4H)-one (**10g**).* Yield 75.3%. mp 126–129 °C. ESI-MS *m/z*: 188.23 $[M+H]^+$.

*6.2.2.8. 1-(4-methoxyphenyl)-3-methyl-1H-pyrazol-5(4H)-one (**10h**).* Yield 75.5%. mp 124–126 °C. ESI-MS *m/z*: 204.23 $[M+H]^+$.

*6.2.3. General procedure for preparation of (Z)-4-((dimethylamino) methylene)-3-methyl-1-(substituted phenyl)-1H-pyrazol-5(4H)-one (**11a–h**)*

To a solution of an appropriate intermediate **10a–h** (0.023 mol) dissolved in *N*,*N*-Dimethylformamide dimethyl acetal (DMF-DMA) (20 mL). Upon completing the addition and the reaction mixture was stirred at 50 °C for 2 h and cooled to room temperature. The solid is filtered and washed with ether, the cake was dried to give yellow solid **11a–h**.

*6.2.3.1. (Z)-4-((dimethylamino)methylene)-3-methyl-1-phenyl-1H-pyrazol-5(4H)-one (**11a**).* Yield 95.4%. mp 134–136 °C. ESI-MS *m/z*: 230.2 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, *J* = 7.7 Hz,

2H), 7.33 (t, *J* = 8.0 Hz, 2H), 7.07 (t, *J* = 7.4 Hz, 1H), 6.95 (s, 1H), 3.82 (s, 3H), 3.23 (s, 3H), 2.16 (s, 3H).

*6.2.3.2. (Z)-4-((dimethylamino)methylene)-3-methyl-1-(2-(trifluoromethyl)phenyl)-1H-pyrazol-5. (4H)-one (**11b**).* Yield 94.8%. mp 133–134 °C. ESI-MS *m/z*: 298.2 $[M + H]^+$.

*6.2.3.3. (Z)-4-((dimethylamino)methylene)-1-(4-fluorophenyl)-3-methyl-1H-pyrazol-5(4H)-one (**11c**).* Yield 92.4%. mp 132–133 °C. ESI-MS *m/z*: 248.27 $[M + H]^+$.

*6.2.3.4. (Z)-1-(4-chlorophenyl)-4-((dimethylamino)methylene)-3-methyl-1H-pyrazol-5(4H)-one (**11d**).* Yield 93.6%. mp 135–137 °C. ESI-MS *m/z*: 265.72 $[M + H]^+$.

*6.2.3.5. (Z)-1-(3,4-difluorophenyl)-4-((dimethylamino)methylene)-3-methyl-1H-pyrazol-5(4H)-one (**11e**).* Yield 92.8%. mp 132.3–134 °C. ESI-MS *m/z*: 266.26 $[M + H]^+$.

*6.2.3.6. (Z)-1-(3-chloro-4-fluorophenyl)-4-((dimethylamino)methylene)-3-methyl-1H-pyrazol-5(4H)-one (**11f**).* Yield 94.2%. mp 131–132 °C. ESI-MS *m/z*: 282.71 $[M + H]^+$.

*6.2.3.7. (Z)-4-((dimethylamino)methylene)-3-methyl-1-(o-tolyl)-1H-pyrazol-5(4H)-one (**11g**).* Yield 95.2%. mp 130–132 °C. ESI-MS *m/z*: 243.30 $[M + H]^+$.

*6.2.3.8. (Z)-4-((dimethylamino)methylene)-1-(4-methoxyphenyl)-3-methyl-1H-pyrazol-5(4H)-one (**11h**).* Yield 94.8%. mp 131–133 °C. ESI-MS *m/z*: 259.30 $[M + H]^+$.

*6.3. General procedure for preparation of target compounds (**12–32**)*

To a solution of an appropriate aniline **8a–e** (0.486 mmol) and intermediate **11a–h** (0.65 mmol) dissolved in glacial acetic acid (10 mL), After the completion of addition and the reaction mixture was heated under refluxed with stirring until the starting materials could no longer be detected by TLC. The solvent was evaporated under reduced pressure and the residue was dissolved in DCM and saturated sodium bicarbonate solution, the mixture was washed with saturated sodium bicarbonate solution (20 mL × 3), brine (20 mL × 3) in sequence, and the organic phase was separated, dried, and evaporated. The crude product was purified by chromatography on silica gel using CH_2Cl_2/MeOH (35:1) to afford light yellow solid **12–32**.

*6.3.1. (Z)-4-(((3-fluoro-4-((6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy) quinolin-4-yl)oxy)phenyl)amino)methylene)-3-methyl-1-phenyl-1H-pyrazol-5(4H)-one (**12**)*

Light yellow solid, 77% yield. mp: 122–123 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (d, *J* = 4.9 Hz, 1H), 8.01 (d, *J* = 8.1 Hz, 2H), 7.87 (s, 1H), 7.56 (s, 1H), 7.49–7.39 (m, 3H), 7.34 (t, *J* = 8.5 Hz, 1H), 7.19 (t, *J* = 10.5 Hz, 2H), 7.09 (d, *J* = 8.7 Hz, 1H), 6.42 (d, *J* = 5.1 Hz, 1H), 4.29 (t, *J* = 6.6 Hz, 2H), 4.06 (s, 3H), 2.69 (t, *J* = 7.3 Hz, 2H), 2.56 (s, 4H), 2.35 (s, 3H), 2.19 (dt, *J* = 13.6, 6.7 Hz, 2H), 1.81 (t, *J* = 13.8, 4H). ESI-MS *m/z*: 596.4 $(M + H)^+$. Anal. calcd. for $C_{34}H_{34}FN_5O_4$ (%): C, 68.56; H, 5.75; N, 11.76. Found (%): C, 68.73; H, 5.77; N, 11.96.

*6.3.2. (Z)-4-(((3-fluoro-4-((6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy) quinolin-4-yl)oxy)phenyl)amino)methylene)-3-methyl-1-(2-(trifluoromethyl)phenyl)-1H-pyrazol-5(4H)-one (**13**)*

Light yellow solid, 78% yield. mp: 121–122 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.42 (brs, 1H), 8.52 (d, *J* = 5.1 Hz, 1H), 7.90 (s, 1H), 7.56–7.49 (m, 2H), 7.46 (s, 1H), 7.34 (t, *J* = 8.1 Hz, 2H), 7.25–7.21 (m, 2H), 7.17 (d, *J* = 10.5 Hz, 1H), 7.08 (d, *J* = 8.8 Hz, 1H), 6.42 (d, *J* = 5.2 Hz, 1H), 4.29 (t, *J* = 6.5 Hz, 2H), 4.08 (s, 3H), 2.71 (t, *J* = 7.4 Hz, 2H), 2.57 (t, *J* = 14.2, 4H), 2.35 (s, 3H), 2.18 (dt, *J* = 12.6, 6.1 Hz, 2H), 1.81 (t, *J* = 13.8, 4H). ESI-MS *m/z*: 664. 6 $(M + H)^+$. Anal. calcd. for $C_{35}H_{33}F_4N_5O_4$ (%): C, 63.34; H, 5.01; N, 10.55. Found (%): C, 63.73; H, 5.07; N, 10.56.

*6.3.3. (Z)-4-(((3-fluoro-4-((6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy) quinolin-4-yl)oxy)phenyl)amino)methylene)-1-(4-fluorophenyl)-3-methyl-1H-pyrazol-5(4H)-one (**14**)*

Light yellow solid, 75% yield. mp: 132–133 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.56 (brs, 1H), 8.52 (d, *J* = 3.0 Hz, 1H), 7.98 (dd, *J* = 8.9, 4.9 Hz, 2H), 7.89 (s, 1H), 7.56 (d, *J* = 4.3 Hz, 1H), 7.46 (s, 1H), 7.36 (t, *J* = 8.5 Hz, 1H), 7.19 (dd, *J* = 10.2, 1.5 Hz, 1H), 7.13 (t, *J* = 8.6 Hz, 3H), 6.43 (d, *J* = 4.7 Hz, 1H), 4.29 (t, *J* = 6.3 Hz, 2H), 4.06 (s, 3H), 2.71 (t, *J* = 5.8 Hz, 2H), 2.58 (d, *J* = 0.7 Hz, 4H), 2.35 (s, 3H), 2.24–2.13 (m, 2H), 1.82 (t, *J* = 13.9, 4H). ESI-MS *m/z*: 614.4 $(M + H)^+$. Anal. calcd. for $C_{34}H_{33}F_2N_5O_4$ (%): C, 66.55; H, 5.42; N, 11.41. Found (%): C, 66.73; H, 5.47; N, 11.46.

*6.3.4. (Z)-1-(3,4-difluorophenyl)-4-(((3-fluoro-4-((6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl)amino) methylene)-3-methyl-1H-pyrazol-5(4H)-one (**15**)*

Light yellow solid, 74% yield. mp: 126–127 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.57 (brs, 1H), 8.53 (d, *J* = 3.1 Hz, 1H), 7.98 (dd, *J* = 8.7, 4.9 Hz, 2H), 7.85 (s, 1H), 7.58 (d, *J* = 4.2 Hz, 1H), 7.46 (s, 1H), 7.37 (t, *J* = 8.5 Hz, 1H), 7.19 (dd, *J* = 10.2, 1.5 Hz, 1H), 7.15 (t, *J* = 8.5 Hz, 2H), 6.43 (d, *J* = 4.7 Hz, 1H), 4.28 (t, *J* = 6.2 Hz, 2H), 4.06 (s, 3H), 2.70 (t, *J* = 5.9 Hz, 2H), 2.57 (d, *J* = 0.8 Hz, 4H), 2.34 (s, 3H), 2.25–2.14 (m, 2H), 1.83 (s, 4H). ESI-MS *m/z*: 632. 4 $(M + H)^+$. Anal. calcd. for $C_{34}H_{32}F_3N_5O_4$ (%):C, 64.65; H, 5.11; N, 11.09. Found (%): C, 64.73; H, 5.17; N, 11.09.

*6.3.5. (Z)-4-(((3-fluoro-4-((6-methoxy-7-(3-morpholinopropoxy) quinolin-4-yl)oxy)phenyl)amino)methylene)-3-methyl-1-phenyl-1H-pyrazol-5(4H)-one (**16**)*

Light yellow solid, 72% yield. mp: 128–129 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.50 (brs, 1H), 8.51 (d, *J* = 3.9 Hz, 1H), 7.98 (d, *J* = 8.8 Hz, 2H), 7.84 (s, 1H), 7.57 (s, 1H), 7.46 (s, 1H), 7.35 (dd, *J* = 17.2, 8.6 Hz, 4H), 7.17 (d, *J* = 10.5 Hz, 1H), 7.10 (d, *J* = 8.3 Hz, 1H), 6.42 (d, *J* = 4.3 Hz, 1H), 4.29 (t, *J* = 6.3 Hz, 2H), 4.06 (s, 3H), 3.74 (t, 4H), 2.59 (t, *J* = 7.0 Hz, 2H), 2.50 (s, 4H), 2.34 (s, 3H), 2.19–2.10 (m, 2H). ESI-MS *m/z*: 612.5 $(M + H)^+$. Anal. calcd. for $C_{34}H_{34}FN_5O_5$ (%):C, 66.76; H, 5.60; N, 11.45. Found (%): C, 66.78; H, 5.67; N, 11.46.

*6.3.6. (Z)-4-(((3-fluoro-4-((6-methoxy-7-(3-morpholinopropoxy) quinolin-4-yl)oxy)phenyl)amino)methylene)-3-methyl-1-(2-(trifluoromethyl)phenyl)-1H-pyrazol-5(4H)-one (**17**)*

Light yellow solid, 76% yield. mp: 122–123 °C. IR (KBr) cm^{-1}: 3582.3, 1955.9, 2852.7, 2812.2, 1688.5, 1621.9, 1597.5, 1509.9, 1478.8, 1455.0, 1432.2, 1348.2, 1318.1, 1251.2, 1212.4, 1146.5, 1125.9, 1062.1, 1035.0, 855.2; ^{1}H NMR (600 MHz, $CDCl_3$) δ11.42 (brs, 1H),8.49 (d, *J* = 4.6 Hz, 1H), 7.86 (s, 1H), 7.52 (s, 1H), 7.45 (s, 1H), 7.43 (s, 1H), 7.26 (s, 2H), 7.22–7.15 (m, 2H), 7.14–7.08 (m, 1H), 7.02 (d, *J* = 8.5 Hz, 1H), 6.38 (d, *J* = 4.6 Hz, 1H), 4.26 (t, *J* = 6.4 Hz, 2H), 4.05 (s, 3H), 3.72 (t, *J* = 4.5 Hz, 4H), 2.56 (t, *J* = 7.3 Hz, 2H), 2.46 (t, *J* = 4.7 Hz, 4H), 2.30 (s, 3H), 2.16–2.05 (m, 2H). ^{13}C NMR (600 MHz, $CDCl_3$) δ 160.53, 159.75, 155.52, 153.90, 152.62, 150.23, 148.75, 146.74, 145.55, 138.22, 138.04, 137.82, 136.23, 133.41, 131.04, 130.42, 129.86, 128.25, 124.22, 116.52, 115.77, 109.86, 109.65, 108.73, 102.42, 99.84, 67.45, 66.96 (2C), 56.42, 55.64, 53.86 (2C), 25.91, 20.93; ESI-MS *m/z*: 680.66 $(M + H)^+$. Anal. calcd. for $C_{35}H_{33}F_4N_5O_5$ (%):C, 61.85; H, 4.89; N, 10.30. Found (%): C, 61.87; H, 4.90; N, 10.36.

*6.3.7. (Z)-1-(4-chlorophenyl)-4-(((3-fluoro-4-((6-methoxy-7-(3-morpholinopropoxy)quinolin-4-yl)oxy)phenyl)amino)methylene)-3-methyl-1H-pyrazol-5(4H)-one (**18**)*

Light yellow solid, 72% yield. mp: 142–143 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.51 (brs, 1H), 8.52 (d, *J* = 3.9 Hz, 1H), 7.99 (d, *J* = 8.7 Hz, 2H), 7.86 (s, 1H), 7.56 (s, 1H), 7.46 (s, 1H), 7.36 (dd, *J* = 17.1, 8.6 Hz, 3H), 7.18 (d, *J* = 10.6 Hz, 1H), 7.10 (d, *J* = 8.5 Hz, 1H), 6.42 (d, *J* = 4.3 Hz, 1H), 4.29 (t, *J* = 6.3 Hz, 2H), 4.06 (s, 3H), 3.74 (t, 4H), 2.59 (t, *J* = 7.0 Hz, 2H), 2.50 (s, 4H), 2.34 (s, 3H), 2.19–2.10 (m, 2H). ESI-MS *m/z*: 646.2 $(M + H)^+$. Anal. calcd. for $C_{34}H_{33}ClFN_5O_5$ (%):C, 63.20; H, 5.15; N, 10.84. Found (%): C, 65.73; H, 5.37; N, 10.96.

*6.3.8. (Z)-1-(3-chloro-4-fluorophenyl)-4-(((3-fluoro-4-((6-methoxy-7-(3-morpholinopropoxy)quinolin-4-yl)oxy)phenyl)amino)methylene)-3-methyl-1H-pyrazol-5(4H)-one (**19**)*

Light yellow solid, 74% yield. mp 122–123 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.45 (br, 1H), 8.53 (d, *J* = 4.8 Hz, 1H), 7.97 (dd, *J* = 11.9, 7.4 Hz, 1H), 7.88 (s, 1H), 7.83–7.73 (m, 1H), 7.57 (s, 1H), 7.47 (s, 1H), 7.36 (t, *J* = 8.5 Hz, 1H), 7.25–7.15 (m, 2H), 7.11 (d, *J* = 9.3 Hz, 1H), 6.43 (d, *J* = 4.9 Hz, 1H), 4.30 (t, *J* = 6.5 Hz, 2H), 4.06 (s, 3H), 3.79–3.70 (m, 4H), 2.60 (t, *J* = 7.0 Hz, 2H), 2.51 (s, 4H), 2.34 (s, 3H), 2.20–2.11 (m, 2H). ESI-MS *m/z*: 664.2 $(M + H)^+$. Anal. calcd. for $C_{34}H_{32}ClF_2N_5O_5$ (%):C, 61.49; H, 4.86; N, 10.55. Found (%): C, 61.50; H, 4.89; N, 10.56.

*6.3.9. (Z)-4-(((3-fluoro-4-((6-methoxy-7-(3-(piperidin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl)amino)methylene)-3-methyl-1-phenyl-1H-pyrazol-5(4H)-one (**20**)*

Light yellow solid, 74% yield. mp: 132–133 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.61 (brs, 1H), 8.52 (d, *J* = 4.9 Hz, 1H), 8.01 (d, *J* = 8.0 Hz, 2H), 7.87 (s, 1H), 7.56 (s, 1H), 7.49–7.40 (m, 3H), 7.34 (t, *J* = 8.4 Hz, 1H), 7.19 (t, *J* = 10.9 Hz, 2H), 7.09 (d, *J* = 8.7 Hz, 1H), 6.42 (d, *J* = 5.1 Hz, 1H), 4.27 (t, *J* = 6.6 Hz, 2H), 4.05 (s, 3H), 2.54 (t, *J* = 7.2 Hz, 2H), 2.43 (s, 4H), 2.35 (s, 3H), 2.15 (dt, *J* = 11.7, 5.9 Hz, 2H), 1.67–1.55 (m, 4H), 1.46 (d, *J* = 4.1 Hz, 2H). ESI-MS *m/z*: 610.5 $(M + H)^+$. Anal. calcd. for $C_{35}H_{36}FN_5O_4$ (%):C, 68.95; H, 5.95; N, 11.49. Found (%): C, 68.97; H, 5.97; N, 11.56.

*6.3.10. (Z)-4-(((3-fluoro-4-((6-methoxy-7-(3-(piperidin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl)amino)methylene)-3-methyl-1-(2-(trifluoromethyl)phenyl)-1H-pyrazol-5(4H)-one (**21**)*

Light yellow solid, 71% yield. mp: 125–126 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.42 (br, 1H), 8.52 (d, *J* = 5.1 Hz, 1H), 7.90 (s, 1H), 7.57–7.49 (m, 2H), 7.44 (d, *J* = 11.8 Hz, 1H), 7.37–7.30 (m, 2H), 7.27–7.20 (m, 2H), 7.18–7.13 (m, 1H), 7.09–7.05 (m, 1H), 6.42 (d, *J* = 5.0 Hz, 1H), 4.27 (t, *J* = 6.5 Hz, 2H), 4.05 (s, 3H), 2.59–2.50 (m, 2H), 2.43 (d, *J* = 1.3 Hz, 4H), 2.35 (s, 3H), 2.15 (dt, *J* = 13.6, 6.8 Hz, 2H), 1.61 (dt, *J* = 10.7, 5.4 Hz, 4H), 1.46 (d, *J* = 4.7 Hz, 2H). ESI-MS *m/z*: 678.69 $(M + H)^+$. Anal. calcd. for $C_{36}H_{35}F_4N_5O_4$ (%):C, 63.80; H, 5.21; N, 10.33. Found (%): C, 63.81; H, 5.27; N, 10.36.

*6.3.11. (Z)-1-(3,4-difluorophenyl)-4-(((3-fluoro-4-((6-methoxy-7-(3-(piperidin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl)amino)methylene)-3-methyl-1H-pyrazol-5(4H)-one (**22**)*

Light yellow solid, 78% yield. mp 137–139 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.42 (brs, 1H), 8.52 (d, *J* = 5.1 Hz, 1H), 7.90 (s, 1H), 7.57–7.49 (m, 2H), 7.44 (d, *J* = 11.8 Hz, 1H), 7.37–7.30 (m, 1H), 7.27–7.20 (m, 2H), 7.18–7.13 (m, 1H), 7.09–7.05 (m, 1H), 6.42 (d, *J* = 5.0 Hz, 1H), 4.27 (t, *J* = 6.5 Hz, 2H), 4.05 (s, 3H), 2.59–2.50 (m, 2H), 2.43 (d, *J* = 1.3 Hz, 4H), 2.35 (s, 3H), 2.15 (dt, *J* = 13.6, 6.8 Hz, 2H), 1.61 (dt, *J* = 10.7, 5.4 Hz, 4H), 1.46 (d, *J* = 4.7 Hz, 2H). ESI-MS *m/z*: 646.6 $(M + H)^+$. Anal. calcd. for $C_{35}H_{34}F_3N_5O_4$ (%):C, 65.11; H, 5.31; N, 10.85. Found (%): C, 65.13; H, 5.37; N, 10.86.

*6.3.12. (Z)-4-(((3-fluoro-4-((6-methoxy-7-(3-(4-methylpiperidin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl)amino)methylene)-3-methyl-1-phenyl-1H-pyrazol-5(4H)-one (**23**)*

Light yellow solid, 71% yield. mp 145–147 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.42 (brs, 1H), 8.52 (d, *J* = 4.8 Hz, 1H), 7.94 (d, *J* = 8.7 Hz, 2H), 7.86 (s, 1H), 7.54–7.48 (m, 4H), 7.45 (d, *J* = 13.0 Hz, 1H), 7.34 (t, *J* = 8.5 Hz, 1H), 7.17 (dd, *J* = 10.7, 1.9 Hz, 1H), 7.12 (d, *J* = 8.6 Hz, 1H), 6.43 (d, *J* = 5.0 Hz, 1H), 4.29 (t, *J* = 6.6 Hz, 2H), 4.05 (s, 3H), 2.92 (d, *J* = 11.2 Hz, 2H), 2.58 (t, *J* = 7.3 Hz, 2H), 2.38 (s, 3H), 2.20–2.14 (m, 2H), 1.98 (t, *J* = 11.2 Hz, 2H), 1.68 (d, *J* = 12.5 Hz, 2H), 1.31–1.22 (m, 3H), 0.97 (d, *J* = 6.3 Hz, 3H). ESI-MS *m/z*: 624.4 $(M + H)^+$. Anal. calcd. for $C_{36}H_{38}FN_5O_4$ (%):C, 69.32; H, 6.14; N, 11.23. Found (%): C, 69.33; H, 6.17; N, 11.26.

*6.3.13. (Z)-1-(3-chloro-4-fluorophenyl)-4-(((3-fluoro-4-((6-methoxy-7-(3-(4-methylpiperidin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl)amino)methylene)-3-methyl-1H-pyrazol-5(4H)-one (**24**)*

Light yellow solid, 72% yield. mp 136–138 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.48 (brs, 1H), 8.52 (d, *J* = 4.8 Hz, 1H), 7.96 (dd, *J* = 11.0, 8.5 Hz, 1H), 7.89 (s, 1H), 7.79 (d, *J* = 9.0 Hz, 1H), 7.56 (s, 1H), 7.44 (s, 1H), 7.36 (t, *J* = 8.5 Hz, 1H), 7.20 (q, *J* = 9.1 Hz, 2H), 7.11 (d, *J* = 9.1 Hz, 1H), 6.43 (d, *J* = 5.0 Hz, 1H), 4.27 (t, *J* = 6.7 Hz, 2H), 4.06 (s, 3H), 2.93 (d, *J* = 11.3 Hz, 2H), 2.56 (t, *J* = 7.4 Hz, 2H), 2.35 (s, 3H), 2.20–2.10 (m, 2H), 1.96 (t, *J* = 11.3 Hz, 2H), 1.64 (d, *J* = 12.6 Hz, 2H), 1.31–1.24 (m, 3H), 0.94 (d, *J* = 6.2 Hz, 3H). ESI-MS *m/z*: 676.4 $(M + H)^+$. Anal. calcd. for $C_{36}H_{36}ClF_2N_5O_4$ (%):C, 63.95; H, 5.37; N, 10.36. Found (%): C,63.98; H, 5.39; N, 10.39.

*6.3.14. (Z)-4-(((3-fluoro-4-((6-methoxy-7-(3-(4-methylpiperazin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl)amino)methylene)-3-methyl-1-phenyl-1H-pyrazol-5(4H)-one (**25**)*

Light yellow solid, 70% yield. mp 152–153 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.56 (brs, 1H), 8.53 (d, *J* = 3.4 Hz, 1H), 8.01 (d, *J* = 8.0 Hz, 2H), 7.87 (s, 1H), 7.56 (s, 1H), 7.48–7.39 (m, 3H), 7.35 (t, *J* = 8.5 Hz, 1H), 7.20 (t, *J* = 9.5 Hz, 2H), 7.10 (d, *J* = 9.3 Hz, 1H), 6.43 (d, *J* = 4.0 Hz, 1H), 4.28 (t, *J* = 6.6 Hz, 2H), 4.06 (s, 3H), 2.54 (br, *J* = 14.3, 10.9, 5.6 Hz, 10H), 2.36 (s, 3H), 2.31 (s, 3H), 2.15 (dt, *J* = 13.4, 6.7 Hz, 2H). ESI-MS *m/z*: 625.6 $(M + H)^+$. Anal. calcd. for $C_{35}H_{37}FN_6O_4$ (%):C, 67.29; H, 5.97; N, 13.45. Found (%): C, 67.33; H, 5.99; N, 13.46.

*6.3.15. (Z)-4-(((3-fluoro-4-((6-methoxy-7-(3-(4-methylpiperazin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl)amino)methylene)-1-(4-fluorophenyl)-3-methyl-1H-pyrazol-5(4H)-one (**26**)*

Light yellow solid, 78% yield. mp 135–136 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.42 (brs, 1H), 8.51 (d, *J* = 4.9 Hz, 1H), 7.93 (d, *J* = 8.5 Hz, 2H), 7.87 (s, 1H), 7.57–7.50 (m, 3H), 7.45 (d, *J* = 12.7 Hz, 1H), 7.36 (t, *J* = 8.5 Hz, 1H), 7.19 (d, *J* = 10.7 Hz, 1H), 7.11 (d, *J* = 8.6 Hz, 1H), 6.43 (d, *J* = 4.9 Hz, 1H), 4.27 (t, *J* = 6.5 Hz, 2H), 4.06 (s, 3H), 2.53 (br, *J* = 16.2, 13.0, 7.1 Hz, 10H), 2.35 (s, 3H), 2.30 (s, 3H), 2.19–2.13(m, *J* = 12.6, 6.3 Hz, 2H). ESI-MS *m/z*: 643.4 $(M + H)^+$. Anal. calcd. for $C_{35}H_{36}F_2N_6O_4$ (%):C, 65.41; H, 5.65; N, 13.08. Found (%): C, 65.43; H, 5.67; N, 13.16.

*6.3.16. (Z)-1-(3-chloro-4-fluorophenyl)-4-(((3-fluoro-4-((6-methoxy-7-(3-(4-methylpiperazin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl)amino)methylene)-3-methyl-1H-pyrazol-5(4H)-one (**27**)*

Light yellow solid, 77% yield. mp 135–136 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.48 (brs, 1H), 8.53 (d, *J* = 5.1 Hz, 1H), 8.16 (dd, *J* = 7.4, 1.1 Hz, 1H), 7.99–7.91 (m, 1H), 7.88 (s, 1H), 7.56 (s, 1H), 7.46 (s, 1H), 7.36 (t, *J* = 7.0 Hz, 1H), 7.19 (dd, *J* = 10.4, 6.5 Hz, 2H), 7.11 (d, *J* = 8.5 Hz, 1H), 6.43 (d, *J* = 5.1 Hz, 1H), 4.28 (t, *J* = 6.6 Hz, 2H), 4.06 (s, 3H), 2.55 (br, 10H), 2.35 (s, 3H), 2.31 (s, 3H),

2.19–2.09 (m, 2H). ESI-MS *m/z*: 677.3 $(M+H)^+$. Anal. calcd. for $C_{35}H_{35}ClF_2N_6O_4$ (%):C, 62.08; H, 5.21; N, 12.41. Found (%): C, 62.09; H, 5.23; N, 12.44.

*6.3.17. (Z)-4-(((3-fluoro-4-((6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl)amino)methylene)-3-methyl-1-(o-tolyl)-1H-pyrazol-5(4H)-one (**28**)*

Light yellow solid, 76% yield. mp 140–142 °C. ^{1}H NMR (400 MHz, CDC_{l3}) δ 11.47 (brs, 1H), 8.51 (d, *J* = 5.0 Hz, 1H), 7.86 (d, *J* = 7.9 Hz, 3H), 7.56 (d, *J* = 11.9 Hz, 1H), 7.43 (d, *J* = 12.4 Hz, 1H), 7.32 (t, *J* = 8.6 Hz, 1H), 7.16 (d, *J* = 10.8 Hz, 1H), 7.11–7.01 (m, 1H), 6.96 (d, *J* = 8.7 Hz, 2H), 6.41 (d, *J* = 5.1 Hz, 1H), 4.26 (t, *J* = 6.6 Hz, 2H), 4.04 (s, 3H), 2.83 (s, 3H), 2.70 (t, *J* = 5.8 Hz, 2H), 2.57 (t, *J* = 7.7 Hz, 4H), 2.34 (s, 3H), 2.23–2.13 (m, 2H), 1.81 (t, *J* = 7.9, 4H). ESI-MS *m/z*: 609.7 $(M+H)^+$. Anal. calcd. for $C_{35}H_{36}FN_5O_4$ (%): C, 68.95; H, 5.95; N, 11.49. Found (%): C, 68.99; H, 5.98; N, 11.50.

*6.3.18. (Z)-4-(((3-fluoro-4-((6-methoxy-7-(3-morpholinopropoxy) quinolin-4-yl)oxy)phenyl)amino)methylene)-3-methyl-1-(o-tolyl)-1H-pyrazol-5(4H)-one (**29**)*

Light yellow solid, 79% yield. mp 137–139 °C. ^{1}H NMR (400 MHz, CDCl3) δ 11.49 (brs, 1H), 8.54 (d, *J* = 5.0 Hz, 1H), 7.89 (d, *J* = 7.9 Hz, 3H), 7.58 (d, *J* = 11.9 Hz, 1H), 7.46 (d, *J* = 12.4 Hz, 1H), 7.35 (t, *J* = 8.6 Hz, 1H), 7.19 (d, *J* = 10.8 Hz, 1H), 7.15–7.06 (m, 1H), 6.99 (d, *J* = 8.7 Hz, 2H), 6.43 (d, *J* = 5.1 Hz, 1H), 4.29 (t, *J* = 6.3 Hz, 2H), 4.05 (s, 3H), 2.94 (s, 3H), 3.75 (t, *J* = 7.2 Hz, 4H), 2.59 (t, *J* = 7.0 Hz, 2H), 2.50 (t, *J* = 7.4 Hz, 4H), 2.34 (s, 3H), 2.19–2.13 (m, 2H). ESI-MS *m/z*: 625.69 $(M+H)^+$. Anal. calcd. for $C_{35}H_{36}FN_5O_5$ (%): C, 67.19; H, 5.80; N, 11.19. Found (%): C, 67.20; H, 5.82; N, 11.22.

*6.3.19. (Z)-4-(((3-fluoro-4-((6-methoxy-7-(3-(piperidin-1-yl)propoxy) quinolin-4-yl)oxy)phenyl)amino)methylene)-1-(4-methoxyphenyl)-3-methyl-1H-pyrazol-5(4H)-one (**30**)*

Light yellow solid, 78% yield. mp 138–139 °C. ^{1}H NMR (400 MHz, CDC_{l3}) δ 11.48 (br, 1H), 8.52 (d, *J* = 5.0 Hz, 1H), 7.87 (d, *J* = 7.9 Hz, 3H), 7.57 (d, *J* = 11.9 Hz, 1H), 7.44 (d, *J* = 12.4 Hz, 1H), 7.33 (t, *J* = 8.6 Hz, 1H), 7.17 (d, *J* = 10.8 Hz, 1H), 7.12–7.02 (m, 1H), 6.97 (d, *J* = 8.7 Hz, 2H), 6.42 (d, *J* = 5.1 Hz, 1H), 4.27 (t, *J* = 6.6 Hz, 2H), 4.05 (s, 3H), 3.84 (s, 3H), 2.59–2.48 (m, 2H), 2.43 (m, 4H), 2.34 (s, 3H), 2.21–2.08 (m, 2H), 1.66–1.55 (m, 4H), 1.46 (d, *J* = 4.5 Hz, 2H). ESI-MS *m/z*: 639.72 $(M+H)^+$. Anal. calcd. for $C_{36}H_{38}FN_5O_5$ (%): C, 67.59; H, 5.99; N, 10.95. Found (%): C, 68.12; H, 6.04; N, 11.04.

*6.3.20. (Z)-4-(((3-fluoro-4-((6-methoxy-7-(3-(4-methylpiperidin-1-yl) propoxy)quinolin-4-yl)oxy)phenyl)amino)methylene)-1-(4-methoxyphenyl)-3-methyl-1H-pyrazol-5(4H)-one (**31**)*

Light yellow solid, 75% yield. mp 134–136 °C. ^{1}H NMR (400 MHz, CDC_{l3}) δ 11.53 (br, 1H), 8.52 (d, *J* = 5.0 Hz, 1H), 7.88 (d, *J* = 6.7 Hz, 3H), 7.57 (d, *J* = 8.2 Hz, 1H), 7.49–7.40 (m, 1H), 7.34 (t, *J* = 8.4 Hz, 1H), 7.17 (d, *J* = 10.4 Hz, 1H), 7.12–7.06 (m, 1H), 6.97 (d, *J* = 8.6 Hz, 2H), 6.42 (d, *J* = 4.9 Hz, 1H), 4.27 (t, *J* = 6.4 Hz, 2H), 4.06 (s, 3H), 3.85 (s, 3H), 2.93 (d, *J* = 11.2 Hz, 2H), 2.56 (t, *J* = 7.1 Hz, 2H), 2.34 (s, 3H), 2.16 (dt, *J* = 12.9, 6.5 Hz, 2H), 1.96 (t, *J* = 11.3 Hz, 2H), 1.64 (d, *J* = 12.4 Hz, 2H), 1.26 (d, *J* = 9.2 Hz, 3H), 0.94 (d, *J* = 6.2 Hz, 3H). ESI-MS *m/z*: 653.74 $(M+H)^+$. Anal. calcd. for $C_{37}H_{40}FN_5O_5$ (%): C, 67.98; H, 6.17; N, 10.71. Found (%): C, 68.10; H, 6.19; N, 10.75.

*6.3.21. (Z)-4-(((3-fluoro-4-((6-methoxy-7-(3-(4-methylpiperazin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl)amino)methylene)-3-methyl-1-(o-tolyl)-1H-pyrazol-5(4H)-one (**32**)*

Light yellow solid, 75% yield. mp 143–145 °C. ^{1}H NMR (400 MHz, CDC_{l3}) δ 11.46 (brs, 1H), 8.53 (d, *J* = 5.1 Hz, 1H), 8.15 (dd, *J* = 7.4, 1.1 Hz, 1H), 7.99–7.94 (m, 2H), 7.85 (s, 1H), 7.56 (s, 1H), 7.44 (s, 1H), 7.35 (t, *J* = 7.0 Hz, 1H), 7.18 (dd, *J* = 10.4, 6.5 Hz, 2H), 7.12 (d, *J* = 8.5 Hz, 1H), 6.45 (d, *J* = 5.1 Hz, 1H), 4.28 (t, *J* = 6.6 Hz, 2H), 4.06 (s, 3H), 3.84 (s, 3H), 2.54 (br, *J* = 14.3, 10.9, 5.6 Hz, 10H), 2.36 (s, 3H), 2.31 (s, 3H), 2.15 (dt, *J* = 13.4, 6.7 Hz, 2H). ESI-MS *m/z*: 638.74 $(M+H)^+$. Anal. calcd. for $C_{36}H_{39}FN_6O_4$ (%): C, 67.69; H, 6.15; N, 13.16. Found (%): C, 67.71; H, 6.17; N, 13.18.

6.4. Preparation of 2,4-imidazolinedione-based quinolones derivatives

*6.4.1. General procedure for preparation intermediates of substituted phenyl phenylcarbamate (**33a–f**)*

Phenyl chloroformate (17.2 g, 0.11 mol) was added dropwise to a stirred mixture of 2-methylbenzenamine (10.7 g, 0.1 mol), pyridine (8.5 g, 0.11 mol) and DCM (200 mL) at 0 °C. The mixture was stirred for 3 h at room temperature, then washed with water (200 mL × 3), dried over anhydrous Na_2SO_4, and filtrated. The solvent was evaporated under reduced pressure and the deposited solid were collected and washed with hexane to give **33a** as yellow solid (19.71 g, 92.5%). The product can be used directly in the next step without further purification.

*6.4.1.1. Phenyl o-tolylcarbamate (**33a**).* Yield 92.5%. mp 108–110 °C. ESI-MS *m/z*: 228 $(M+H)^+$.^{1}H NMR (400 MHz, $CDCl_3$) δ 10.11(s, 1H), 6.74-7.44 (m, 9H), 2.55 (s, 3H).

*6.4.1.2. Phenyl (2-(trifluoromethyl)phenyl)carbamate (**33b**).* Yield 92.5%. mp 107–109 °C. ESI-MS *m/z*: 282 $(M+H)^+$.

*6.4.1.3. Phenyl (2-methoxyphenyl)carbamate (**33c**).* Yield 91.5%. mp 109–110 °C. ESI-MS *m/z*: 244 $(M+H)^+$.

*6.4.1.4. Phenyl (2-fluorophenyl)carbamate (**33d**).* Yield 92.6%. mp 106–108 °C. ESI-MS *m/z*: 232 $(M+H)^+$.

*6.4.1.5. Phenyl (4-chlorophenyl)carbamate (**33e**).* Yield 93.2%. mp 107–110 °C. ESI-MS *m/z*: 248 $(M+H)^+$.

*6.4.1.6. Phenyl (3-chloro-4-fluorophenyl)carbamate (**33f**).* Yield 90.8%. mp 108–111 °C. ESI-MS *m/z*: 266 $(M+H)^+$.

*6.4.2. General procedure for preparation of ethyl 2-(1-methyl-3-substituted phenylureido)acetate (**34a–f**)*

To a solution of **33a** (3.0 g, 13 mmol) and pyridine (1.0 mL) in 100 mL of dichloromethane was added a solution of sarcosine ethyl ester hydrochloride (2.1 g, 13.5 mmol) in 10 mL of dichloromethane dropwise at 0 °C. The resulting mixture was stirred at r.t. for 5 h before poured into ice-water. The mixture was extracted with DCM (3 × 100 mL). The combined organic phases were washed with 0.5 N aq. HCl and brine, dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated to give the crude product, which was purified by column to afford 2.1 g of ethyl 2-(1-methyl-3-(o-tolyl)ureido)acetate **34a** (94 %). ESI-MS *m/z*: 282 $(M+H)^+$.

*6.4.2.1. Ethyl 2-(1-methyl-3-(2-(trifluoromethyl)phenyl)ureido) acetate (**34b**).* Yield 93.5%. ESI-MS *m/z*: 305 $(M+H)^+$.

*6.4.2.2. Ethyl 2-(3-(2-methoxyphenyl)-1-methylureido)acetate (**34c**).* Yield 92.5%. ESI-MS *m/z*: 267 $(M+H)^+$.

*6.4.2.3. Ethyl 2-(3-(2-fluorophenyl)-1-methylureido)acetate (**34d**).* Yield 94.6%. ESI-MS *m/z*: 255 $(M+H)^+$.

*6.4.2.4. Ethyl 2-(3-(4-chlorophenyl)-1-methylureido)acetate (**34e**).* Yield 91.2%. ESI-MS *m/z*: 271 $(M+H)^+$.

*6.4.2.5. Ethyl 2-(3-(3-chloro-4-fluorophenyl)-1-methylureido)acetate (**34f**).* Yield 92.8%. ESI-MS *m/z*: 281 $(M + H)^+$.

*6.4.3. General procedure for preparation of 1-methyl-3-(substituted phenylimidazolidine)-2,4-dione (**35a–f**)*

To a solution of 500 mg (1.77 mmol) of **34a** in 20 mL of ethanol, 20 mL of 10 N HCl were added. The resulting solution was refluxed for 3 h, and the solvent was remove under reduced pressure. The residue was taken up with DCM and washed with water. The organic phase was dried over Na_2SO_4 and the filtrate was concentrated to give the crude product, which was purified by column to afford 350 mg, (84% yield) of **35a** were obtained by crystallization from diethyl ether. ^1H NMR (400 MHz, DMSO-d_6) δ 8.2 (s, 1H), 7.4 (m, 1H), 7.3 (d, *J* = 8.5 Hz, 2H), 4.0 (s, 2H), 2.58 (s, 3H), 1.48 (s, 3H). ESI-MS *m/z*: 205.27 $[M + H]^+$.

*6.4.3.1. 1-methyl-3-(2-(trifluoromethyl)phenyl)imidazolidine-2,4-dione (**35b**).* Yield 85.2%. ESI-MS *m/z*: 259 $(M + H)^+$.

*6.4.3.2. 3-(2-methoxyphenyl)-1-methylimidazolidine-2,4-dione (**35c**).* Yield 83.2%. ESI-MS *m/z*: 221 $(M + H)^+$.

*6.4.3.3. 3-(2-fluorophenyl)-1-methylimidazolidine-2,4-dione (**35d**).* Yield 84.5%. ESI-MS *m/z*: 209 $(M + H)^+$.

*6.4.3.4. 3-(4-chlorophenyl)-1-methylimidazolidine-2,4-dione (**35e**).* Yield 83.6%. ESI-MS *m/z*: 225 $(M + H)^+$.

*6.4.3.5. 3-(3-chloro-4-fluorophenyl)-1-methylimidazolidine-2,4-dione (**35f**).* Yield 84.1%. ESI-MS *m/z*: 243 $(M + H)^+$.

*6.4.4. General procedure for preparation of (Z)-5-((dimethylamino) methylene)-1-methyl-3-(substituted phenylimidazolidine)-2,4-dione (**36a–f**)*

To a solution of an appropriate intermediate **35a–f** (0.023 mol) and *N*,*N*-Dimethylformamide dimethyl acetal (DMF-DMA) (5 mL) dissolved in acetonitrile (20 mL). Upon completing the addition and the reaction mixture was stirred at 50 °C for 2 h and cooled to room temperature. The solid is filtered and washed with ether, the cake was dried to give yellow solid **36a–f**.

*6.4.4.1. (E)-5-((dimethylamino)methylene)-1-methyl-3-(o-tolyl)imidazolidine-2,4-dione (**36a**).* Yield 89.1%. mp 137–139 °C. ESI-MS *m/z*: 260 $(M + H)^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, *J* = 7.7 Hz, 1H), 7.47 (t, *J* = 7.4 Hz, 1H), 7.33 (t, *J* = 8.0 Hz, 1H), 7.07 (t, *J* = 7.4 Hz, 1H), 6.95 (s, 1H), 3.82 (s, 3H), 3.23 (s, 3H), 3.16 (s, 3H), 2.26 (s, 3H).

*6.4.4.2. (E)-5-((dimethylamino)methylene)-1-methyl-3-(2-(trifluoromethyl)phenyl)imidazolidine-2,4-dione (**36b**).* Yield 88.3%. mp 136–140 °C. ESI-MS *m/z*: 314 $(M + H)^+$.

*6.4.4.3. (E)-5-((dimethylamino)methylene)-3-(2-methoxyphenyl)-1-methylimidazolidine-2,4-dione (**36c**).* Yield 88.9%. mp 138–141 °C. ESI-MS *m/z*: 276 $(M + H)^+$.

*6.4.4.4. (E)-5-((dimethylamino)methylene)-3-(2-fluorophenyl)-1-methylimidazolidine-2,4-dione (**36d**).* Yield 89.5%. mp 137–140 °C. ESI-MS *m/z*: 264 $(M + H)^+$.

*6.4.4.5. (E)-3-(4-chlorophenyl)-5-((dimethylamino)methylene)-1-methylimidazolidine-2,4-dione (**36e**).* Yield 89.0%. mp 139–142 °C. ESI-MS *m/z*: 280 $(M + H)^+$.

*6.4.4.6. (E)-3-(3-chloro-4-fluorophenyl)-5-((dimethylamino)methylene)-1-methylimidazolidine-2,4-dione (**36f**).* Yield 88.3%. mp 136–138 °C. ESI-MS *m/z*: 298 $(M + H)^+$.

*6.5. General procedure for preparation of target compounds (**37–46**)*

To a solution of an appropriate aniline **8a–e** (0.5 mmol) and intermediate **36a–f** (0.75 mmol) dissolved in glacial acetic acid (10 mL), After the completion of addition and the reaction mixture was heated under refluxed with stirring until the starting materials could no longer be detected by TLC. The solvent was evaporated under reduced pressure and the residue was dissolved in DCM and saturated sodium bicarbonate solution, the mixture was washed with saturated sodium bicarbonate solution (20 mL × 3), brine (20 mL × 3) in sequence, and the organic phase was separated, dried, and evaporated. The crude product was purified by chromatography on silica gel using CH_2Cl_2/MeOH (35:1) to afford light yellow solid **37–46**.

*6.5.1. (E)-5-(((3-fluoro-4-((6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy) quinolin-4-yl)oxy)phenyl)amino)methylene)-1-methyl-3-(2-methylphenyl)imidazolidine-2,4-dione (**37**)*

Light yellow solid, 76% yield. mp: 145–146 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 11.48 (brs, 1H), 8.52 (d, *J* = 5.0 Hz, 1H), 7.87 (d, *J* = 7.9 Hz, 3H), 7.57 (d, *J* = 11.9 Hz, 1H), 7.44 (d, *J* = 12.4 Hz, 1H), 7.33 (t, *J* = 8.6 Hz, 1H), 7.17 (d, *J* = 10.8 Hz, 1H), 7.12–7.02 (m, 1H), 6.97 (d, *J* = 8.7 Hz, 2H), 6.42 (d, *J* = 5.1 Hz, 1H), 4.27 (t, *J* = 6.6 Hz, 2H), 4.05 (s, 3H), 2.84 (s, 3H), 2.71 (t, *J* = 5.8 Hz, 2H), 2.58 (d, *J* = 0.7 Hz, 4H), 2.35 (s, 3H), 2.24–2.13 (m, 2H), 1.82 (t, *J* = 13.7, 4H). ESI-MS *m/z*: 626.3 $(M + H)^+$. Anal. calcd. for $C_{35}H_{36}FN_5O_5$ (%):C, 67.19; H, 5.80; N, 11.19. Found (%): C, 67.23; H, 5.82; N, 11.26.

*6.5.2. (E)-5-(((3-fluoro-4-((6-methoxy-7-(3-(pyrrolidin-1-yl) propoxy)quinolin-4-yl)oxy)phenyl)amino)methylene)-1-methyl-3-(2-(trifluoromethyl)phenyl)imidazolidine-2,4-dione (**38**)*

Light yellow solid, 75% yield. mp: 132–133 °C. IR (KBr) cm^{-1}: 3591.1, 2958.9, 2792.9, 1685.6, 1622.6, 1605.7, 1509.6, 1478.9, 1456.4, 1432.2, 1348.7, 1316.1, 1251.4, 1212.6, 1172.1, 1146.0, 1113.6, 1061.9, 1035.0, 971.9; ^1H NMR (400 MHz, $CDCl_3$) δ 11.56 (brs, 1H), 8.52 (d, *J* = 3.0 Hz, 1H), 7.98 (dd, *J* = 8.9, 4.9 Hz, 2H), 7.89 (s, 1H), 7.56 (d, *J* = 4.3 Hz, 1H), 7.46 (s, 1H), 7.36 (t, *J* = 8.5 Hz, 1H), 7.19 (dd, *J* = 10.2, 1.5 Hz, 1H), 7.13 (t, *J* = 8.6 Hz, 3H), 6.43 (d, *J* = 4.7 Hz, 1H), 4.29 (t, *J* = 6.3 Hz, 2H), 4.06 (s, 3H), 2.71 (t, *J* = 5.8 Hz, 2H), 2.58 (d, *J* = 0.7 Hz, 4H), 2.35 (s, 3H), 2.24–2.13 (m, 2H), 1.82 (t, *J* = 13.9, 4H). ^{13}C NMR (600 MHz, $CDCl_3$) δ 160.67, 160.49, 159.79, 155.59, 153.93, 152.70, 150.25, 148.76, 146.81, 145.56, 138.78, 138.566, 136.69, 136.46, 132.58, 130.82, 129.85, 128.34, 123.97, 116.55, 115.56, 109.88, 109.73, 108.74, 102.25, 99.56, 67.45, 56.27, 54.32 (2C), 53.08, 28.32, 23.65 (2C), 20.75; ESI-MS *m/z*: 680.2 $(M + H)^+$. Anal. calcd. for $C_{35}H_{33}F_4N_5O_5$ (%):C, 61.85; H, 4.89; N, 10.30. Found (%): C, 61.89; H, 4.90; N, 10.36.

*6.5.3. (E)-5-(((3-fluoro-4-((6-methoxy-7-(3-morpholinopropoxy) quinolin-4-yl)oxy)phenyl)amino)methylene)-1-methyl-3-(2-methylphenyl)imidazolidine-2,4-dione (**39**)*

Light yellow solid, 79% yield. mp: 156–157 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 11.48 (brs, 1H), 8.52 (d, *J* = 5.0 Hz, 1H), 7.87 (d, *J* = 7.9 Hz, 3H), 7.57 (d, *J* = 11.9 Hz, 1H), 7.44 (d, *J* = 12.4 Hz, 1H), 7.33 (t, *J* = 8.6 Hz, 1H), 7.17 (d, *J* = 10.8 Hz, 1H), 7.12–7.02 (m, 1H), 6.97 (d, *J* = 8.7 Hz, 2H), 6.42 (d, *J* = 5.1 Hz, 1H), 4.29 (t, *J* = 6.3 Hz, 2H), 4.06 (s, 3H), 2.92 (s, 3H),3.74 (t, 4H), 2.59 (t, *J* = 7.0 Hz, 2H), 2.50 (s, 4H), 2.34 (s, 3H), 2.19–2.10 (m, 2H). ESI-MS *m/z*: 642.5 $(M + H)^+$. Anal. calcd. for $C_{35}H_{36}FN_5O_6$ (%): C, 65.51; H, 5.65; N, 10.91. Found (%): C, 65.53; H, 5.67; N, 10.96.

*6.5.4. (E)-5-(((3-fluoro-4-((6-methoxy-7-(3-morpholinopropoxy) quinolin-4-yl)oxy)phenyl)amino)m ethylene)-3-(2-fluorophenyl)-1-methylimidazolidine-2,4-dione (**40**)*

Light yellow solid, 76% yield. mp: 135–136 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ11.51 (brs, 1H), 8.52 (d, *J* = 3.9 Hz, 1H), 7.99 (d, *J* = 8.7 Hz, 2H), 7.86 (s, 1H), 7.56 (s, 1H), 7.46 (s, 1H), 7.36 (dd, *J* = 17.1, 8.6 Hz, 3H), 7.18 (d, *J* = 10.6 Hz, 1H), 7.10 (d, *J* = 8.5 Hz, 1H), 6.42 (d, *J* = 4.3 Hz, 1H), 4.26 (t, *J* = 6.5 Hz, 2H), 4.02 (s, 3H), 3.71 (t, *J* = 4.4 Hz, 4H), 2.56 (t, *J* = 7.1 Hz, 2H), 2.47 (s, 4H), 2.30 (s, 3H), 2.17–2.04 (m, 2H). ESI-MS *m/z*: 646.4 $(M+H)^+$. Anal. calcd. for $C_{34}H_{33}F_2N_5O_6$ (%):C, 63.25; H, 5.15; N, 10.85. Found (%): C, 63.27; H, 5.17; N, 10.86.

*6.5.5. (E)-5-(((3-fluoro-4-((6-methoxy-7-(3-(piperidin-1-yl)propoxy) quinolin-4-yl)oxy)phenyl)amino)methylene)-3-(2-methoxyphenyl)-1-methylimidazolidine-2,4-dione (**41**)*

Light yellow solid, 75% yield. mp: 146–147 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.48 (brs, 1H), 8.52 (d, *J* = 5.0 Hz, 1H), 7.87 (d, *J* = 7.9 Hz, 3H), 7.57 (d, *J* = 11.9 Hz, 1H), 7.44 (d, *J* = 12.4 Hz, 1H), 7.33 (t, *J* = 8.6 Hz, 1H), 7.17 (d, *J* = 10.8 Hz, 1H), 7.12–7.02 (m, 1H), 6.97 (d, *J* = 8.7 Hz, 2H), 6.42 (d, *J* = 5.1 Hz, 1H), 4.27 (t, *J* = 6.6 Hz, 2H), 4.05 (s, 3H), 3.84 (s, 3H), 2.59–2.48 (m, 2H), 2.43 (s, 4H), 2.34 (s, 3H), 2.21–2.08 (m, 2H), 1.66–1.55 (m, 4H), 1.46 (d, *J* = 4.5 Hz, 2H). ESI-MS *m/z*: 656.5 $(M+H)^+$. Anal. calcd. for $C_{36}H_{38}FN_5O_6$ (%): C, 63.34; H, 5.01; N, 10.55. Found (%): C, 63.36; H, 5.07; N, 10.56.

*6.5.6. (E)-3-(4-chlorophenyl)-5-(((3-fluoro-4-((6-methoxy-7-(3-(piperidin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl)amino)methylene)-1-methylimidazolidine-2,4-dione (**42**)*

Light yellow solid, 73% yield. mp: 158–159 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.45 (brs, 1H), 8.52 (d, *J* = 3.9 Hz, 1H), 7.97 (dd, *J* = 8.7, 4.8 Hz, 2H), 7.88 (s, 1H), 7.57 (d, *J* = 13.1 Hz, 1H), 7.44 (d, *J* = 12.1 Hz, 1H), 7.35 (t, *J* = 8.4 Hz, 1H), 7.19 (d, *J* = 9.9 Hz, 1H), 7.14–7.00 (m, 3H), 6.42 (d, *J* = 4.7 Hz, 1H), 4.27 (t, *J* = 6.5 Hz, 2H), 4.06 (s, 3H), 2.55 (t, *J* = 7.2 Hz, 2H), 2.43 (d, *J* = 0.4 Hz, 4H), 2.35 (s, 3H), 2.19–2.08 (m, 2H), 1.66–1.55 (m, 4H), 1.46 (d, *J* = 4.7 Hz, 2H). ESI-MS *m/z*: 660.4 $(M+H)^+$. Anal. calcd. for $C_{35}H_{35}ClFN_5O_5$ (%): C, 63.68; H, 5.34; N, 10.61. Found (%): C, 63.69; H, 5.37; N, 10.66.

*6.5.7. (E)-5-(((3-fluoro-4-((6-methoxy-7-(3-(4-methylpiperidin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl)amino)methylene)-1-methyl-3-(2-methylphenyl)imidazolidine-2,4-dione (**43**)*

Light yellow solid, 71% yield. mp: 152–153 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.53 (brs, 1H), 8.52 (d, *J* = 5.0 Hz, 1H), 7.88 (d, *J* = 6.7 Hz, 3H), 7.57 (d, *J* = 8.2 Hz, 1H), 7.49–7.40 (m, 1H), 7.34 (t, *J* = 8.4 Hz, 1H), 7.17 (d, *J* = 10.4 Hz, 1H), 7.12–7.06 (m, 1H), 6.97 (d, *J* = 8.6 Hz, 2H), 6.42 (d, *J* = 4.9 Hz, 1H), 4.27 (t, *J* = 6.4 Hz, 2H), 4.06 (s, 3H), 2.82 (s, 3H), 2.93 (d, *J* = 11.2 Hz, 2H), 2.56 (t, *J* = 7.1 Hz, 2H), 2.34 (s, 3H), 2.16 (dt, *J* = 12.9, 6.5 Hz, 2H), 1.96 (t, *J* = 11.3 Hz, 2H), 1.64 (d, *J* = 12.4 Hz, 2H), 1.26 (d, *J* = 9.2 Hz, 3H), 0.94 (d, *J* = 6.2 Hz, 3H). ESI-MS *m/z*: 654.5 $(M+H)^+$. Anal. calcd. for $C_{37}H_{40}FN_5O_5$ (%):C, 67.98; H, 6.17; N, 10.71. Found (%): C, 67.99; H, 6.20; N, 10.76.

*6.5.8. (E)-5-(((3-fluoro-4-((6-methoxy-7-(3-(4-methylpiperidin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl)amino)methylene)-1-methyl-3-(2-(trifluoromethyl)phenyl)imidazolidine-2,4-dione (**44**)*

Light yellow solid, 72% yield. mp: 124–126 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.45 (brs, 1H), 8.53 (d, *J* = 4.8 Hz, 1H), 7.95 (d, *J* = 8.7 Hz, 2H), 7.87 (s, 1H), 7.58–7.49 (m, 3H), 7.44 (d, *J* = 13.0 Hz, 1H), 7.36 (t, *J* = 8.5 Hz, 1H), 7.19 (dd, *J* = 10.7, 1.9 Hz, 1H), 7.11 (d, *J* = 8.6 Hz, 1H), 6.42 (d, *J* = 5.0 Hz, 1H), 4.27 (t, *J* = 6.6 Hz, 2H), 4.06 (s, 3H), 2.93 (d, *J* = 11.2 Hz, 2H), 2.56 (t, *J* = 7.3 Hz, 2H), 2.35 (s, 3H), 2.20–2.10 (m, 2H), 1.96 (t, *J* = 11.2 Hz, 2H), 1.64 (d, *J* = 12.5 Hz, 2H), 1.31–1.24 (m, 3H), 0.94 (d, *J* = 6.3 Hz, 3H). ESI-MS *m/z*: 708.4 $(M+H)^+$. Anal. calcd. for $C_{37}H_{37}F_4N_5O_5$ (%): C, 62.79; H, 5.27; N, 9.90. Found (%): C, 62.80; H, 5.29; N, 9.96.

*6.5.9. (E)-5-(((3-fluoro-4-((6-methoxy-7-(3-(4-methylpiperazin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl)amino)methylene)-1-methyl-3-(2-methylphenyl)imidazolidine-2,4-dione (**45**)*

Light yellow solid, 73% yield. mp: 153–154 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.47 (brs, 1H), 8.52 (d, *J* = 5.1 Hz, 1H), 8.15 (dd, *J* = 7.4, 1.1 Hz, 1H), 7.99–7.93 (m, 2H), 7.87 (s, 1H), 7.54 (s, 1H), 7.45 (s, 1H), 7.33 (t, *J* = 7.0 Hz, 1H), 7.18 (dd, *J* = 10.4, 6.5 Hz, 2H), 7.12 (d, *J* = 8.5 Hz, 1H), 6.42 (d, *J* = 5.1 Hz, 1H), 4.28 (t, *J* = 6.6 Hz, 2H), 4.06 (s, 3H), 3.84 (s, 3H),2.54 (br, *J* = 14.3, 10.9, 5.6 Hz, 10H), 2.36 (s, 3H), 2.31 (s, 3H), 2.15 (dt, *J* = 13.4, 6.7 Hz, 2H). ESI-MS *m/z*: 655.4 $(M+H)^+$. Anal. calcd. for $C_{36}H_{39}FN_6O_5$ (%): C, 66.04; H, 6.00; N, 12.84. Found (%): C, 66.10; H, 6.07; N, 12.86.

*6.5.10. (E)-3-(3-chloro-4-fluorophenyl)-5-(((3-fluoro-4-((6-methoxy-7-(3-(4-methylpiperazin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl) amino)methylene)-1-methylimidazolidine-2,4-dione (**46**)*

Light yellow solid, 77% yield. mp: 135–136 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.48 (brs, 1H), 8.53 (d, *J* = 5.1 Hz, 1H), 8.16 (dd, *J* = 7.4, 1.1 Hz, 1H), 7.99–7.91 (m, 1H), 7.88 (s, 1H), 7.56 (s, 1H), 7.46 (s, 1H), 7.36 (t, *J* = 7.0 Hz, 1H), 7.19 (dd, *J* = 10.4, 6.5 Hz, 2H), 7.11 (d, *J* = 8.5 Hz, 1H), 6.43 (d, *J* = 5.1 Hz, 1H), 4.28 (t, *J* = 6.6 Hz, 2H), 4.06 (s, 3H), 2.55 (br, 10H), 2.35 (s, 3H), 2.31 (s, 3H), 2.19–2.09 (m, 2H). ESI-MS *m/z*: 693.3 $(M+H)^+$. Anal. calcd. for $C_{35}H_{35}ClF_2N_6O_5$ (%): C, 60.65; H, 5.09; N, 12.12. Found (%): C, 60.68; H, 5.11; N, 12.16.

Acknowledgments

The work was supported by Program for Innovative Research Team of the Ministry of Education of the People's Republic of China and Program for Liaoning Innovative Research Team in University.

Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bioorg.2014.07.011.

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