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Discovery of novel 6,7-disubstituted-4-phenoxyquinoline derivatives bearing 5-(aminomethylene)pyrimidine-2,4,6-trione moiety as c-Met kinase inhibitors

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ABSTRACT

A series of novel quinoline derivatives bearing 5-(aminomethylene)pyrimidine-2,4,6-trione moiety were designed, synthesized, and evaluated for their c-Met kinase inhibitory activities and antiproliferative activities against 5 cancer cell lines (HT-29, H460, MKN-45, A549, and U87MG) in vitro. Most compounds showed moderate to excellent potency, with the most promising analogue **45** (c-Met half-maximal inhibitory concentration [IC_{50}] = 1.15 nM) showing high selectivity versus 5 other tyrosine kinases, VEGFR-2, Flt-3, PDGFR-β, c-Kit, and EGFR. Structure–activity relationship studies indicated that electron-donating groups on the phenyl ring at the 3-position of pyrimidine-2,4,6-trione were required to increase the electron density on the 5-(aminomethylene)pyrimidine-2,4,6-trione moiety.

1. Introduction

c-Met, known as a hepatocyte growth factor receptor (HGFR), belongs to a subfamily of receptor tyrosine kinases (RTKs) that are composed of an extracellular α chain and a membrane-spanning β chain connected through a disulfide bond.[1–3] In normal physiology, the HGF/Met pathway regulates several cellular responses including cell proliferation, invasion, motility, survival, and morphogenesis.[4,5] c-Met has been shown to be frequently amplified or overexpressed in various cancers, including brain, colorectal, gastric, lung, head, neck, and stomach cancers;[6–8] and circulating HGF levels are elevated in most cancers.[9,10] Both amplifications/overexpression are associated with poor clinical outcomes,[11–15] underscoring the importance of increased c-Met signaling in these cancer types. Therefore, c-Met shows high potential as a therapeutic target for human cancer.

In recent years, research has highlighted c-Met as an attractive cancer drug target, triggering a number of approaches to disrupt HGF/Met signaling. Both small-molecule c-Met kinase inhibitors and antibodies targeting c-Met or HGF have exhibited antitumor activities in clinical/preclinical models.[16–28] Recently, significant progress has been made in the development of small-molecule c-Met inhibitors, resulting in the marketing of cabozantinib (**3**, Fig. 1) and more than 10 candidates currently under clinical trials.[29–31] Many structure types of these derivatives were included, such as thieno[2,3-*b*]pyridine, 2-amino-3-chloropyridine, and 6,7-disubstitutedquinoline series (**1**, **2**, and **3**–**6**, respectively, Fig. 1).[32–38] However, the main modification of these different series of derivatives was focused on the 5-atom linker between moiety A and moiety B, which was characterized by the illustrated '5 atoms regulation' and 'hydrogen-bond donor or acceptor'.[41,42] In our previous study, we introduced pyridine, semicarbazone, quinoline, and 1,4-dihydrocinnoline fragments into the 5-atom linker based on the '5 atoms regulation'/'hydrogen-bond donor or acceptor', and the resulting derivatives **7**–**10** (Fig. 2) showed excellent potency.[39–42] These compounds all contained an amide group in the linker.

Pyrimidine-2,4,6-trione (PYT) is widely used as a building block in the design of anticancer agents because of its ability to form hydrogen-bonding interactions with drug targets (**11**–**14**, Fig. 3).[43–46] To make further study, we replaced the amide group in the 5-atom linker with an aminomethylene group, and introduced PYT to form the $\mathbf{C_1}$ fragment (Fig. 4) based on the '5 atoms

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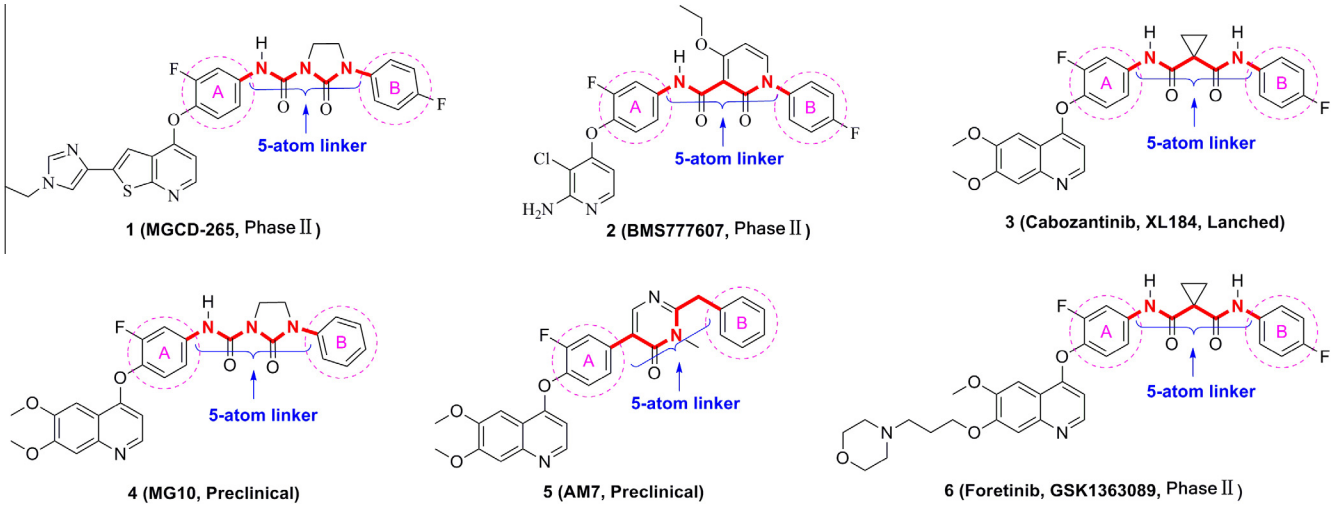


Figure 1. The representative small-molecule c-Met kinase inhibitors.

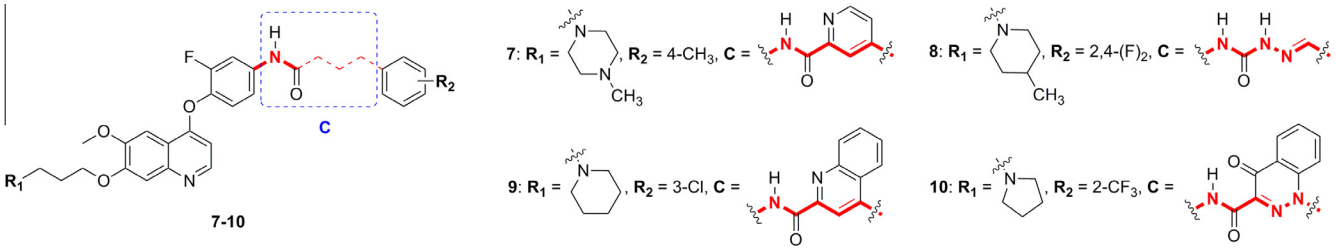


Figure 2. Our previous work on small-molecule c-Met kinase inhibitors.

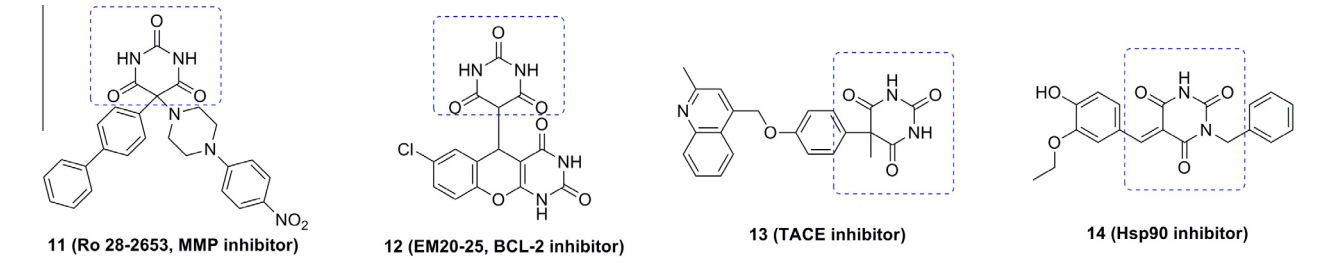


Figure 3. Anticancer agents bearing pyrimidine-2,4,6-trione fragments.

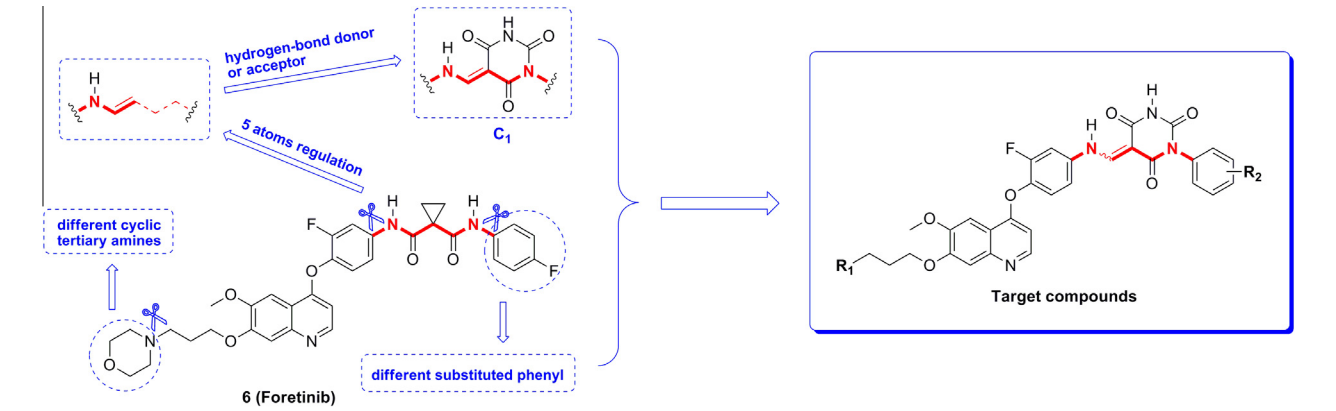
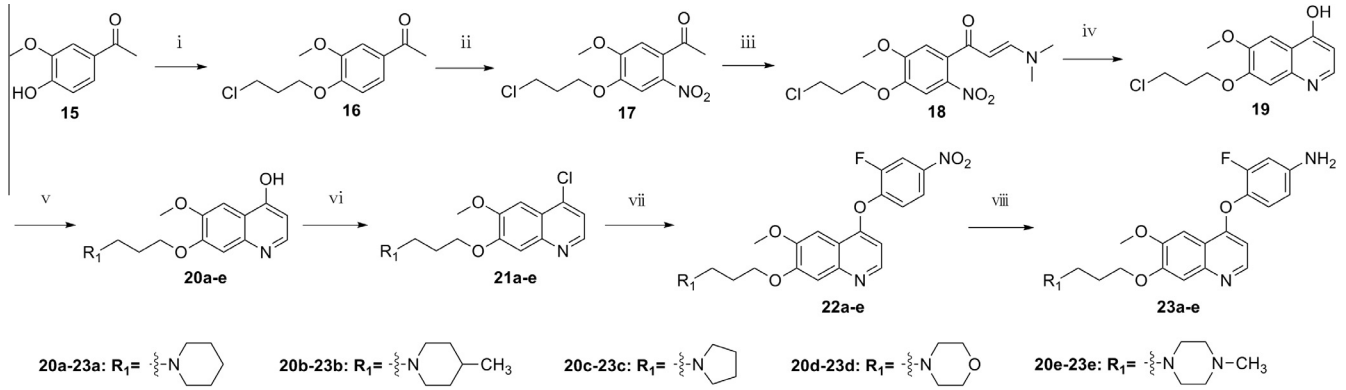
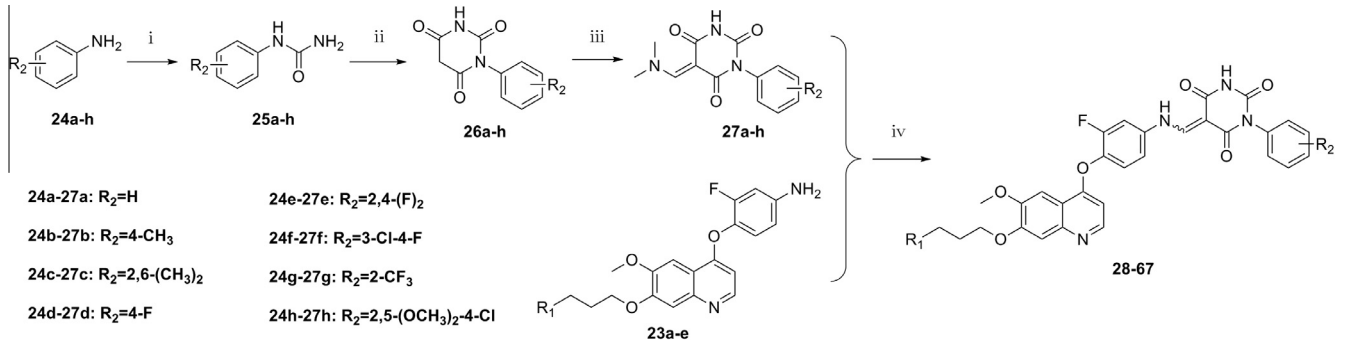


Figure 4. Design strategy for the quinoline derivatives bearing 5-(aminomethylene)pyrimidine-2,4,6-trione moiety.



Scheme 1. Reagents and conditions: (i) $Br(CH_2)_3Cl$, acetone, 0 °C, 30 min, rt, 12 h; (ii) 98% HNO_3, CH_2Cl_2, 0 °C, 4 h; (iii) DMF-DMA, toluene, 110 °C, 10 h; (iv) Fe powder, AcOH, 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, 40 °C, 2–4 h; (ii) dimethyl malonate, EtONa, EtOH, reflux, 8–12 h; (iii) DMF-DMA, 50 °C, 6–10 h; (iv) appropriate aniline, AcOH, 80 °C, 20–30 h.

regulation'. In this study, a 5-(aminomethylene)pyrimidine-2,4,6-trione moiety was used as the 5-atom linker.

According to our previous study, the 3-carbon tether at the 7 position of quinoline was reserved, while the morpholinyl group was replaced by four other water-soluble substituents, including piperidinyl, 4-methyl piperidinyl, pyrrolidinyl, and 4-methyl piperazinyl groups, to observe the effects of the different cyclic tertiary amino groups on activity of the new compounds. Furthermore, various substituents were introduced at the phenyl ring (moiety B) to investigate their effects on activity. Accordingly, we designed a novel series of 6,7-disubstituted-4-phenoxyquinoline derivatives bearing 5-(aminomethylene)pyrimidine-2,4,6-trione moiety.

The target compounds synthesized were evaluated for their c-Met kinase activities and antiproliferative activities against 5 cancer cell lines included the HT-29 (human colon cancer), H460 (human lung cancer), A549 (human lung adenocarcinoma), MKN-45 (human gastric cancer), and U87MG (human glioblastoma).

2. Chemistry

The synthesis of the key intermediates of 6,7-disubstituted-4-phenoxyquinolines **23a**–**e** was achieved in 8 steps from commercially available 1-(4-hydroxy-3-methoxyphenyl)ethanone as shown in Scheme 1, which has been illustrated in detail in our previous study.[41,42]

The target compounds **28**–**67** were prepared as illustrated in Scheme 2. Condensation of commercially available substituted phenylamines **24a**–**h** with sodium cyanate (NaOCN) in AcOH/H_2O (1:1 v/v) at 40 °C resulted in high yield of intermediates **25a**–**h** as white solids.[47] Acylation of the 1-substitutedphenylureas **25a**–**h** with dimethyl malonate in the presence of sodium ethylate ($NaOC_2H_5$) in refluxing ethanol (EtOH) yielded 1-substitutedphenylpyrimidine-2,4,6-triones **26a**–**h**.[48] Subsequent aminomethylenation using modified Vilsmeier–Haack reagent *N*,*N*-dimethyl formamide dimethyl acetal (DMF-DMA) at 50 °C afforded intermediates **27a**–**h** as yellow solids.[49] Reaction of amides **23a**–**e** with **27a**–**h** promoted by hot AcOH yielded the target compounds **28**–**67**.

The chemical structures of the target compounds were determined by mass spectrometry (MS), ^1H nuclear magnetic resonance (NMR), ^{13}C NMR, and infrared (IR) spectra. All target compounds were found to exist in the *E* and *Z* isomeric forms with carbon–carbon double bonds. In our study, a single isomeric form was not obtained because the silica gel column chromatography could not separate the *E* and *Z* isomeric forms due to their similar polarity. For the representative compound **53**, 2 groups of peaks were observed for the *E* isomeric form (**H_1**: d, J = 13.4 Hz, 0.57H, δ = 11.86 ppm; **H_2**: s, 0.57H, δ = 11.26 ppm; **H_3**: d, J = 13.4 Hz, 0.58H, δ = 8.64 ppm) and *Z* isomeric form (**H_1'**: d, J = 12.6 Hz, 0.42H, δ = 12.01 ppm; **H_2'**: s, 0.42H, δ = 11.41 ppm; **H_3'**: d, J = 12.6 Hz, 0.42H, δ = 8.57 ppm) in ^1H NMR as shown in Figure 5. **H_4** (d, J = 5.2 Hz, 1H) at the 2-position of the quinoline ring showed the same chemical shift at δ = 8.47 ppm in the *E* and *Z* isomeric forms.

3. Biology

3.1. HTRF kinase assay

The c-Met kinase assays of all compounds were performed by homogeneous time-resolved fluorescence (HTRF) assay as

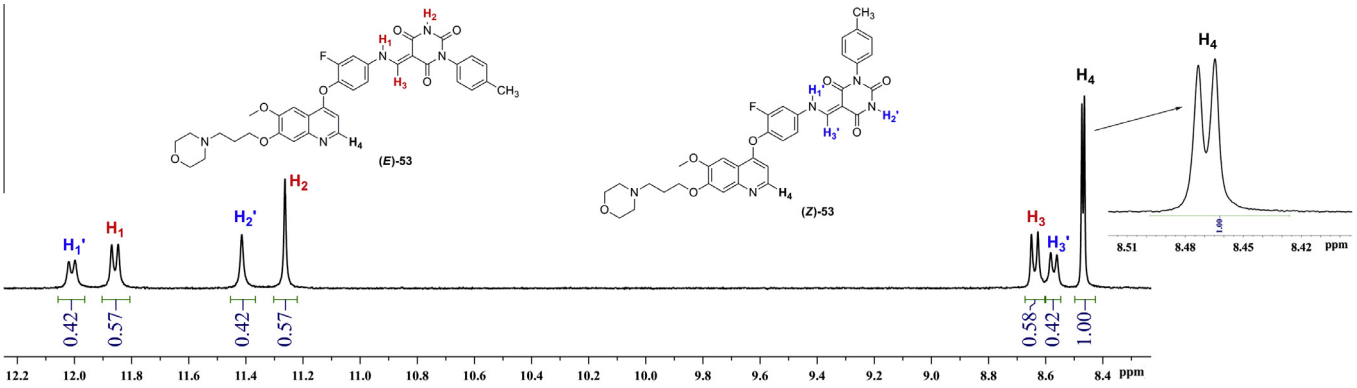
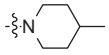
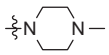


Figure 5. ^{1}H NMR (600 MHz) for compound **53** in DMSO-d_6.

Table 1
c-Met kinase activities of the target compounds **28–67**

Compd	R_1	R_2	c-Met IC_{50} (nM)
28		H	4.31 ± 0.15
29		4-CH_3	2.58 ± 0.18
30		2,6-$(CH_3)_2$	3.72 ± 0.31
31		4-F	3.64 ± 0.45
32		2,4-$(F)_2$	9.27 ± 1.42
33		3-Cl-4-F	3.15 ± 0.19
34		2-CF_3	18.54 ± 1.62
35		2,5-$(OCH_3)_2$-4-Cl	27.91 ± 2.43
36		H	3.84 ± 0.23
37		4-CH_3	**1.64 ± 0.16**[a]
38		2,6-$(CH_3)_2$	2.83 ± 0.42
39		4-F	3.09 ± 0.53
40		2,4-$(F)_2$	15.96 ± 2.39
41		3-Cl-4-F	4.82 ± 0.56
42		2-CF_3	18.25 ± 1.25
43		2,5-$(OCH_3)_2$-4-Cl	19.15 ± 1.43
44		H	3.36 ± 0.45
45		4-CH_3	**1.15 ± 0.16**
46		2,6-$(CH_3)_2$	2.35 ± 0.14
47		4-F	2.68 ± 0.48
48		2,4-$(F)_2$	12.39 ± 1.51
49		3-Cl-4-F	2.38 ± 0.38
50		2-CF_3	7.51 ± 0.76
51		2,5-$(OCH_3)_2$-4-Cl	16.8 ± 2.15
52		H	4.57 ± 0.27
53		4-CH_3	2.16 ± 0.63
54		2,6-$(CH_3)_2$	3.03 ± 0.16
55		4-F	3.58 ± 0.35
56		2,4-$(F)_2$	12.36 ± 1.25
57		3-Cl-4-F	5.14 ± 0.48
58		2-CF_3	21.24 ± 2.18
59		2,5-$(OCH_3)_2$-4-Cl	32.82 ± 2.25
60		H	3.29 ± 0.24
61		4-CH_3	2.68 ± 0.62
62		2,6-$(CH_3)_2$	3.26 ± 0.28
63		4-F	3.15 ± 0.35
64		2,4-$(F)_2$	8.35 ± 1.06
65		3-Cl-4-F	3.15 ± 0.23
66		2-CF_3	8.14 ± 2.38
67		2,5-$(OCH_3)_2$-4-Cl	24.72 ± 3.35
Foretinib[b]			1.86 ± 0.11

[a] Bold values show the IC_{50} values of the target compounds lower than the value of the positive control.
[b] Used as the positive control.

previously reported protocol.[50,51] In order to examine the selectivity of the most promising compound **45** on c-Met over other tyrosine kinases, it was screened against VEGFR-2, Flt-3, PDGFR-β, c-Kit, and EGFR. Briefly, 20 μg/mL poly (Glu, Tyr) 4:1 (Sigma) was preloaded as a substrate in 384-well plates. Then 50 μL of 10 mM ATP (Invitrogen) solution diluted in kinase reaction buffer (50 mM HEPES, pH 7.0, 1 M DTT, 1 M $MgCl_2$, 1 M $MnCl_2$, and 0.1% NaN_3) was added to each well. Various concentrations of compounds diluted in 10 μL of 1% DMSO (v/v) were used as the negative control. The kinase reaction was initiated by the addition of purified tyrosine kinase proteins diluted in 39 μL of kinase reaction buffer solution. The incubation time for the reactions was 30 min at 25 °C, and the reactions were stopped by the addition of 5 μL of Streptavidin-XL665 and 5 μL Tk Antibody Cryptate working solution to all of wells. The plates were read using Envision (PerkinElmer) 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. Cytotoxic activities against tumor cells assay

The cytotoxic activities of compounds **28–67** were evaluated against the HT-29, H460, MKN-45, A549, and U87MG cell lines using the standard MTT assay in vitro, with foretinib used as the positive control.[52,53] The cancer cell lines were cultured in minimum essential medium (MEM) supplemented 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 compounds tested at the indicated final concentrations were added to the culture medium and the cell cultures were continued for 72 h. Fresh MTT was added to each well at a terminal concentration of 5 μg/mL, and incubated with cells at 37 °C for 4 h. The formazan crystals were dissolved in 100 mL DMSO of 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 of the compounds were tested in triplicate in each cell line. The results expressed as IC_{50} (inhibitory concentration 50%) were the averages of three determinations and calculated by using the Bacus Laboratories Incorporated Slide Scanner (Bliss) software.

4. Results and discussion

4.1. In vitro enzymatic assays

The c-Met enzymatic assays of all synthesized compounds were evaluated using homogeneous time-resolved fluorescence (HTRF) assay. Foretinib was used as a positive control, with the results expressed as the half-maximal inhibitory concentration (IC_{50})

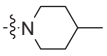
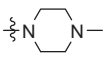
values presented in Table 1; the mean values of experiments performed in triplicate are shown.

As illustrated in Table 1, these novel 6,7-disubstituted-4-phenoxyquinoline derivatives bearing 5-(aminomethylene)pyrimidine-2,4,6-trione moiety were found to be active against c-Met kinase with IC_{50} values ranging from 1.15–32.82 nM; 2 of them (**45**, IC_{50} = 1.15 nM; **37**, IC_{50} = 1.64 nM) showed higher potency than foretinib (IC_{50} = 1.86 nM), indicating that replacement of the cyclopropane-1,1-dicarboxamide fragment in foretinib with the 5-(aminomethylene)pyrimidine-2,4,6-trione moiety maintained the c-Met inhibitory efficacy.

According to the data shown in Table 1, enzymatic assays data showed no preference for activity when the R_1 group was introduced to other different cyclic tertiary amino groups, indicating that the R_1 group contributed little to c-Met inhibitory efficacy. For example, the IC_{50} value of compound **44** was 3.36 nM, which was comparable to the values of **28**, **36**, **52**, and **60**, which were 4.31, 3.84, 4.57, and 3.29 nM, respectively.

Further studies were performed to examine the effect of different substituents on the phenyl ring (moiety B) on potency. Both the mono-electron-donating groups (mono-EDGs) and mono-electron-withdrawing groups (mono-EWGs) introduced to the phenyl ring increased the c-Met inhibitory efficacy, while incorporation of the mono-EDGs showed a higher preference. For example, compound **44**, with no substituent on the phenyl ring, showed a c-Met IC_{50} value 3.36 nM. Introduction of mono-EDGs to R_2 (**45**, R_2 = 4-CH_3, IC_{50} = 1.15 nM, increased 2.9-fold) increased the inhibitory efficacy to a greater extent than that of mono-EWGs (**47**, R_2 = 4-F, IC_{50} = 2.68 nM, increased 1.3-fold). This was further confirmed by introduction of these 2 types of groups in compounds **29**/**31**, **53**/**55**, and **61**/**63**. However, incorporation of double electron-donating groups (double-EDGs) and double electron-withdrawing groups (double-EWGs) showed opposite trend in potency of the compounds. Incorporation of double-EDGs increased the c-Met inhibitory efficacy; in contrast, the double-EWGs clearly decreased the potency, such as **46** (R_2 = 2,6-$(CH_3)_2$, IC_{50} = 2.35 nM) and **48** (R_2 = 2,4-$(F)_2$, IC_{50} = 12.39 nM). Similarly to our previous study, regulating electron density on the 5-atom linker to a proper degree was a key factor in improving inhibitory activity.[39] The pyrimidine-2,4,6-trione ring, which is part of the 5-atom linker, has lower electron density because of the electronic withdrawing effect of the 3 carbonyl groups. Therefore, EDGs (such as methyl) were required to increase the lower electron density on the 5-(aminomethylene)pyrimidine-2,4,6-trione moiety.

Table 2
Cytotoxic activities of the target compounds **28**–**67** against the HT-29, H460, MKN-45, A549, and U87MG cancer cell lines in vitro

Compd	R_1	R_2	IC_{50} (μM) ± SD				
			HT-29	H460	MKN-45	A549	U87MG
28		H	0.16 ± 0.058	0.22 ± 0.074	0.28 ± 0.063	0.51 ± 0.040	1.3 ± 0.10
29		4-CH_3	**0.12 ± 0.027** [a]	**0.10 ± 0.040**	0.19 ± 0.058	0.38 ± 0.035	1.5 ± 0.37
30		2,6-$(CH_3)_2$	0.20 ± 0.12	**0.16 ± 0.051**	0.49 ± 0.012	0.31 ± 0.024	1.2 ± 0.21
31		4-F	**0.14 ± 0.021**	**0.16 ± 0.030**	0.48 ± 0.020	ND[b]	ND
32		2,4-$(F)_2$	0.42 ± 0.018	1.1 ± 0.14	3.9 ± 0.15	ND	ND
33		3-Cl-4-F	0.20 ± 0.052	**0.08 ± 0.0062**	0.04 ± 0.0060	0.18 ± 0.051	**1.0 ± 0.28**
34		2-CF_3	1.3 ± 0.36	0.93 ± 0.043	0.10 ± 0.032	ND	ND
35		2,5-$(OCH_3)_2$-4-Cl	2.6 ± 0.32	1.2 ± 0.37	1.97 ± 0.21	ND	ND
36		H	0.28 ± 0.070	**0.17 ± 0.075**	0.046 ± 0.0050	0.39 ± 0.022	1.42 ± 0.43
37		4-CH_3	**0.14 ± 0.080**	**0.059 ± 0.0046**	0.056 ± 0.0080	0.99 ± 0.024	**0.92 ± 0.072**
38		2,6-$(CH_3)_2$	**0.12 ± 0.052**	**0.15 ± 0.042**	0.13 ± 0.025	ND	ND
39		4-F	0.22 ± 0.090	**0.11 ± 0.0070**	0.12 ± 0.082	0.35 ± 0.036	3.2 ± 0.37
40		2,4-$(F)_2$	5.1 ± 0.27	0.26 ± 0.026	0.46 ± 0.031	ND	ND
41		3-Cl-4-F	**0.15 ± 0.053**	**0.087 ± 0.0056**	0.065 ± 0.0054	ND	ND
42		2-CF_3	0.60 ± 0.035	0.38 ± 0.030	0.31 ± 0.032	ND	ND
43		2,5-$(OCH_3)_2$-4-Cl	0.63 ± 0.015	0.57 ± 0.035	0.46 ± 0.015	0.64 ± 0.014	3.4 ± 0.18
44		H	0.20 ± 0.021	0.29 ± 0.022	0.21 ± 0.030	ND	ND
45		4-CH_3	**0.13 ± 0.060**	**0.051 ± 0.0080**	0.057 ± 0.0040	**0.072 ± 0.0060**	**0.64 ± 0.045**
46		2,6-$(CH_3)_2$	**0.12 ± 0.071**	0.16 ± 0.030	0.90 ± 0.014	0.23 ± 0.057	1.24 ± 0.16
47		4-F	0.49 ± 0.060	0.62 ± 0.015	1.2 ± 0.26	ND	ND
48		2,4-$(F)_2$	0.71 ± 0.026	0.24 ± 0.060	2.8 ± 0.37	ND	ND
49		3-Cl-4-F	0.19 ± 0.043	**0.054 ± 0.0045**	0.072 ± 0.0090	0.19 ± 0.015	**0.68 ± 0.030**
50		2-CF_3	0.37 ± 0.011	0.36 ± 0.031	1.4 ± 0.20	ND	ND
51		2,5-$(OCH_3)_2$-4-Cl	9.4 ± 0.41	0.71 ± 0.040	0.35 ± 0.061	0.38 ± 0.025	2.8 ± 0.35
52		H	0.35 ± 0.016	0.26 ± 0.063	0.31 ± 0.052	0.93 ± 0.064	4.8 ± 0.26
53		4-CH_3	0.18 ± 0.030	**0.061 ± 0.0050**	0.21 ± 0.040	**0.11 ± 0.030**	8.5 ± 0.50
54		2,6-$(CH_3)_2$	**0.14 ± 0.025**	**0.085 ± 0.0041**	5.5 ± 0.16	2.2 ± 0.14	7.1 ± 0.43
55		4-F	0.24 ± 0.074	**0.12 ± 0.032**	0.74 ± 0.063	ND	ND
56		2,4-$(F)_2$	0.56 ± 0.060	0.85 ± 0.026	0.78 ± 0.080	ND	ND
57		3-Cl-4-F	0.28 ± 0.026	0.12 ± 0.014	0.11 ± 0.031	0.27 ± 0.053	**0.58 ± 0.080**
58		2-CF_3	3.7 ± 0.53	2.3 ± 0.64	18.4 ± 1.5	ND	ND
59		2,5-$(OCH_3)_2$-4-Cl	1.3 ± 0.13	0.54 ± 0.063	2.4 ± 0.35	ND	ND
60		H	0.19 ± 0.034	0.29 ± 0.052	0.52 ± 0.080	ND	ND
61		4-CH_3	0.49 ± 0.090	**0.070 ± 0.0053**	0.16 ± 0.037	0.43 ± 0.024	3.2 ± 0.31
62		2,6-$(CH_3)_2$	0.26 ± 0.060	**0.17 ± 0.010**	0.45 ± 0.026	ND	ND
63		4-F	0.31 ± 0.048	**0.12 ± 0.041**	0.12 ± 0.010	0.51 ± 0.060	
64		2,4-$(F)_2$	1.5 ± 0.17	1.17 ± 0.13	0.51 ± 0.032	0.38 ± 0.034	1.6 ± 0.32
65		3-Cl-4-F	**0.15 ± 0.013**	**0.076 ± 0.0032**	0.066 ± 0.0040	0.31 ± 0.042	**0.75 ± 0.066**
66		2-CF_3	7.3 ± 0.46	4.2 ± 0.14	3.5 ± 0.21	ND	ND
67		2,5-$(OCH_3)_2$-4-Cl	7.7 ± 0.12	1.8 ± 0.24	0.48 ± 0.030	ND	ND
Foretinib[c]			0.16 ± 0.015	0.19 ± 0.036	0.032 ± 0.0052	0.13 ± 0.010	1.1 ± 0.12

[a] Bold values show the IC_{50} values of the target compounds lower than the values of the positive control.
[b] ND: Not determined.
[c] Used as the positive control.

Table 3
Inhibition of tyrosine kinases by compound **45**

Kinase	Enzyme IC_{50} (nM)
VEGFR-2	384.1
Flt-3	496.3
PDGFR-β	530.6
c-Kit	652.5
EGFR	>100,000

A preference was observed for the number of substituents on the phenyl ring (moiety B), with following rank order: 1 > 2 > 0 > 3, including **29** (R_2 = 4-CH_3, IC_{50} = 2.58 nM), **30** (R_2 = 2,6-$(CH_3)_2$, IC_{50} = 3.72 nM), **28** (R_2 = H, IC_{50} = 4.31 nM), and **35** (R_2 = 2,5-$(OCH_3)_2$-4-Cl, IC_{50} = 27.91 nM). Moreover, potency decreased with the incorporation of bulky groups on the phenyl ring, such as a trifluoromethyl group (**34**, **42**, **50**, **58**, and **66**).

4.2. In vitro cytotoxic activities

Using foretinib as the positive control, the cytotoxic activities of all target compounds **28**–**67** have been evaluated against the HT-29, H460, and MKN-45 cell lines using the MTT assay. Some potent compounds were further evaluated against the A549 and U87MG cell lines. The results expressed as IC_{50} values are shown in Table 2 as the mean values of triplicate experiments.

All target compounds showed moderate to excellent cytotoxic activity against different cancer cells with potencies in the single-digit μM range, and 19 of them were more potent than foretinib against one or more cell lines. The IC_{50} values of the most promising compound, **45**, were 0.13, 0.051, 0.072, and 0.64 μM against the HT29, H460, A549, and U87MG cell lines, respectively, indicating that this compound was 1.2-, 3.7-, 1.8-, and 1.7-times more active than foretinib (IC_{50} values: 0.16, 0.19, 0.13, and 1.1 μM, respectively). Examination of the structure–activity relationships (SARs) indicated that these analogs had similar SARs as summarized in the c-Met kinase level: (a) different cyclic tertiary amino groups (R_1 group) contributed only minimally to the potency of the target compounds; (b) the pyrimidine-2,4,6-trione ring, which was a part of the 5-atom linker, required EDGs (such as methyl) to increase the electron density; (c) the number, size, and electronic property of substituents (R_2 group) on the phenyl ring (moiety B) were key factors in improving the potency.

4.3. Enzymatic selectivity assays

To examine the selectivity of compound **45** on c-Met over other kinases, this compound was screened against 5 other tyrosine kinases. As shown in Table 3, compound **45** exhibited excellent selectivity versus VEGFR-2 (IC_{50} = 384.1 nM, 334-fold), Flt-3 (IC_{50} = 496.3 nM, 432-fold), PDGFR-β (IC_{50} = 530.6 nM, 461-fold), and c-Kit (IC_{50} = 652.5 nM, 567-fold), with no inhibition activity against EGFR (IC_{50} > 100 μM). These data suggest that compound **45** may be a selective single target c-Met kinase inhibitor.

5. Binding model analysis

To further elucidate the binding mode of compounds, docking analysis was performed. In our study, the co-crystal structure of foretinib (GSK1363089) with c-Met kinase was selected as the

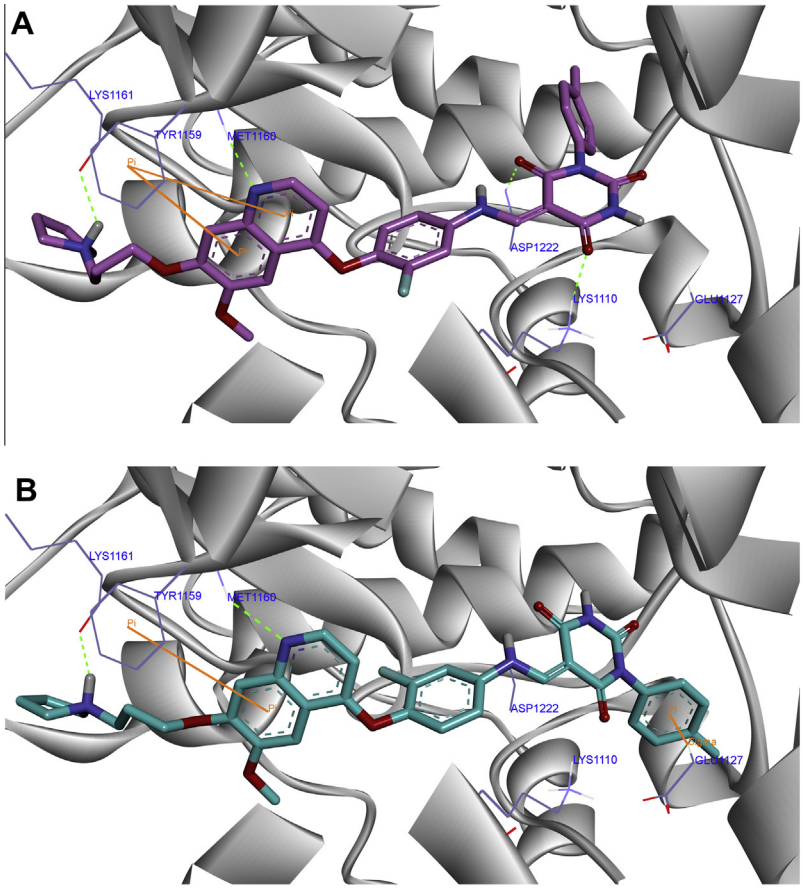


Figure 6. Binding poses of compound ***Z*-45** (**A**) and ***E*-45** (**B**) with c-Met. The proteins were displayed by silver ribbon. Compound ***Z*-45** and ***E*-45** were displayed by pink and cyan sticks, respectively. H-bonding interactions between the **45** and c-Met were indicated with dashed lines in green. Pi–Pi and Pi–Sigma interactions were shown with orange–yellow lines.

docking model (PDB ID: 3LQ8). The docking simulation was conducted using Glide XP (Schrödinger2013), 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 3.0 system. The binding model was exemplified by the interaction of compound **45** with c-Met. As shown in Figure 6, the protonated nitrogen atom of pyrrolidine and the nitrogen atom of the quinoline ring in **45** formed hydrogen-bonding interactions with LYS1161 and MET1160, respectively. The Pi-Pi interactions had been formed between the quinoline ring and TYR1159. In addition, two oxygen atoms of PYT in ***Z*-45** formed two hydrogen bonds with ASP1222 and LYS1110. While, the Pi-Sigma interaction was forged between the phenyl ring (moiety B) in ***E*-45** and GLU1127.

6. Conclusions

In summary, we designed and synthesized 40 quinoline derivatives bearing a 5-(aminomethylene)pyrimidine-2,4,6-trione scaffold. c-Met kinase and 5 human cancer cell lines (HT-29, H460, MKN-45, A549, and U87MG) were used to evaluate the potency of the synthesized compounds. Compared with foretinib, 2 of the derivatives showed higher c-Met kinase inhibitory activity, and 19 were more potent against one or more cell lines. The most promising compound, **45**, showed excellent inhibition on c-Met kinase (IC_{50} = 1.15 nM) compared to the 5 other tyrosine kinases screened in this report; its cytotoxic activity against the HT-29, H460, A549, and U87MG cell lines (IC_{50} values: 0.13, 0.051, 0.072, and 0.64 μM, respectively) were 1.2-, 3.7-, 1.8-, and 1.7-times more active than that of foretinib, respectively. Analysis of SARs indicated that EDGs on the phenyl ring (moiety B) were required to increase the electron density on the 5-(aminomethylene)pyrimidine-2,4,6-trione moiety. In addition, the hydrophobic pocket of c-Met was probably not sufficiently large to accommodate moiety B with bulky groups. Therefore, a methyl group was the most favorable substituent on the phenyl ring. Further studies on SARs and the mechanism of action of these compounds are underway in our laboratory.

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-300, 300 MHz; 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).

7.1. General procedure for preparation of 3-fluoro-4-(6,7-disubstituted quinolin-4-yloxy)anilines (23a–23e)

The preparation of the key intermidiates **23a**–**23e** has been illustrated in detail in our previous work,[41,42] and so the synthesis method would not be listed here.

7.1.1. 3-Fluoro-4-(6-methoxy-7-(3-(piperdin-1-yl)propoxy)quinolin-4-yloxy)aniline (23a)

Gray solid; yield: 86%; mp 196–197 °C; IR (KBr) cm^{-1}: 3482.2, 3387.0, 2946.5, 2835.1, 2788.1, 1621.1, 1587.8, 1512.8, 1483.4, 1252.9, 1215.4, 853.5; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.46 (d, J = 5.3 Hz, 1H), 7.58 (s, 1H), 7.41 (s, 1H), 7.03 (t, J = 8.7 Hz, 1H), 6.56 (dd, J = 11.8, 2.6 Hz, 1H), 6.50 (m, 1H), 6.39 (dd, J = 5.3, 1.1 Hz, 1H), 4.24 (t, J = 6.8 Hz, 2H), 4.04 (d, J = 3.8 Hz, 3H), 3.81 (s, 2H), 2.54 (m, 2H), 2.43 (s, 4H), 2.14 (m, 2H), 1.60 (m, 4H), 1.45 (d, J = 5.2 Hz, 2H); MS m/z (ESI): 426.4 $[M+H]^+$, 448.4 $[M+Na]^+$.

7.1.2. 3-Fluoro-4-(6-methoxy-7-(3-(4-methylpiperdin-1-yl)propoxy)quinolin-4-yl-oxy)aniline (23b)

White solid; yield: 77%; mp 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 m/z (ESI): 440.3 $[M+H]^+$.

7.1.3. 3-Fluoro-4-(6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy)quinolin-4-yloxy)aniline (23c)

Light yellow solid; yield: 72%; mp 208–209 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.49 (d, J = 5.2 Hz, 1H), 7.55 (s, 1H), 7.44 (s, 1H), 7.08 (t, J = 9.0 Hz, 1H), 6.57 (d, J = 14.1 Hz, 1H), 6.46 (m, J = 12.8, 7.1 Hz, 2H), 4.28 (t, J = 5.7 Hz, 2H), 3.96 (s, 3H), 3.59 (s, 2H), 3.04 (m, 9H), 2.28 (m, 2H), 1.96 (d, J = 28.0 Hz, 4H); MS m/z (ESI): 412.2 $[M+H]^+$.

7.1.4. 3-Fluoro-4-(6-methoxy-7-(3-morpholinopropoxy)quinolin-4-yloxy)aniline (23d)

White solid; yield: 82%; mp 217–218 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.47 (d, J = 5.2 Hz, 1H), 7.58 (s, 1H), 7.44 (s, 1H), 7.04 (t, J = 8.7 Hz, 1H), 6.57 (dd, J = 11.9, 2.6 Hz, 1H), 6.50 (m, 1H), 6.41 (d, J = 5.3 Hz, 1H), 4.27 (t, J = 6.6 Hz, 2H), 4.04 (s, 3H), 3.82 (s, 2H), 3.74 (m, 4H), 2.60 (t, J = 7.1 Hz, 2H), 2.51 (d, J = 4.2 Hz, 4H), 2.13 (m, 2H); MS m/z (ESI): 428.3 $[M+H]^+$.

7.1.5. 3-Fluoro-4-(6-methoxy-7-(3-(4-methylpiperazin-1-yl)propoxy)quinolin-4-yl-oxy)aniline (23e)

White solid; yield: 77%; mp 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 m/z (ESI): 441.4 $[M+H]^+$.

7.2. General procedure for preparation of 1-substitutedphenylureas (25a–25h)

To the mixture of an appropriately substituted phenylamine (0.43 mol), glacial acetic acid (120 mL) and H_2O (120 mL), and sodium cyanate (0.86 mol) was added slowly at room temperature. Upon the completion of addition, the reaction mixture was stirred at 40 °C for 2–4 h and monitored by thin-layer chromatography (TLC). The reaction mixture was poured into water (500 mL) and stirred for 0.5 h; the precipitated was collected by filtration and dried to give the corresponding substituted phenylureas **25a**–**25h** as white solids.

7.2.1. 1-Phenylurea (25a)

Yield: 82%; mp 257–258 °C; IR (KBr) cm^{-1}: 3429.8, 3414.2, 2919.2, 2850.5, 1655.8, 1614.3, 1592.4, 1554.3, 1449.2, 1127.6,

696.9, 620.2, 588.5; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.51 (s, 1H), 7.40 (d, J = 7.9 Hz, 2H), 7.21 (t, J = 7.8 Hz, 2H), 6.89 (t, J = 7.3 Hz, 1H), 5.86 (s, 2H); MS m/z (ESI): 159.1 [M+Na]$^+$.

7.2.2. 1-*p*-Tolylurea (25b)

Yield: 85%; mp 242–243 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.39 (s, 1H), 7.27 (d, J = 8.2 Hz, 2H), 7.01 (d, J = 8.1 Hz, 2H), 5.78 (s, 2H), 2.21 (s, 3H); MS m/z (ESI): 151.2 [M+H]$^+$, 173.4 [M+Na]$^+$.

7.2.3. 1-(2,6-Dimethylphenyl)urea (25c)

Yield: 82%; mp 229–230 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.53 (s, 1H), 7.03–6.95 (m, 3H), 5.70 (s, 2H), 2.17 (s, 6H); MS m/z (ESI): 165.4 [M+H]$^+$.

7.2.4. 1-(4-Fluorophenyl)urea (25d)

Yield: 86%; mp 245–246 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.56 (s, 1H), 7.48–7.31 (m, 2H), 7.04 (t, J = 8.9 Hz, 2H), 5.84 (s, 2H).MS m/z (ESI): 151.2 [M+H]$^+$.

7.2.5. 1-(2,4-Difluorophenyl)urea (25e)

Yield: 85%; mp 243–244 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.76 (s, 1H), 7.74–7.52 (m, 1H), 7.32–7.18 (m, 1H), 7.08–6.92 (m, 1H), 5.97 (s, 2H); MS m/z (ESI): 173.1 [M+H]$^+$, 367.2 [2M+Na]$^+$.

7.2.6. 1-(3-Chloro-4-fluorophenyl)urea (25f)

Yield: 81%; mp 235–236 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.84 (s, 1H), 7.78 (dd, J = 6.9, 2.4 Hz, 1H), 7.30–7.16 (m, 2H), 6.00 (s, 2H); MS m/z (ESI): 189.6 [M+H]$^+$.

7.2.7. 1-(2-(Trifluoromethyl)phenyl)urea (25g)

Yield: 83%; mp 234–236 °C; IR (KBr) cm^{-1}: 3437.5, 3340.3, 2919.1, 2850.5, 1656.2, 1617.8, 1590.2, 1522.1, 1321.0, 1109.1, 761.1, 649.7, 597.6; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.94 (d, J = 8.2 Hz, 1H), 7.81 (s, 1H), 7.63–7.49 (m, 2H), 7.18 (t, J = 7.6 Hz, 1H), 6.39 (s, 2H); MS m/z (ESI): 205.3 [M+H]$^+$.

7.2.8. 1-(4-Chloro-2,5-dimethoxyphenyl)urea (25h)

Yield: 84%; mp 213–214 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.91 (s, 1H), 7.58 (s, 1H), 7.06 (s, 1H), 6.19 (s, 2H), 3.70 (s, 3H), 3.62 (s, 3H); MS m/z (ESI): 231.4 [M+H]$^+$.

7.3. General procedure for preparation of 1-substitutedphenylpyrimidine-2,4,6-triones (26a–26h)

Sodium (7.4 g, 0.32 mol) was added into anhydrous EtOH (300 mL) in batches in an ice bath. After disappearance of the solid sodium in anhydrous EtOH, an appropriate substituted phenylurea (0.16 mol) and dimethyl malonate (20.2 g, 0.19 mol) was added slowly at room temperature and stirred for 0.5 h. The reaction mixture then was stirred at reflux for 8–12 h and monitored by TLC. The solvent was concentrated in a vacuum and the residue was resolved with water (400 mL), acidified with hydrochloric acid to pH 2, and stirred for 0.5 h. The precipitated was collected by filtration and dried to give the corresponding 4-substitutedphenylpyrimidine-2,4,6-triones at moderate yield.

7.3.1. 1-Phenylpyrimidine-2,4,6-trione (26a)

Yield: 76%; mp 247–248 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.58 (s, 1H), 7.43–7.26 (m, 5H), 3.73 (s, 2H); MS m/z (ESI): 205.2 [M+H]$^+$.

7.3.2. 1-*p*-Tolylpyrimidine-2,4,6-trione (26b)

Yield: 71%; mp 235–237 °C; IR (KBr) cm^{-1}: 3437.2, 3204.5, 3153.9, 3086.6, 2882.9, 1730.4, 1686.0, 1515.5, 1428.8, 1342.4, 1209.3, 822.1, 718.8, 627.5, 483.2; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.47 (s, 1H), 7.25 (d, J = 8.1 Hz, 2H), 7.10 (d, J = 8.2 Hz, 2H), 3.72 (s, 2H), 2.35 (s, 3H); MS m/z (ESI): 217.1 [M−H]$^-$.

7.3.3. 1-(2,6-Dimethylphenyl)pyrimidine-2,4,6-trione (26c)

Yield: 73%; mp 214–217 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.62 (s, 1H), 7.20 (d, J = 7.2 Hz, 1H), 7.13 (d, J = 7.4 Hz, 2H), 3.90 (s, 2H), 2.06 (s, 6H); MS m/z (ESI): 233.4 [M+H]$^+$.

7.3.4. 1-(4-Fluorophenyl)pyrimidine-2,4,6-trione (26d)

Yield: 76%; mp 221–222 °C; IR (KBr) cm^{-1}: 3439.0, 3204.0, 3151.5, 3084.9, 2885.7, 1730.5, 1689.2, 1511.2, 1430.3, 1345.2, 1244.7, 1209.2, 843.3, 722.0, 539.2, 500.3; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.54 (s, 1H), 7.29 (d, J = 6.8 Hz, 4H), 3.74 (s, 2H); MS m/z (ESI): 223.5 [M+H]$^+$.

7.3.5. 1-(2,4-Difluorophenyl)pyrimidine-2,4,6-trione (26e)

Yield: 70%; mp 228–229 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.64 (s, 1H), 7.45 (s, 2H), 7.16 (s, 1H), 3.75 (s, 2H); MS m/z (ESI): 241.6 [M+H]$^+$, 263.2 [M+Na]$^+$.

7.3.6. 1-(3-Chloro-4-fluorophenyl)pyrimidine-2,4,6-trione (26f)

Yield: 74%; mp 224–225 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.61 (s, 1H), 7.69–7.41 (m, 2H), 7.30 (ddd, J = 8.7, 4.3, 2.5 Hz, 1H), 3.73 (s, 2H); MS m/z (ESI): 256.9 [M−H]$^-$.

7.3.7. 1-(2-(Trifluoromethyl)phenyl)pyrimidine-2,4,6-trione (26g)

Yield: 72%; mp 223–224 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.72 (s, 1H), 7.86 (d, J = 8.0 Hz, 1H), 7.81 (d, J = 7.6 Hz, 1H), 7.68 (t, J = 7.5 Hz, 1H), 7.55 (d, J = 7.7 Hz, 1H), 4.08 (d, J = 21.1 Hz, 1H), 3.67 (d, J = 21.1 Hz, 1H); MS m/z (ESI): 297.3 [M+Na]$^+$.

7.3.8. 1-(4-Chloro-2,5-dimethoxyphenyl)pyrimidine-2,4,6-trione (26h)

Yield: 73%; mp 214–215 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.53 (s, 1H), 7.16 (s, 1H), 7.02 (s, 1H), 3.72 (s, 3H), 3.64 (s, 3H), 3.72 (s, 2H); MS m/z (ESI): 299.5 [M+H]$^+$.

7.4. General procedure for preparation of 5-((dimethylamino)methylene)-1-substitutedphenylpyrimidine-2,4,6-triones (27a–27h)

A mixture of an appropriately 1-substituted phenylpyrimidine-2,4,6-trione (0.05 mol) and DMF-DMA (66 mL, 0.5 mol) was heated at 50 °C for 6–10 h and monitored by TLC. Upon cooling the reaction mixture to room temperature, the precipitate was collected by filtration, washed with Et_2O (40 mL), and dried to give the corresponding 5-((dimethylamino)methylene)-1-substituted-phenylpyrimidine-2,4,6-triones as yellow solids.

7.4.1. (*E*)-5-((Dimethylamino)methylene)-1-phenylpyrimidine-2,4,6-trione (27a)

Yield: 71%; mp 292–293 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.12 (s, 1H), 7.32–7.11 (m, 5H), 3.43 (s, 3H), 3.24 (s, 3H); MS m/z (ESI): 282.4 [M+Na]$^+$.

7.4.2. (*E*)-5-((Dimethylamino)methylene)-1-*p*-tolylpyrimidine-2,4,6-trione (27b)

Yield: 69%; mp 287–288 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.12 (s, 1H), 7.23 (d, J = 8.1 Hz, 2H), 7.09 (d, J = 8.2 Hz, 2H), 3.43 (s, 3H), 3.24 (s, 3H), 2.34 (s, 3H); MS m/z (ESI): 274.1 [M+H]$^+$.

7.4.3. (*E*)-5-((Dimethylamino)methylene)-1-(2,6-dimethylphenyl)pyrimidine-2,4,6-trione (27c)

Yield: 73%; mp 275–276 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.12 (s, 1H), 7.21–7.06 (m, 3H), 3.43 (s, 3H), 3.24 (s, 3H); MS m/z (ESI): 288.3 [M+H]$^+$, 310.6 [M+Na]$^+$.

7.4.4. (*E*)-5-((Dimethylamino)methylene)-1-(4-fluorophenyl)pyrimidine-2,4,6-trione (27d)

Yield: 71%; mp 283–284 °C; IR (KBr) cm^{-1}: 3434.8, 3178.6, 3060.0, 2919.9, 2849.9, 1721.8, 1676.4, 1644.7, 1518.3, 1432.0, 1384.3, 1285.9, 1144.2, 777.7, 650.1, 617.0, 541.2; ^1H NMR (400 MHz, DMSO-d_6) δ 10.55 (br, 1H), 8.12 (s, 1H), 7.38–7.19 (m, 4H), 3.43 (s, 3H), 3.24 (s, 3H), 2.07 (s, 3H), 2.05 (s, 3H); MS *m*/*z* (ESI): 277.3, 278.3 $[M+H]^+$.

7.4.5. (*E*)-5-((Dimethylamino)methylene)-1-(2,4-difluorophenyl)pyrimidine-2,4,6-trione (27e)

Yield: 72%; mp 278–279 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 10.51 (br, 1H), 8.12 (s, 1H), 7.47 (s, 2H), 7.13 (s, 1H), 3.43 (s, 3H), 3.24 (s, 3H); MS *m*/*z* (ESI): 296.5 $[M+H]^+$.

7.4.6. (*E*)-5-((Dimethylamino)methylene)-1-(3-chloro-4-fluorophenyl)pyrimidine-2,4,6-trione (27f)

Yield: 68%; mp 268–269 °C; IR (KBr) cm^{-1}: 3436.3, 3198.8, 3066.5, 2920.0, 2850.5, 1724.3, 1679.8, 1626.9, 1501.0, 1438.1, 1384.5, 1264.1, 1143.7, 776.5, 529.1; ^1H NMR (400 MHz, DMSO-d_6) δ 8.12 (s, 1H), 7.58 (dd, *J* = 6.8, 2.4 Hz, 1H), 7.47 (t, *J* = 9.0 Hz, 1H), 7.29 (ddd, *J* = 8.7, 4.4, 2.5 Hz, 1H), 3.44 (s, 3H), 3.24 (s, 3H); MS *m*/*z* (ESI): 332.3, 334.0 $[M+Na]^+$, 644.9, 646.0 $[2M+Na]^+$.

7.4.7. (*E*)-5-((Dimethylamino)methylene)-1-(2-(trifluoromethyl)phenyl)pyrimidine-2,4,6-trione (27g)

Yield: 70%; mp 270–271 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 8.12 (s, 1H), 7.84 (d, *J* = 8.1 Hz, 1H), 7.80 (d, *J* = 7.8 Hz, 1H), 7.67 (t, *J* = 7.6 Hz, 1H), 7.53 (d, *J* = 7.6 Hz, 1H), 3.43 (s, 3H), 3.24 (s, 3H); MS *m*/*z* (ESI): 328.5 $[M+H]^+$.

7.4.8. (*E*)-5-((Dimethylamino)methylene)-1-(4-chloro-2,5-dimethoxyphenyl)pyrimidine-2,4,6-trione (27h)

Yield: 71%; mp 264–265 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 8.12 (s, 1H), 7.15 (s, 1H), 7.01 (s, 1H), 3.71 (s, 3H), 3.63 (s, 3H), 3.43 (s, 3H), 3.24 (s, 3H); MS *m*/*z* (ESI): 354.4 $[M+H]^+$.

7.5. General procedure for preparation of the target compounds (28–67)

A mixture of an appropriately 5-((dimethylamino)methylene)-1-substitutedphenylpyrimidine-2,4,6-trione and glacial acetic acid was heated at 80 °C for 20–30 h and monitored by TLC. The solvent was concentrated in a vacuum and the residue was resolved with dichloromethane (300 mL), washed with 5% Na_2CO_3 (80 mL × 5), brine (80 mL), dried over anhydrous Na_2SO_4, and concentrated in a vacuum. The crude product was purified by chromatography on silica gel using MeOH/CH_2Cl_2 to afford the white solids **28–67**.

7.5.1. 5-((3-Fluoro-4-(6-methoxy-7-(3-(piperidin-1-yl)propoxy)quinolin-4-yloxy)phenylamino)methylene)-1-phenylpyrimidine-2,4,6-trione (28)

Yield: 52%; mp 248–249 °C; ^1H NMR (300 MHz, DMSO-d_6) δ 8.54 (br, 1H), 8.44 (d, *J* = 5.0 Hz, 1H), 7.63 (d, *J* = 12.4 Hz, 1H), 7.48 (s, 1H), 7.44–7.29 (m, 5H), 7.23 (d, *J* = 7.0 Hz, 2H), 7.11 (d, *J* = 7.8 Hz, 1H), 6.43 (d, *J* = 5.2 Hz, 1H), 4.14 (t, *J* = 6.4 Hz, 2H), 3.90 (s, 3H), 2.38 (t, *J* = 7.0 Hz, 2H), 2.31 (br, 4H), 1.99–1.83 (m, 2H), 1.52–1.41 (m, 4H), 1.39–1.28 (m, 2H); MS *m*/*z* (ESI): 640.2 $[M+H]^+$; Anal. Calcd for $C_{35}H_{34}FN_5O_6$: C, 65.72; H, 5.36; N, 10.95. Found: C, 65.56; H, 5.38; N, 10.96.

7.5.2. 5-((3-Fluoro-4-(6-methoxy-7-(3-(piperidin-1-yl)propoxy)quinolin-4-yloxy)phenylamino)methylene)-1-*p*-tolylpyrimidine-2,4,6-trione (29)

Yield: 54%; mp 264–265 °C; ^1H NMR (300 MHz, DMSO-d_6) δ 8.49 (br, 1H), 8.43 (d, *J* = 5.3 Hz, 1H), 7.48 (s, 1H), 7.40 (d, *J* = 8.8 Hz, 1H), 7.35 (s, 1H), 7.19 (d, *J* = 8.4 Hz, 2H), 7.13 (d, *J* = 7.8 Hz, 1H), 7.05 (d, *J* = 8.1 Hz, 2H), 6.95 (d, *J* = 8.2 Hz, 1H), 6.42 (d, *J* = 4.9 Hz, 1H), 4.14 (t, *J* = 6.3 Hz, 2H), 3.90 (s, 3H), 2.38 (t, *J* = 7.1 Hz, 2H), 2.31 (br, 4H), 2.28 (s, 3H), 1.98–1.84 (m, 2H), 1.52–1.41 (m, 4H), 1.39–1.28 (m, 2H); MS *m*/*z* (ESI): 654.3 $[M+H]^+$, 676.4 $[M+Na]^+$; Anal. Calcd for $C_{36}H_{36}FN_5O_6$: C, 66.14; H, 5.55; N, 10.71. Found: C, 66.18; H, 5.59; N, 10.81.

7.5.3. 5-((3-Fluoro-4-(6-methoxy-7-(3-(piperidin-1-yl)propoxy)quinolin-4-yloxy)phenylamino)methylene)-1-(2,6-dimethylphenyl)pyrimidine-2,4,6-trione (30)

Yield: 55%; mp 236–237 °C; ^1H NMR (300 MHz, DMSO-d_6) δ 11.88 (br, 1H), 11.36 (br, 1H), 8.62 (br, 1H), 8.44 (d, *J* = 5.4 Hz, 1H), 7.88 (d, *J* = 12.5 Hz, 1H), 7.50 (s, 1H), 7.48 (s, 1H), 7.38 (s, 1H), 7.21–7.03 (m, 4H), 6.44 (d, *J* = 5.2 Hz, 1H), 4.18 (t, *J* = 6.4 Hz, 2H), 3.90 (s, 3H), 2.87–2.58 (m, 6H), 2.02 (s, 6H), 1.69–1.52 (m, 4H), 1.48–1.34 (m, 2H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 165.42, 164.56, 162.33, 159.43, 155.30, 153.66, 152.40, 150.14, 150.07, 149.29, 146.89, 138.77, 138.03, 136.44, 133.43, 128.77, 128.47 (2C), 125.16, 116.69, 114.95, 109.20, 108.99, 102.75, 99.43, 93.35, 67.17, 56.24, 55.37, 54.33 (2C), 26.25, 25.67 (2C), 24.19, 17.75 (2C); MS *m*/*z* (ESI): 668.1 $[M+H]^+$; Anal. Calcd for $C_{37}H_{38}FN_5O_6$: C, 66.55; H, 5.74; N, 10.49. Found: C, 66.57; H, 5.69; N, 10.51.

7.5.4. 5-((3-Fluoro-4-(6-methoxy-7-(3-(piperidin-1-yl)propoxy)quinolin-4-yloxy)phenylamino)methylene)-1-(4-fluorophenyl)pyrimidine-2,4,6-trione (31)

Yield: 49%; mp 273–274 °C; IR (KBr) cm^{-1}: 3437.3, 3074.4, 2923.2, 2851.0, 1729.5, 1683.8, 1635.6, 1614.6, 1588.1, 1512.3, 1466.2, 1432.6, 1384.4, 1350.1, 1308.2, 1211.7, 1156.0, 1127.3, 1.17.9, 842.4, 780.8, 618.5, 531.6, 518.1, 428.4; ^1H NMR (300 MHz, DMSO-d_6) δ 11.81 (br, 1H), 11.30 (br, 1H), 8.58 (br, 1H), 8.44 (d, *J* = 4.8 Hz, 1H), 7.87 (d, *J* = 12.1 Hz, 1H), 7.48 (s, 3H), 7.36 (s, 3H), 7.27 (d, *J* = 7.9 Hz, 2H), 6.44 (d, *J* = 4.2 Hz, 1H), 4.15 (t, *J* = 6.6 Hz, 2H), 3.90 (s, 3H), 2.62–2.35 (m, 6H, superposed with DMSO), 2.02–1.88 (m, 2H), 1.58–1.43 (m, 4H), 1.41–1.27 (m, 2H); MS *m*/*z* (ESI): 658.6 $[M+H]^+$; Anal. Calcd for $C_{35}H_{32}F_2N_5O_6$: C, 63.92; H, 5.06; N, 10.65. Found: C, 64.02; H, 5.01; N, 10.69.

7.5.5. 5-((3-Fluoro-4-(6-methoxy-7-(3-(piperidin-1-yl)propoxy)quinolin-4-yloxy)phenylamino)methylene)-1-(2,4-difluorophenyl)pyrimidine-2,4,6-trione (32)

Yield: 48%; mp 263–264 °C; ^1H NMR (300 MHz, DMSO-d_6) δ 8.55 (br, 1H), 8.44 (d, *J* = 5.8 Hz, 1H), 7.68 (s, 1H), 7.56–7.31 (m, 6H), 7.17 (d, *J* = 7.8 Hz, 1H), 6.42 (d, *J* = 5.4 Hz, 1H), 4.14 (t, *J* = 6.6 Hz, 2H), 3.90 (s, 3H), 2.38 (t, *J* = 7.2 Hz, 2H), 2.31 (br, 4H), 1.97–1.85 (m, 2H), 1.52–1.41 (m, 4H), 1.39–1.30 (m, 2H); MS *m*/*z* (ESI): 676.4 $[M+H]^+$, 698.6 $[M+Na]^+$; Anal. Calcd for $C_{35}H_{32}F_3N_5O_6$: C, 62.22; H, 4.77; N, 10.37. Found: C, 62.28; H, 4.72; N, 10.15.

7.5.6. 5-((3-Fluoro-4-(6-methoxy-7-(3-(piperidin-1-yl)propoxy)quinolin-4-yloxy)phenylamino)methylene)-1-(3-chloro-4-fluorophenyl)pyrimidine-2,4,6-trione (33)

Yield: 46%; mp 252–253 °C; ^1H NMR (300 MHz, DMSO-d_6) δ 8.51 (br, 1H), 8.43 (d, *J* = 5.0 Hz, 1H), 7.57 (d, *J* = 6.8 Hz, 2H), 7.49–7.24 (m, 6H), 6.41 (d, *J* = 5.2 Hz, 1H)), 4.14 (t, *J* = 6.7 Hz, 2H), 3.90 (s, 3H), 2.39 (t, *J* = 6.4 Hz, 2H), 2.30 (br, 4H), 1.98–1.82 (m, 2H), 1.52–1.39 (m, 4H), 1.38–1.26 (m, 2H); MS *m*/*z* (ESI): 692.6 $[M+H]^+$, 714.3 $[M+Na]^+$; Anal. Calcd for $C_{35}H_{32}ClF_2N_5O_6$: C, 60.74; H, 4.66; N, 10.12. Found: C, 61.02; H, 4.69; N, 10.15.

7.5.7. 5-((3-Fluoro-4-(6-methoxy-7-(3-(piperidin-1-yl)propoxy)quinolin-4-yloxy)phenylamino)methylene)-1-(2-(trifluoromethyl)phenyl)pyrimidine-2,4,6-trione (34)

Yield: 49%; mp 247–248 °C; ^1H NMR (300 MHz, DMSO-d_6) δ 8.51 (br, 1H), 8.43 (d, *J* = 5.2 Hz, 1H), 7.49 (s, 1H), 7.47–7.36 (m,

5H), 7.35 (s, 1H), 7.24 (s, 1H), 6.42 (d, J = 5.6 Hz, 1H), 4.15 (t, J = 6.5 Hz, 2H), 3.91 (s, 3H), 2.38 (t, J = 7.1 Hz, 2H), 2.31 (br, 4H), 1.97–1.86 (m, 2H), 1.51–1.40 (m, 4H), 1.39–1.28 (m, 2H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 165.43, 164.51, 160.60, 159.60, 152.35, 151.17, 150.56, 150.05, 149.28, 146.77, 145.76, 132.66, 130.69, 129.87, 127.88, 124.72, 121.07, 117.09, 114.89, 110.57, 108.93, 108.87, 106.11, 101.95, 99.44, 95.45, 67.28, 56.23, 55.57, 54.59 (2C), 26.57, 26.08 (2C), 24.62; MS m/z (ESI): 730.6 $[M+Na]^+$; Anal. Calcd for $C_{36}H_{33}F_4N_5O_6$: C, 61.10; H, 4.70; N, 9.90. Found: C, 61.14; H, 4.87; N, 10.03.

7.5.8. 5-((3-Fluoro-4-(6-methoxy-7-(3-(piperidin-1-yl)propoxy)quinolin-4-yloxy)phenylamino)methylene)-1-(4-chloro-2,5-dimethoxyphenyl)pyrimidine-2,4,6-trione (35)

Yield: 50%; mp 212–213 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.44 (br, 1H), 8.42 (d, J = 5.4 Hz, 1H), 7.49 (s, 1H), 7.35 (s, 1H), 7.17 (s, 1H), 7.13 (s, 1H), 7.06–6.98 (m, 2H), 6.95 (s, 1H), 6.40 (d, J = 5.3 Hz, 1H), 4.14 (s, 2H), 3.90 (d, J = 3.1 Hz, 3H), 3.71 (s, 3H), 3.63 (s, 3H), 2.38 (t, J = 7.1 Hz, 3H), 2.30 (br, 4H), 1.95–1.86 (m, 2H), 1.52–1.41 (m, 4H), 1.38–1.27 (m, 2H); MS m/z (ESI): 734.5 $[M+H]^+$; Anal. Calcd for $C_{37}H_{37}ClFN_5O_8$: C, 60.53; H, 5.08; N, 9.54. Found: C, 60.61; H, 5.09; N, 9.94.

7.5.9. 5-((3-Fluoro-4-(6-methoxy-7-(3-(4-methylpiperidin-1-yl)propoxy)quinolin-4-yloxy)phenylamino)methylene)-1-phenylpyrimidine-2,4,6-trione (36)

Yield: 54%; mp 251–252 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.54 (br, 1H), 8.44 (d, J = 5.4 Hz, 1H), 7.81 (d, J = 12.2 Hz, 1H), 7.48 (s, 1H), 7.45–7.27 (m, 5H), 7.21 (d, J = 7.1 Hz, 2H), 7.09 (d, J = 7.7 Hz, 1H), 6.43 (d, J = 5.4 Hz, 1H), 4.16 (t, J = 6.4 Hz, 2H), 3.90 (s, 3H), 2.83 (d, J = 10.9 Hz, 2H), 2.41 (t, J = 7.1 Hz, 2H), 1.95–1.89 (m, 2H), 1.84 (t, J = 11.2 Hz, 2H), 1.55 (d, J = 13.7 Hz, 2H), 1.19 (br, 1H), 1.13 (d, J = 12.7, Hz, 2H), 0.85 (d, J = 6.4 Hz, 3H); MS m/z (ESI): 654.3 $[M+H]^+$; Anal. Calcd for $C_{36}H_{36}FN_5O_6$: C, 66.14; H, 5.55; N, 10.71. Found: C, 66.08; H, 5.49; N, 10.81.

7.5.10. 5-((3-Fluoro-4-(6-methoxy-7-(3-(4-methylpiperidin-1-yl)propoxy)quinolin-4-yloxy)phenylamino)methylene)-1-*p*-tolylpyrimidine-2,4,6-trione (37)

Yield: 55%; mp 238–239 °C; IR (KBr) cm^{-1}: 3435.6, 3208.2, 3068.4, 2923.4, 2850.0, 1727.8, 1681.5, 1621.7, 1512.2, 1475.8, 1431.3, 1384.1, 1349.3, 1306.7, 1272.5, 1211.4, 1170.4, 1018.6, 852.3, 778.9, 618.7, 526.9, 429.0; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.61 (br, 1H), 8.45 (d, J = 5.4 Hz, 1H), 7.49 (s, 1H), 7.42–7.29 (m, 2H), 7.18 (d, J = 8.4 Hz, 2H), 7.14 (d, J = 8.0 Hz, 1H), 7.04 (d, J = 8.1 Hz, 2H), 6.96 (d, J = 8.1 Hz, 1H), 6.43 (d, J = 5.2 Hz, 1H), 4.16 (t, J = 6.7 Hz, 2H), 3.90 (s, 3H), 2.82 (d, J = 11.2 Hz, 2H), 2.48–2.39 (m, 2H, superposed with DMSO), 2.28 (s, 3H), 1.98–1.86 (m, 2H), 1.82 (t, J = 11.6 Hz, 2H), 1.54 (d, J = 12.7 Hz, 2H), 1.25 (br, 1H), 1.10 (d, J = 12.7 Hz, 2H), 0.84 (d, J = 6.4 Hz, 3H); MS m/z (ESI): 668.1 $[M+H]^+$; Anal. Calcd for $C_{37}H_{38}FN_5O_6$: C, 66.55; H, 5.74; N, 10.49. Found: C, 66.62; H, 5.83; N, 10.45.

7.5.11. 5-((3-Fluoro-4-(6-methoxy-7-(3-(4-methylpiperidin-1-yl)propoxy)quinolin-4-yloxy)phenylamino)methylene)-1-(2,6-dimethylphenyl)pyrimidine-2,4,6-trione (38)

Yield: 46%; mp 234–235 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.60 (br, 1H), 8.48 (d, J = 5.5 Hz, 1H), 7.70 (d, J = 12.4 Hz, 1H), 7.52 (s, 1H), 7.50–7.42 (m, 1H), 7.39 (s, 1H), 7.27–7.05 (m, 4H), 6.46 (d, J = 5.0 Hz, 1H), 4.18 (t, J = 6.4 Hz, 2H), 3.94 (s, 3H), 2.84 (d, J = 10.7 Hz, 2H), 2.43 (t, J = 6.9 Hz, 2H), 2.05 (s, 6H), 1.98–1.90 (m, 2H), 1.85 (t, J = 5.8 Hz, 2H), 1.56 (d, J = 12.6 Hz, 2H), 1.23 (br, 1H), 1.13 (d, J = 12.9 Hz, 2H), 0.88 (d, J = 6.4 Hz, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 165.41, 164.56, 162.97, 159.43, 155.30, 153.68, 152.41, 150.14, 150.07, 149.29, 146.88, 138.76, 138.04, 136.43, 133.56, 128.78, 128.47 (2C), 125.16, 116.68, 114.95, 109.21, 108.99, 102.75, 99.42, 93.35, 67.18, 56.23, 55.19, 53.78 (2C), 34.17 (2C), 30.65, 25.86, 22.17, 11.76 (2C); MS m/z (ESI): 682.4 $[M+H]^+$; Anal. Calcd for $C_{38}H_{40}FN_5O_6$: C, 66.95; H, 5.91; N, 10.27. Found: C, 67.08; H, 5.92; N, 10.21.

7.5.12. 5-((3-Fluoro-4-(6-methoxy-7-(3-(4-methylpiperidin-1-yl)propoxy)quinolin-4-yloxy)phenylamino)methylene)-1-(4-fluorophenyl)pyrimidine-2,4,6-trione (39)

Yield: 47%; mp 247–248 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.59 (br, 1H), 8.44 (d, J = 5.3 Hz, 1H), 7.87 (d, J = 12.1 Hz, 1H), 7.49 (s, 1H), 7.47 (s, 1H), 7.38–7.32 (m, 2H), 7.30–7.18 (m, 4H), 6.45 (d, J = 5.1 Hz, 1H), 6.45 (d, J = 5.1 Hz, 1H), 4.14 (t, J = 6.3 Hz, 2H), 3.90 (s, 3H), 2.86 (d, J = 8.8 Hz, 2H), 2.48–2.43 (m, 2H, superposed with DMSO), 2.01–1.83 (m, 4H), 1.55 (d, J = 13.4 Hz, 2H), 1.30 (br, 1H), 1.09 (d, J = 13.7, 2H), 0.84 (d, J = 6.4 Hz, 3H); MS m/z (ESI): 672.7 $[M+H]^+$; Anal. Calcd for $C_{36}H_{35}F_2N_5O_6$: C, 64.37; H, 5.25; N, 10.43. Found: C, 64.41; H, 5.22; N, 10.31.

7.5.13. 5-((3-Fluoro-4-(6-methoxy-7-(3-(4-methylpiperidin-1-yl)propoxy)quinolin-4-yloxy)phenylamino)methylene)-1-(2,4-difluorophenyl)pyrimidine-2,4,6-trione (40)

Yield: 51%; mp 236–237 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.79 (br, 1H), 11.37 (br, 1H), 8.62 (br, 1H), 8.47 (d, J = 5.2 Hz, 1H), 7.89 (d, J = 12.6 Hz, 1H), 7.59–7.47 (m, 5H), 7.39 (s, 1H), 7.24 (br, 1H), 6.47 (d, J = 5.1 Hz, 1H), 4.17 (t, J = 6.3 Hz, 2H), 3.93 (s, 3H), 2.95–2.83 (m, 2H), 2.52–2.45 (m, 2H, superposed with DMSO), 2.06–1.88 (m, 4H), 1.58 (d, J = 12.3 Hz, 2H), 1.33 (br, 1H), 1.15 (d, J = 12.5, 2H), 0.87 (d, J = 6.5 Hz, 3H); MS m/z (ESI): 690.3 $[M+H]^+$, 712.5 $[M+Na]^+$; Anal. Calcd for $C_{36}H_{34}F_3N_5O_6$: C, 62.69; H, 4.97; N, 10.15. Found: C, 62.75; H, 5.01; N, 10.06.

7.5.14. 5-((3-Fluoro-4-(6-methoxy-7-(3-(4-methylpiperidin-1-yl)propoxy)quinolin-4-yloxy)phenylamino)methylene)-1-(3-chloro-4-fluorophenyl)pyrimidine-2,4,6-trione (41)

Yield: 48%; mp 225–226 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.53 (br, 1H), 8.43 (d, J = 5.2 Hz, 1H), 7.61 (dd, J = 6.9, 2.3 Hz, 1H), 7.54–7.25 (m, 7H), 6.43 (d, J = 5.2 Hz, 1H), 4.13 (t, J = 6.2 Hz, 2H), 3.90 (s, 3H), 2.80 (d, J = 11.6 Hz, 2H), 2.39 (t, J = 7.0 Hz, 2H), 1.99–1.87 (m, 2H), 1.82 (t, J = 11.6 Hz, 2H), 1.52 (d, J = 13.2 Hz, 2H), 1.18 (br, 1H), 1.10 (dd, J = 12.2, 9.0 Hz, 2H), 0.84 (d, J = 6.4 Hz, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 165.07, 163.87, 162.76, 160.62, 159.47, 155.91, 153.63, 152.27, 150.92, 149.85, 149.33, 146.70, 132.39, 131.09, 129.76, 124.55, 119.50, 116.90, 114.96, 110.63, 109.02, 108.97, 102.06, 99.64, 95.91, 93.88, 67.22, 56.23, 55.07, 53.80 (2C), 34.20 (2C), 30.68, 26.47, 22.20; MS m/z (ESI): 706.4 $[M+H]^+$; Anal. Calcd for $C_{36}H_{34}ClF_2N_5O_6$: C, 61.23; H, 4.85; N, 9.92. Found: C, 61.51; H, 4.92; N, 9.99.

7.5.15. 5-((3-Fluoro-4-(6-methoxy-7-(3-(4-methylpiperidin-1-yl)propoxy)quinolin-4-yloxy)phenylamino)methylene)-1-(2-(trifluoromethyl)phenyl)pyrimidine-2,4,6-trione (42)

Yield: 44%; mp 234–235 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.45 (br, 1H), 8.43 (d, J = 5.1 Hz, 1H), 7.49 (s, 1H), 7.46–7.30 (m, 7H), 7.05 (d, J = 7.2 Hz, 1H), 6.40 (d, J = 5.1 Hz, 1H), 4.15 (t, J = 6.4 Hz, 2H), 3.90 (s, 3H), 2.80 (d, J = 10.9 Hz, 2H), 2.39 (t, J = 7.0 Hz, 2H), 1.94–1.88 (m, 2H), 1.83 (t, J = 11.0 Hz, 2H), 1.53 (d, J = 14.1 Hz, 2H), 1.19 (br, 1H), 1.11 (dd, J = 12.9, 9.1 Hz, 2H), 0.84 (d, J = 6.3 Hz, 3H); MS m/z (ESI): 722.8 $[M+H]^+$, 744.3 $[M+Na]^+$; Anal. Calcd for $C_{37}H_{35}F_4N_5O_6$: C, 61.58; H, 4.89; N, 9.70. Found: C, 61.62; H, 4.92; N, 9.91.

7.5.16. 5-((3-Fluoro-4-(6-methoxy-7-(3-(4-methylpiperidin-1-yl)propoxy)quinolin-4-yloxy)phenylamino)methylene)-1-(4-chloro-2,5-dimethoxyphenyl)pyrimidine-2,4,6-trione (43)

Yield: 48%; mp 213–214 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.45 (br, 1H), 8.38 (d, J = 5.3 Hz, 1H), 7.49 (s, 1H), 7.34 (s, 1H),

7.32–7.27 (m, 1H), 7.15 (s, 1H), 7.14 (s, 1H), 6.95 (s, 1H), 6.89–6.86 (m, 1H), 6.40 (d, J = 5.2 Hz, 1H), 4.13 (t, J = 6.7 Hz, 2H), 3.91 (s, 3H), 3.71 (s, 3H), 3.63 (s, 3H), 2.79 (d, J = 11.2 Hz, 2H), 2.39 (t, J = 7.1 Hz, 2H), 1.98–1.86 (m, 2H), 1.83 (t, J = 11.4 Hz, 2H), 1.53 (d, J = 13.4 Hz, 2H), 1.28 (br, 1H), 1.12 (d, J = 12.1 Hz, 2H), 0.84 (d, J = 6.4 Hz, 3H); MS m/z (ESI): 748.6 $[M+H]^+$; Anal. Calcd for $C_{38}H_{39}ClFN_5O_8$: C, 61.00; H, 5.25; N, 9.36. Found: C, 61.46; H, 5.32; N, 9.84.

7.5.17. 5-((3-Fluoro-4-(6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy)quinolin-4-yloxy)phenylamino)methylene)-1-phenylpyrimidine-2,4,6-trione (44)

Yield: 51%; mp 236–237 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.86 (br, 1H), 11.24 (br, 1H), 8.58 (br, 1H), 8.44 (d, J = 5.2 Hz, 1H), 7.84 (d, J = 12.7 Hz, 1H), 7.49–7.34 (m, 7H), 7.27 (d, J = 7.1 Hz, 1H), 6.44 (d, J = 4.8 Hz, 1H), 4.17 (s, 2H), 3.90 (s, 3H), 2.74–2.50 (m, 6H), 2.06–1.93 (m, 2H), 1.70 (s, 4H); MS m/z (ESI): 648.3 $[M+Na]^+$; Anal. Calcd for $C_{34}H_{32}FN_5O_6$: C, 65.27; H, 5.16; N, 11.19. Found: C, 65.23; H, 5.15; N, 11.26.

7.5.18. 5-((3-Fluoro-4-(6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy)quinolin-4-yloxy)phenylamino)methylene)-1-*p*-tolylpyrimidine-2,4,6-trione (45)

Yield: 50%; mp 225–226 °C; IR (KBr) cm^{-1}: 3435.7, 3207.8, 3069.4, 2922.9, 2850.6, 1728.0, 1682.3, 1621.8, 1511.9, 1475.9, 1431.2, 1384.7, 1349.3, 1306.7, 1211.4, 1171.8, 1138.6, 1019.9, 851.4, 779.0, 618.7, 526.9, 429.4; ^{1}H NMR (600 MHz, DMSO-d_6) δ 11.84 (br, 1H), 11.30 (br, 1H), 8.61 (br, 1H), 8.47 (d, J = 5.2 Hz, 1H), 7.90 (d, J = 11.2 Hz, 1H), 7.56–7.47 (m, 3H), 7.38 (s, 1H), 7.25 (d, J = 8.0 Hz, 2H), 7.16 (s, 2H), 6.47 (d, J = 5.1 Hz, 1H), 4.19 (t, J = 6.4 Hz, 2H), 3.93 (s, 3H), 2.62 (br, 2H), 2.51 (br, 4H, superposed with DMSO), 2.34 (s, 3H), 2.01–1.97 (m, 2H), 1.70 (s, 4H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 165.11, 162.95, 162.36, 159.45, 155.35, 153.70, 152.40, 151.12, 150.05, 149.28, 146.88, 138.62, 138.08, 137.94, 129.66 (2C), 129.48 (2C), 125.20, 116.47, 114.93, 108.94, 108.81, 102.74, 99.41, 94.02, 67.09, 56.23, 54.06 (2C), 52.61, 28.17, 23.53 (2C), 21.20; MS m/z (ESI): 640.2 $[M+H]^+$; Anal. Calcd for $C_{35}H_{34}FN_5O_6$: C, 65.72; H, 5.36; N, 10.95. Found: C, 65.59; H, 5.34; N, 10.97.

7.5.19. 5-((3-Fluoro-4-(6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy)quinolin-4-yloxy)phenylamino)methylene)-1-(2,6-dimethylphenyl)pyrimidine-2,4,6-trione (46)

Yield: 52%; mp 214–215 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.83 (br, 1H), 11.40 (br, 1H), 8.62 (br 1H), 8.45 (d, J = 5.2 Hz, 1H), 7.87 (d, J = 13.1 Hz, 1H), 7.50 (s, 1H), 7.48 (s, 1H), 7.38 (s, 1H), 7.23–7.04 (m, 4H), 6.45 (d, J = 5.3 Hz, 1H), 4.21 (t, J = 6.1 Hz, 2H), 3.91 (s, 3H), 2.98 (br, 6H), 2.19–2.08 (m, 2H), 2.02 (s, 6H), 1.82 (s, 4H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 165.42, 164.56, 162.97, 159.43, 155.30, 153.69, 152.40, 150.14, 150.07, 149.29, 146.88, 138.75, 138.04, 136.43, 133.43, 128.78, 128.47 (2C), 125.16, 116.68, 114.95, 109.21, 108.98, 102.75, 99.43, 93.35, 67.15, 56.27, 54.07 (2C), 52.72, 26.26, 23.56 (2C), 17.74 (2C); MS m/z (ESI): 654.8 $[M+H]^+$; Anal. Calcd for $C_{36}H_{36}FN_5O_6$: C, 66.14; H, 5.55; N, 10.71. Found: C, 66.09; H, 5.52; N, 10.86.

7.5.20. 5-((3-Fluoro-4-(6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy)quinolin-4-yloxy)phenylamino)methylene)-1-(4-fluorophenyl)pyrimidine-2,4,6-trione (47)

Yield: 49%; mp 231–232 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.61 (br, 1H), 8.47 (d, J = 5.2 Hz, 1H), 7.89 (d, J = 12.8 Hz, 1H), 7.50 (d, J = 5.9 Hz, 2H), 7.39 (s, 1H), 7.36 (s, 1H), 7.29 (t, J = 8.7 Hz, 2H), 7.23 (dd, J = 6.8, 4.5 Hz, 2H), 6.48 (d, J = 5.1 Hz, 1H), 4.20 (t, J = 6.1 Hz, 2H), 3.93 (s, 3H), 2.69 (br, 2H), 2.60 (br, 4H), 2.09–1.98 (m, 2H), 1.72 (s, 4H); MS m/z (ESI): 644.1 $[M+H]^+$; Anal. Calcd for $C_{34}H_{31}F_2N_5O_6$: C, 63.45; H, 4.85; N, 10.88. Found: C, 63.46; H, 4.89; N, 10.79.

7.5.21. 5-((3-Fluoro-4-(6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy)quinolin-4-yloxy)phenylamino)methylene)-1-(2,4-difluorophenyl)pyrimidine-2,4,6-trione (48)

Yield: 47%; mp 242–243 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.43 (br, 2H), 8.59 (br, 1H), 8.44 (d, J = 5.2 Hz, 1H), 7.88 (d, J = 13.0 Hz, 1H), 7.52 (dd, J = 18.3, 7.6 Hz, 5H), 7.37 (s, 1H), 7.22 (d, J = 7.1 Hz, 1H), 6.45 (d, J = 4.9 Hz, 1H), 4.18 (t, J = 6.0 Hz, 2H), 3.90 (s, 3H), 2.73 (br, 2H), 2.65 (br, 4H), 2.06–1.93 (m, 2H), 1.72 (s, 4H); MS m/z (ESI): 662.7 $[M+H]^+$, 684.5 $[M+Na]^+$; Anal. Calcd for $C_{34}H_{30}F_3N_5O_6$: C, 61.72; H, 4.57; N, 10.59. Found: C, 62.24; H, 4.62; N, 10.87.

7.5.22. 5-((3-Fluoro-4-(6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy)quinolin-4-yloxy)phenylamino)methylene)-1-(3-chloro-4-fluorophenyl)pyrimidine-2,4,6-trione (49)

Yield: 45%; mp 215–216 °C; IR (KBr) cm^{-1}: 3440.3, 3062.4, 2920.1, 2850.8, 1728.5, 1682.4, 1641.4, 1590.8, 1501.6, 1464.0, 1432.9, 1384.3, 1350.6, 1307.0, 1258.7, 1212.3, 1170.9, 1130.0, 1018.7, 848.6, 779.2, 618.6, 530.3, 430.0; ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.43 (br, 2H), 8.59 (br, 1H), 8.44 (d, J = 5.3 Hz, 1H), 7.88 (d, J = 12.7 Hz, 1H), 7.67 (d, J = 5.4 Hz, 1H), 7.52–7.32 (m, 6H), 6.45 (d, J = 5.1 Hz, 1H), 4.17 (t, J = 6.0 Hz, 2H), 3.90 (s, 3H), 2.73 (s, 2H), 2.65 (s, 4H), 2.09–1.95 (m, 2H), 1.72 (s, 4H); MS m/z (ESI): 678.2 $[M+H]^+$; Anal. Calcd for $C_{34}H_{30}ClF_2N_5O_6$: C, 60.22; H, 4.46; N, 10.33. Found: C, 61.83; H, 4.58; N, 10.84.

7.5.23. 5-((3-Fluoro-4-(6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy)quinolin-4-yloxy)phenylamino)methylene)-1-(2-(trifluoromethyl)phenyl)pyrimidine-2,4,6-trione (50)

Yield: 48%; mp 225–226 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.45 (br, 1H), 8.43 (d, J = 5.2 Hz, 1H), 7.49 (s, 1H), 7.47–7.23 (m, 9H), 7.06 (d, J = 7.9 Hz, 1H), 6.41 (d, J = 5.3 Hz, 1H), 4.16 (t, J = 6.5 Hz, 2H), 3.91 (s, 3H), 2.53 (t, J = 7.1 Hz, 2H), 2.42 (br, 4H), 2.00–1.88 (m, 2H), 1.65 (s, 4H); MS m/z (ESI): 694.4 $[M+H]^+$; Anal. Calcd for $C_{35}H_{31}F_4N_5O_6$: C, 60.60; H, 4.50; N, 10.10. Found: C, 61.02; H, 4.58; N, 10.16.

7.5.24. 5-((3-Fluoro-4-(6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy)quinolin-4-yloxy)phenylamino)methylene)-1-(4-chloro-2,5-dimethoxyphenyl)pyrimidine-2,4,6-trione (51)

Yield: 49%; mp 203–204 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.44 (br, 1H), 8.42 (d, J = 5.4 Hz, 1H), 7.49 (s, 1H), 7.34 (s, 1H), 7.17 (s, 1H), 7.13 (s, 1H), 7.01 (s, 2H), 6.94 (s, 1H), 6.40 (d, J = 5.3 Hz, 1H), 4.17 (t, J = 6.1 Hz, 2H), 3.91 (s, 3H), 3.73 (s, 3H), 3.65 (s, 3H), 2.52 (t, J = 7.1 Hz, 3H), 2.41 (br, 4H), 1.98–1.89 (m, 2H), 1.68–1.60 (m, 4H); MS m/z (ESI): 742.2 $[M+Na]^+$; Anal. Calcd for $C_{36}H_{35}ClFN_5O_8$: C, 60.04; H, 4.90; N, 9.72. Found: C, 60.16; H, 5.01; N, 9.78.

7.5.25. 5-((3-Fluoro-4-(6-methoxy-7-(3-morpholinopropoxy) quinolin-4-yloxy)phenylamino)methylene)-1-phenylpyrimidine-2,4,6-trione (52)

Yield: 49%; mp 231–232 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.45 (br, 1H), 8.42 (d, J = 5.6 Hz, 1H), 7.48 (s, 1H), 7.44–7.25 (m, 6H), 7.17 (d, J = 7.0 Hz, 2H), 7.08 (d, J = 6.4 Hz, 1H), 6.41 (d, J = 5.1 Hz, 1H), 4.15 (t, J = 6.4 Hz, 2H), 3.90 (s, 3H), 3.54 (s, 4H), 2.47–2.38 (m, 2H, superposed with DMSO), 2.34 (br, 4H), 2.03–1.88 (m, 2H); MS m/z (ESI): 642.7 $[M+H]^+$, 664.4 $[M+Na]^+$; Anal. Calcd for $C_{34}H_{32}FN_5O_7$ C, 63.64; H, 5.03; N, 10.91. Found: C, 63.68; H, 5.11; N, 10.98.

7.5.26. 5-((3-Fluoro-4-(6-methoxy-7-(3-morpholinopropoxy) quinolin-4-yloxy)phenylamino)methylene)-1-*p*-tolylpyrimidine-2,4,6-trione (53)

Yield: 52%; mp 258–259 °C; IR (KBr) cm^{-1}: 3441.6, 3061.2, 2921.4, 2851.5, 1724.8, 1679.3, 1658.5, 1587.0, 1510.7, 1477.1, 1433.1, 1384.4, 1351.4, 1307.8, 1212.9, 1174.1, 1118.7, 1009.5, 850.5, 779.2, 619.1, 524.8, 514.6, 429.2; ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.01 (d, J = 12.6 Hz, 0.42H), 11.86 (d, J = 13.4 Hz, 0.57H), 11.41 (s, 0.42H), 11.26 (s, 0.57H), 8.64 (d, J = 13.4 Hz, 1H), 8.57 (d, J = 12.6 Hz, 0.42H), 8.47 (d, J = 5.2 Hz, 1H), 7.90 (d, J = 11.9 Hz, 1H), 7.51 (br, 2H), 7.50 (s, 1H), 7.39 (s, 1H), 7.25 (t, J = 8.9 Hz, 2H), 7.18 (d, J = 7.9 Hz, 1H), 7.12 (d, J = 7.9 Hz, 1H), 6.47 (d, J = 5.4 Hz, 1H), 4.18 (t, J = 6.4 Hz, 2H), 3.93 (s, 3H), 3.57 (s, 4H), 2.45 (t, J = 7.0 Hz, 2H), 2.37 (br, 4H), 2.34 (s, 3H), 2.00–1.93 (m, 2H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 165.03, 162.96, 162.52, 159.09, 154.99, 153.34, 152.65, 152.08, 150.75, 149.72, 148.90, 146.54, 138.29, 137.67, 129.30 (2C), 129.14 (2C), 124.83, 116.03, 114.58, 108.61 (2C), 102.38, 99.08, 93.67, 66.78, 66.32 (2C), 55.86, 54.92, 53.48 (2C), 25.78, 20.84; MS m/z (ESI): 656.1 $[M+H]^+$, 678.2 $[M+Na]^+$; Anal. Calcd for $C_{35}H_{34}FN_5O_7$: C, 64.11; H, 5.23; N, 10.68. Found: C, 64.15; H, 5.31; N, 10.72.

7.5.27. 5-((3-Fluoro-4-(6-methoxy-7-(3-morpholinopropoxy) quinolin-4-yloxy)phenylamino)methylene)-1-(2,6-dimethylphenyl)pyrimidine-2,4,6-trione (54)

Yield: 51%; mp 262–263 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.06 (d, J = 13.7 Hz, 0.43H), 11.91 (d, J = 14.1 Hz, 0.57H), 11.55 (s, 0.43H), 11.41 (s, 0.57H), 8.69 (d, J = 14.1 Hz, 0.57H), 8.61 (d, J = 13.7 Hz, 0.43H), 8.48 (d, J = 5.4 Hz, 1H), 7.92 (t, J = 9.7 Hz, 1H), 7.58–7.45 (m, 3H), 7.40 (s, 1H), 7.26–7.12 (m, 3H), 6.47 (dd, J = 11.8, 5.1 Hz, 1H), 4.19 (t, J = 6.6 Hz, 2H), 3.93 (s, 3H), 3.58 (br, 4H), 2.45 (br, 2H), 2.37 (br, 4H), 2.06 (s, 3H), 2.04 (s, 3H), 1.97 (br, 2H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 165.39, 164.56, 162.97, 159.43, 155.30, 153.71, 152.41, 150.14, 150.06, 149.29, 146.88, 138.74, 138.04, 136.43, 133.43, 128.78, 128.47 (2C), 125.16, 116.60, 114.94, 109.22, 108.98, 102.75, 99.42, 93.35, 67.09, 66.64 (2C), 56.24, 55.23, 53.82 (2C), 25.98, 17.76, 17.68; MS m/z (ESI): 670.6 $[M+H]^+$; Anal. Calcd for $C_{36}H_{36}FN_5O_7$: C, 64.56; H, 5.42; N, 10.46. Found: C, 64.52; H, 5.39; N, 10.56.

7.5.28. 5-((3-Fluoro-4-(6-methoxy-7-(3-morpholinopropoxy) quinolin-4-yloxy)phenylamino)methylene)-1-(4-fluorophenyl) pyrimidine-2,4,6-trione (55)

Yield: 48%; mp 267–268 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.60 (br, 1H), 8.44 (d, J = 5.0 Hz, 1H), 7.87 (d, J = 11.7 Hz, 1H), 7.48 (s, 1H), 7.47 (s, 1H), 7.37 (s, 1H), 7.32–7.17 (m, 5H), 6.45 (d, J = 5.0 Hz, 1H), 4.16 (t, J = 6.3 Hz, 2H), 3.90 (s, 3H), 3.59–3.49 (m, 4H), 2.49–2.41 (m, 2H, superposed with DMSO), 2.36 (s, 4H), 2.02–1.83 (m, 2H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 165.36, 162.94, 162.09, 161.09, 159.45, 155.33, 153.69, 152.42, 151.08, 150.07, 149.27, 146.87, 138.67, 138.01, 131.90 (2c), 125.19, 116.08, 115.90, 115.72, 114.94, 108.95, 108.81, 102.75, 99.43, 94.01, 89.56, 67.12, 66.57 (2C), 56.22, 55.24, 53.76 (2C), 26.03; MS m/z (ESI): 660.5 $[M+H]^+$; Anal. Calcd for $C_{34}H_{31}F_2N_5O_7$: C, 61.91; H, 4.74; N, 10.62. Found: C, 62.01; H, 4.68; N, 10.53.

7.5.29. 5-((3-Fluoro-4-(6-methoxy-7-(3-morpholinopropoxy) quinolin-4-yloxy)phenylamino)methylene)-1-(2,4-difluorophenyl)pyrimidine-2,4,6-trione (56)

Yield: 50%; mp 235–236 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.00 (br, 0.40H), 11.77 (br, 0.59H), 11.48 (s, 0.43H), 11.32 (s, 0.57H), 8.59 (br, 1H), 8.44 (d, J = 5.2 Hz, 1H), 7.89 (d, J = 13.0 Hz, 1H), 7.61–7.42 (m, 5H), 7.37 (s, 1H), 7.27–7.14 (m, 1H), 6.45 (d, J = 4.9 Hz, 1H), 4.16 (t, J = 6.1 Hz, 2H), 3.90 (s, 3H), 3.55 (s, 4H), 2.50–2.42 (m, 2H, superposed with DMSO), 2.37 (s, 4H), 2.04–1.85 (m, 2H); MS m/z (ESI): 678.7 $[M+H]^+$; Anal. Calcd for $C_{34}H_{30}F_3N_5O_7$: C, 60.26; H, 4.46; N, 10.34. Found: C, 60.41; H, 4.50; N, 10.42.

7.5.30. 5-((3-Fluoro-4-(6-methoxy-7-(3-morpholinopropoxy) quinolin-4-yloxy)phenylamino)methylene)-1-(3-chloro-4-fluorophenyl)pyrimidine-2,4,6-trione (57)

Yield: 47%; mp 208–209 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.59 (br, 1H), 8.44 (d, J = 5.2 Hz, 1H), 7.88 (d, J = 13.0 Hz, 1H), 7.73–7.39 (m, 6H), 7.36 (s, 1H), 6.45 (d, J = 4.7 Hz, 1H), 4.16 (t, J = 6.2 Hz, 2H), 3.90 (s, 3H), 3.55 (s, 4H), 2.48–2.41 (m, 2H, superposed with DMSO), 2.36 (s, 4H), 2.03–1.84 (m, 2H); MS m/z (ESI): 694.2 $[M+H]^+$; Anal. Calcd for $C_{34}H_{30}ClF_2N_5O_7$: C, 58.84; H, 4.36; N, 10.09. Found: C, 58.92; H, 4.39; N, 10.11.

7.5.31. 5-((3-Fluoro-4-(6-methoxy-7-(3-morpholinopropoxy) quinolin-4-yloxy)phenylamino) methylene)-1-(2-(trifluoromethyl)phenyl)pyrimidine-2,4,6-trione (58)

Yield: 48%; mp 247–248 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.60 (br, 2H), 8.60 (br, 1H), 8.44 (d, J = 5.3 Hz, 1H), 7.83 (d, J = 12.0 Hz, 1H), 7.56–7.43 (m, 7H), 7.36 (s, 1H), 6.44 (d, J = 5.4 Hz, 1H), 4.14 (t, J = 6.5 Hz, 2H), 3.90 (s, 3H), 3.54 (s, 4H), 2.47–2.38 (m, 2H, superposed with DMSO), 2.34 (br, 4H), 2.01–1.83 (m, 2H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 164.80, 163.64, 160.62, 159.46, 155.71, 153.54, 152.48, 150.29, 150.13, 149.25, 146.94, 145.61, 138.78, 132.56, 130.94, 128.11, 125.05, 121.37, 119.15, 116.77, 115.00, 109.23, 109.02, 102.78, 99.49, 93.14, 67.17, 66.69 (2C), 56.21, 55.27, 53.84 (2C), 26.16; MS m/z (ESI): 710.6 $[M+H]^+$, 734.8 $[M+Na]^+$; Anal. Calcd for $C_{35}H_{31}F_4N_5O_7$: C, 69.24; H, 4.40; N, 9.87. Found: C, 69.31; H, 4.38; N, 9.96.

7.5.32. 5-((3-Fluoro-4-(6-methoxy-7-(3-morpholinopropoxy) quinolin-4-yloxy)phenylamino)methylene)-1-(4-chloro-2,5-dimethoxyphenyl)pyrimidine-2,4,6-trione (59)

Yield: 44%; mp 208–209 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.53 (br, 1H), 8.43 (d, J = 5.4 Hz, 1H), 7.48 (s, 1H), 7.35 (s, 1H), 7.32 (s, 1H), 7.18 (s, 1H), 7.14 (s, 1H), 7.03 (s, 1H), 6.98 (s, 1H), 6.43 (d, J = 5.4 Hz, 1H), 4.15 (t, J = 6.7 Hz, 2H), 3.90 (s, 3H), 3.71 (s, 3H), 3.63 (s, 3H), 3.55 (s, 4H), 2.50–2.42 (m, 2H, superposed with DMSO), 2.37 (s, 4H), 2.04–1.85 (m, 2H); MS m/z (ESI): 736.3 $[M+H]^+$; Anal. Calcd for $C_{36}H_{35}ClFN_5O_9$: C, 58.74; H, 4.79; N, 9.51. Found: C, 58.68; H, 4.82; N, 9.57.

7.5.33. 5-((3-Fluoro-4-(6-methoxy-7-(3-(4-methylpiperazin-1-yl)propoxy)quinolin-4-yloxy)phenylamino)methylene)-1-phenylpyrimidine-2,4,6-trione (60)

Yield: 50%; mp 226–227 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.56 (br, 1H), 8.44 (d, J = 5.2 Hz, 1H), 7.88 (d, J = 12.2 Hz, 1H), 7.48 (s, 1H), 7.43–7.24 (m, 5H), 7.25 (d, J = 7.1 Hz, 2H), 7.07 (d, J = 7.7 Hz, 1H), 6.43 (d, J = 5.4 Hz, 1H), 4.14 (t, J = 6.4 Hz, 2H), 3.90 (s, 3H), 2.53–2.31 (m, 10H, superposed with DMSO), 2.14 (s, 3H), 1.98–1.89 (m, 2H); MS m/z (ESI): 655.8 $[M+H]^+$; Anal. Calcd for $C_{35}H_{35}FN_6O_6$: C, 64.21; H, 5.39; N, 12.84. Found: C, 64.18; H, 5.41; N, 12.78.

7.5.34. 5-((3-Fluoro-4-(6-methoxy-7-(3-(4-methylpiperazin-1-yl)propoxy)quinolin-4-yloxy)phenylamino)methylene)-1-*p*-tolylpyrimidine-2,4,6-trione (61)

Yield: 56%; mp 243–244 °C; IR (KBr) cm^{-1}: 3435.2, 3208.7, 2921.1, 2850.0, 2797.8, 1727.5, 1679.6, 1621.9, 1513.3, 1476.3, 1431.6, 1385.0, 1349.4, 1306.4, 1273.4, 1211.6, 1169.5, 1013.9, 853.1, 778.8, 618.6, 527.0, 428.8; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.43 (br, 1H), 8.41 (d, J = 5.3 Hz, 1H), 7.49 (s, 1H), 7.34 (s, 1H), 7.30 (d, J = 8.8 Hz, 1H), 7.22–7.11 (m, 3H), 7.01 (d, J = 8.2 Hz, 2H), 6.96 (d, J = 8.2 Hz, 1H), 6.39 (d, J = 5.1 Hz, 1H), 4.15 (t, J = 6.0 Hz, 2H), 3.90 (s, 3H), 2.42–2.19 (m, 13H), 2.10 (s, 3H), 1.95–1.87 (m,

2H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 165.16, 162.92, 162.37, 159.56, 155.35, 153.82, 152.48, 151.29, 150.11, 149.27, 146.91, 137.73, 129.81, 129.59 (2C), 129.54 (2C), 129.36, 124.93, 116.75, 114.98, 109.18, 109.01, 102.70, 101.99, 99.51, 67.23, 56.24, 55.25 (2H), 54.82, 53.20 (2H), 46.20, 26.53, 21.15; MS *m*/*z* (ESI): 669.4 $[M+H]^+$; Anal. Calcd for $C_{36}H_{37}FN_6O_6$: C, 64.66; H, 5.58; N, 12.57. Found: C, 64.53; H, 5.46; N, 12.59.

7.5.35. 5-((3-Fluoro-4-(6-methoxy-7-(3-(4-methylpiperazin-1-yl)propoxy)quinolin-4-yloxy)phenylamino)methylene)-1-(2,6-dimethylphenyl)pyrimidine-2,4,6-trione (62)

Yield: 55%; mp 251–252 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.62 (br, 1H), 8.45 (d, J = 5.4 Hz, 1H), 7.88 (d, J = 12.4 Hz, 1H), 7.51 (s, 1H), 7.48 (s, 1H), 7.36 (s, 1H), 7.22–7.02 (m, 4H), 6.44 (d, J = 5.2 Hz, 1H), 4.18 (t, J = 6.2 Hz, 2H), 3.90 (s, 3H), 2.51–2.29 (m, 10H, superposed with DMSO), 2.15 (s, 3H), 2.06 (s, 6H), 2.01–1.91 (m, 2H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 165.42, 164.56, 162.97, 159.43, 155.30, 153.68, 152.41, 150.14, 150.07, 149.29, 146.89, 138.75, 138.03, 136.44, 133.43, 128.77, 128.47 (2C), 125.16, 116.68, 114.95, 109.21, 108.99, 102.75, 99.43, 93.35, 67.40, 56.20, 55.21 (2C), 54.79, 53.16 (2C), 46.15, 26.42, 17.74 (2C); MS *m*/*z* (ESI): 707.3 $[M+Na]^+$; Anal. Calcd for $C_{35}H_{39}FN_6O_6$: C, 65.09; H, 5.76; N, 12.31. Found: C, 65.12; H, 5.65; N, 12.27.

7.5.36. 5-((3-Fluoro-4-(6-methoxy-7-(3-(4-methylpiperazin-1-yl)propoxy)quinolin-4-yloxy)phenylamino)methylene)-1-(4-fluorophenyl)pyrimidine-2,4,6-trione (63)

Yield: 50%; mp 262–263 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.76 (br, 1H), 11.24 (br, 1H), 8.58 (br, 1H), 8.47 (d, J = 5.0 Hz, 1H), 7.86 (d, J = 12.0 Hz, 1H), 7.52–7.41 (m, 4H), 7.35–7.21 (m, 4H), 6.46 (d, J = 5.0 Hz, 1H), 4.17 (t, J = 6.4 Hz, 2H), 3.90 (s, 3H), 2.96–2.48 (m, 13H, superposed with DMSO), 2.07–1.89 (m, 2H); MS *m*/*z* (ESI): 673.5 $[M+H]^+$; Anal. Calcd for $C_{35}H_{34}F_2N_6O_6$: C, 62.49; H, 5.09; N, 12.49. Found: C, 62.56; H, 5.13; N, 12.53.

7.5.37. 5-((3-Fluoro-4-(6-methoxy-7-(3-(4-methylpiperazin-1-yl)propoxy)quinolin-4-yloxy)phenylamino)methylene)-1-(2,4-difluorophenyl)pyrimidine-2,4,6-trione (64)

Yield: 51%; mp 271–272 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.55 (br, 1H), 8.46 (d, J = 5.2 Hz, 1H), 7.54–7.41 (m, 5H), 7.38 (s, 1H), 7.18 (s, 1H), 7.05 (s, 1H), 6.45 (d, J = 5.3 Hz, 1H), 4.17 (t, J = 6.5 Hz, 2H), 3.93 (s, 3H), 2.47–2.20 (m, 10H), 2.13 (s, 3H), 1.97–1.92 (m, 2H); MS *m*/*z* (ESI): 691.6 $[M+H]^+$; Anal. Calcd for $C_{35}H_{33}F_3N_6O_6$: C, 60.86; H, 4.28; N, 12.17. Found: C, 60.98; H, 4.35; N, 12.05.

7.5.38. 5-((3-Fluoro-4-(6-methoxy-7-(3-(4-methylpiperazin-1-yl)propoxy)quinolin-4-yloxy)phenylamino)methylene)-1-(3-chloro-4-fluorophenyl)pyrimidine-2,4,6-trione (65)

Yield: 46%; mp 241–242 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.61 (br, 1H), 8.47 (d, J = 5.2 Hz, 1H), 7.88 (d, J = 12.1 Hz, 1H), 7.68 (br, 1H), 7.58–7.42 (m, 5H), 7.38 (s, 1H), 6.47 (d, J = 5.1 Hz, 1H), 4.17 (t, J = 6.3 Hz, 2H), 3.92 (s, 3H), 2.55–2.30 (m, 10H, superposed with DMSO), 2.19 (s, 3H), 1.99–1.91 (m, 2H); MS *m*/*z* (ESI): 707.3 $[M+H]^+$, 729.6 $[M+Na]^+$; Anal. Calcd for $C_{35}H_{33}ClF_2N_6O_6$: C, 59.45; H, 4.76; N, 11.88. Found: C, 60.02; H, 4.82; N, 11.54.

7.5.39. 5-((3-Fluoro-4-(6-methoxy-7-(3-(4-methylpiperazin-1-yl)propoxy)quinolin-4-yloxy)phenylamino)methylene)-1-(2-(trifluoromethyl)phenyl)pyrimidine-2,4,6-trione (66)

Yield: 47%; mp 238–239 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.47 (br, 1H), 8.43 (d, J = 5.3 Hz, 1H), 7.50–7.33 (m, 8H), 7.12–6.98 (m, 1H), 6.41 (d, J = 6.7 Hz, 1H), 4.13 (t, J = 6.2 Hz, 2H), 3.90 (s, 3H), 2.44–2.18 (m, 10H), 2.10 (s, 3H), 1.96–1.85 (m, 2H); MS *m*/*z* (ESI): 723.7 $[M+H]^+$; Anal. Calcd for $C_{36}H_{34}F_4N_6O_6$: C, 59.83; H, 4.73; N, 11.63. Found: C, 60.03; H, 4.82; N, 11.48.

7.5.40. 5-((3-Fluoro-4-(6-methoxy-7-(3-(4-methylpiperazin-1-yl)propoxy)quinolin-4-yloxy)phenylamino)methylene)-1-(4-chloro-2,5-dimethoxyphenyl)pyrimidine-2,4,6-trione (67)

Yield: 45%; mp 225–226 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.53 (br, 1H), 8.44 (d, J = 5.3 Hz, 1H), 7.48 (s, 1H), 7.44–7.39 (m, 1H), 7.35 (s, 1H), 7.21 (s, 1H), 7.12 (s, 2H), 6.94–6.91 (m, 1H), 6.42 (d, J = 5.4 Hz, 1H), 4.14 (t, J = 6.7 Hz, 2H), 3.90 (s, 3H), 3.73 (s, 3H), 3.67 (s, 3H), 2.43–2.19 (m, 10H), 2.10 (s, 3H), 1.97–1.86 (m, 2H); MS *m*/*z* (ESI): 749.3 $[M+H]^+$; Anal. Calcd for $C_{37}H_{38}ClFN_6O_8$: C, 59.32; H, 5.11; N, 11.22. Found: C, 59.39; H, 5.25; N, 11.24.

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Supplementary data

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