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Design, synthesis and biological evaluation of novel 6,7-disubstituted-4-phenoxyquinoline derivatives bearing 4-oxo-3,4-dihydrophthalazine-1-carboxamide moieties as c-Met kinase inhibitors

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ABSTRACT

A series of 6,7-disubstituted-4-phenoxyquinoline derivatives bearing 4-oxo-3,4-dihydrophthalazine-1-carboxamide moieties were designed, synthesized and evaluated for their c-Met kinase inhibition and cytotoxicity against H460, MKN-45, HT-29 and MDA-MB-231 cancer cell lines in vitro. Most compounds displayed good to excellent potency against four tested cancer cell lines as compared with foretinib. The SAR analyses indicated that compounds with halogen groups, especially fluoro groups at 4-position on the phenyl ring (moiety B) were more effective than those with nitro groups or methoxy groups. In this study, a promising compound **33** (c-Met IC_{50} = 1.63 nM) was identified, which showed the most potent antitumor activities with IC_{50} values of 0.055 μM, 0.071 μM, 0.13 μM, and 0.43 μM against H460, MKN-45, HT-29 and MDA-MB-231 cell lines, respectively.

1. Introduction

The receptor tyrosine kinase, c-Met, and its natural ligand, hepatocyte growth factor (HGF), are involved in cell proliferation, migration and invasion, and are essential for normal embryonic development.[1] Binding of active HGF ligand to the c-Met extracellular domain causes receptor polymerization and phosphorylation of tyrosine residues in the intracellular c-Met domains.[2,3] Aberrant HGF/c-Met signaling has been identified in a wide range of human malignancies, including bladder, breast, cervical, colorectal, endometrial, gastric, kidney, liver, lung, pancreatic, prostate, and thyroid cancers.[4–10] Therefore, c-Met has gained considerable attention as a potential target for cancer treatment.

In recent years, research has highlighted c-Met as an attractive cancer drug target, triggering a number of approaches to disrupt HGF/c-Met signaling. Both small-molecule c-Met kinase inhibitors and antibodies targeting c-Met or HGF have exhibited antitumor activities in preclinical models.[11–19] Recently, significant progress has been made on the development of c-Met inhibitors resulting in more than ten candidates have been in clinical trials, including foretinib (**1**, Phase II), cabozantinib (**2**, Phase III), as well as several newly developed compounds bearing 6,7-disubstituted-4-phenoxyquinoline frameworks, such as AM7 (**3**, Preclinical), MG10 (**4**, Preclinical) and Amgen (**5**, Preclinical) et al., as the primary pharmacophoric scaffolds (Fig. 1).[20–24]

The structure–activity relationships (SARs) of 6,7-disubstituted-4-phenoxyquinoline based inhibitors suggested that quinoline pharmacophores were responsible for forming hydrogen bonds with the backbone of c-Met kinase, and an aryl fragment (moiety B) probably extended into the hydrophobic pocket.[25–27] Apparently, there are two structural characteristics in the linkers between moiety A and moiety B. One is '5 atoms regulation', which means the distance of six chemical bonds exists between moiety A and moiety B; the other is the linker containing both hydrogen-bond donor or acceptor and at least one amide group. In view of above-mentioned results, our research group have introduced different biologically active fragments, such as pyridine, pyrimidine, semicarbazone, quinoline, 1,4-dihydrocinnoline and pyrimidine-2,4,6-trione into the 5-atom linker and the resulting derivatives **6**–**10** (Fig. 2) showed excellent potency.[28–34]

As an extension of our work on the development of novel potent c-Met inhibitors, we noticed that compounds **11**–**13** (Fig. 3), which contain a 2-phenylphthalazin-1(2*H*)-one (PHTZ) framework, displayed a multitude of biological activities, including antitumor,

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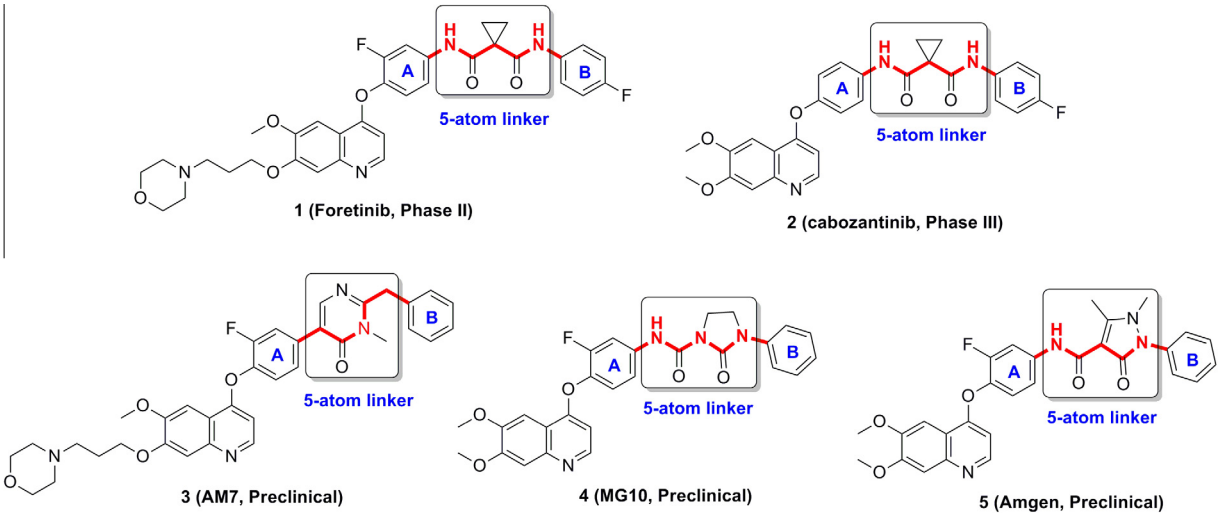


Figure 1. The representative small-molecule c-Met inhibitors based on the 6,7-disubstituted-4-phenoxyquinoline scaffold.

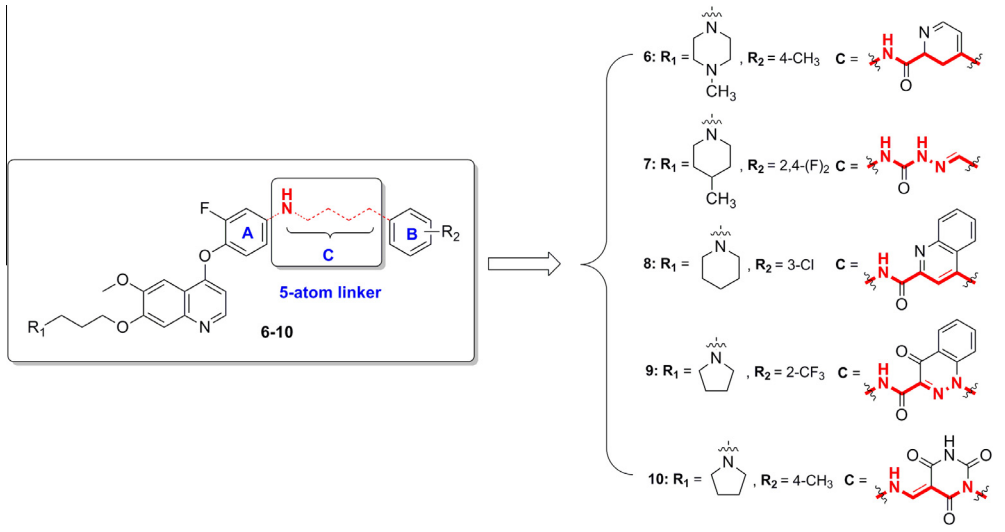


Figure 2. Representative compounds in our previous work on small-molecule c-Met kinase inhibitors.

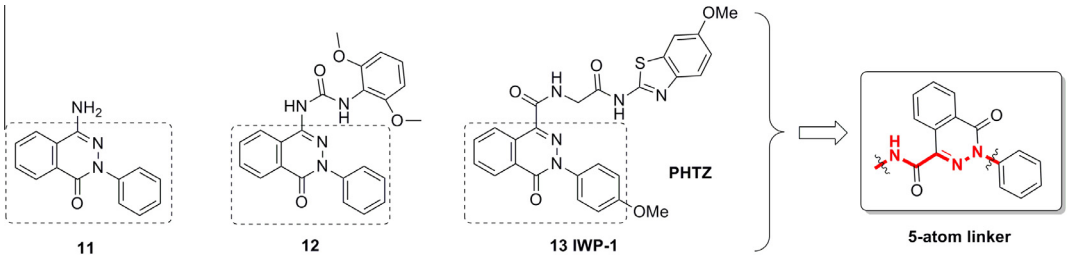


Figure 3. Structures of several PHTZ derivatives and 5-atom linker.

anti-autoimmune and anti-inflammatory activities.[35–37] Recently, some PHTZ derivatives have been reported as the core skeleton for the design of potent and selective human A_3 adenosine receptor (hA_3 AR) antagonists, especially the 2,5-dimethoxyphenylphthalazin-1(2*H*)-one **12** being the most potent and selective hA_3 AR antagonist (K_i = 0.776 nM; hA_1/hA_3 and hA_{2A}/hA_3 >12,000).[38] Considering its strong potency and basing on the '5 atoms regulation', we introduced PHTZ as a part of the 5-atom linker to the 6,7-disubstituted-4-phenoxyquinoline moiety via an amide bond, which was called 4-oxo-3,4-dihydrophthalazine-1-carboxamide moiety (Fig. 3).

According to our previous studies, 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. Furthermore, various substituents were introduced at the phenyl ring (moiety B) with the aim to

explore the effect of substituents on biological activity. Accordingly, we designed a novel series of 6,7-disubstituted-4-phenoxyquinoline derivatives bearing 4-oxo-3,4-dihydrophthalazine-1-carboxamide moieties as c-Met kinase inhibitors (Fig. 4).

In the current study, all target compounds were evaluated for their antiproliferative activity in vitro against four cancer cell lines: H460 (human lung cancer), MKN-45 (human gastric cancer), HT-29 (human colon cancer) and MDA-MB-231 (human breast cancer). Additionally, to determine c-Met kinase inhibition and selectivity, the enzymatic assays of several potent compounds were evaluated, and most of them showed promising inhibition. Furthermore, a docking analysis was also performed to elucidate the binding mode of the target compound **33** with c-Met kinase.

2. Chemistry

The synthesis of the key intermediates of 4-(2-fluorophenoxy)quinolines **21a–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[28–34] (see also Supplementary information).

Target compounds **25–59** were prepared as outlined in Scheme 2. The side chains **24a–h** were synthesized from naphthalene, which was dissolved in 0.5 N NaOH and refluxed with $KMnO_4$ aq. for 2 h to afford 2-(carboxycarbonyl)benzoic acid **22**.[39] Subsequently, **22** was reacted with various substituted phenyl hydrazines to achieve PHTZ derivatives **23a–h**,[40] which were refluxed in $SOCl_2$ for 6 h to provide acyl chlorides **24a–h**. Finally, compounds **25–59** were successfully obtained via the reaction of the amides **21a–e** with **24a–h** in the presence of triethylamine in dichloromethane at room temperature overnight.

3. Biology

3.1. Cytotoxic activities against tumor cells assay

The antiproliferative activities of compounds **25–59** were evaluated against H460, MKN-45, HT-29 and MDA-MB-231 cell lines by the standard MTT assay in vitro, with foretinib as the positive control.[41,42] 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 into 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 incubated for 72 h. Fresh MTT was added to each well at the terminal concentration of 5 μg/mL, and incubated with cells at 37 °C for 4 h. The formazan crystals in each well were dissolved in 100 μL DMSO, 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 three times in each of the cell lines. The results, expressed as IC_{50} (inhibitory concentration 50%), were

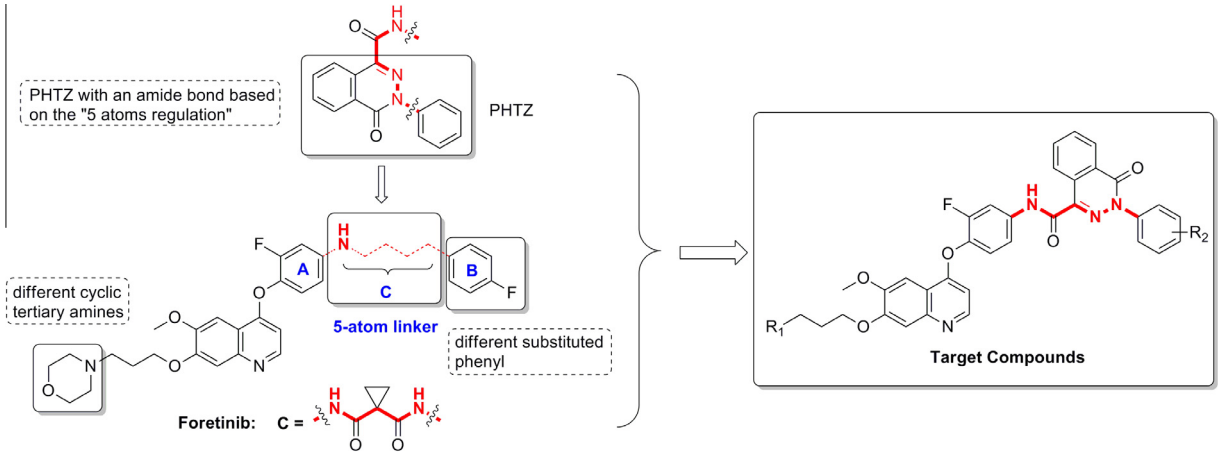
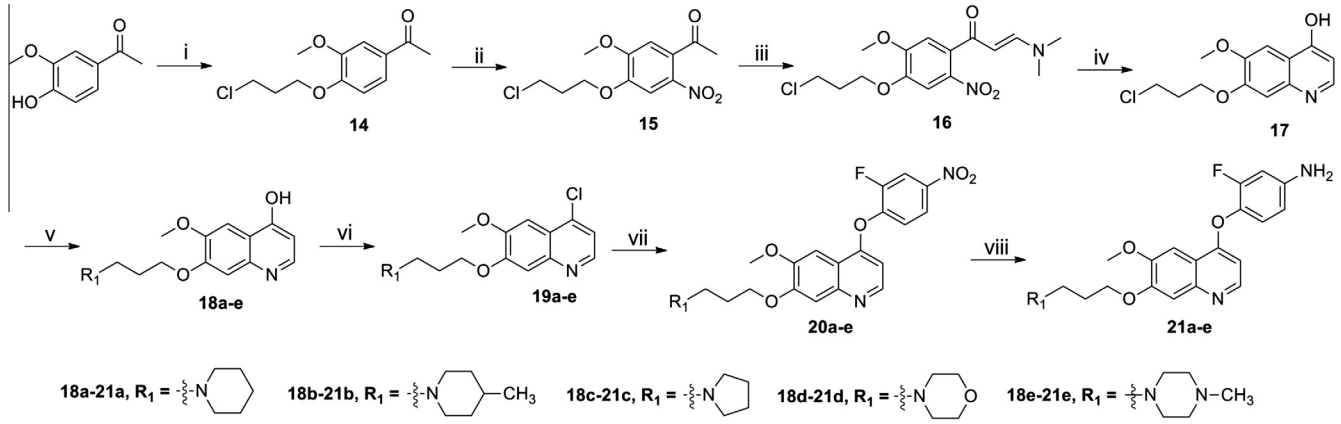
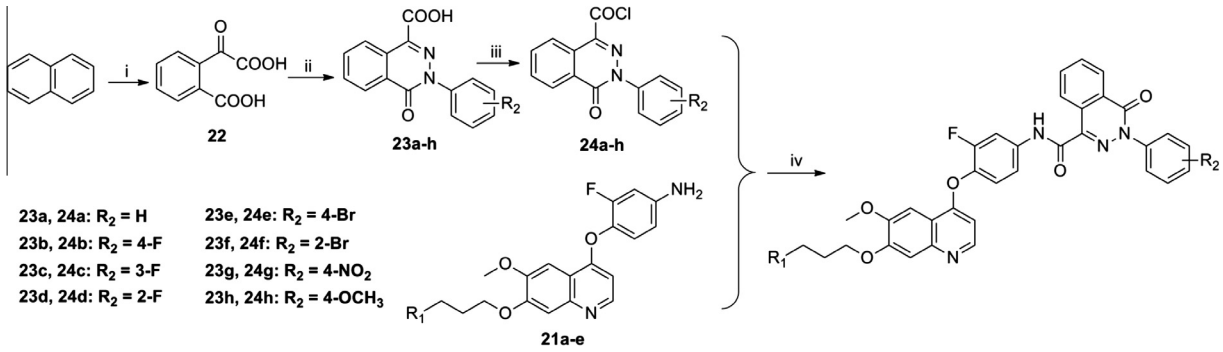


Figure 4. Design strategy for the 6,7-disubstituted-4-phenoxyquinoline derivatives bearing 4-oxo-3,4-dihydrophthalazine-1-carboxamide moieties.



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) 0.5 mol/L NaOH aq, $KMnO_4$, H_2O, reflux, 2 h; (ii) substituted phenyl hydrazine, EtOH, rt, 15 h; (iii) $SOCl_2$, reflux, 6 h; (iv) appropriate aniline, carbonyl chloride, Et_3N, DCM, rt, overnight.

the averages of three determinations and calculated by the Bacus Laboratories Incorporated Slide Scanner (Bliss) software.

3.2. HTRF kinase assay

The c-Met kinase assays of tested compounds were performed by homogeneous time-resolved fluorescence (HTRF) assay as previously reported protocol.[43,44] To examine the selectivity of the most promising compound **33** on c-Met over other tyrosine kinases, it was screened against c-Kit, Flt-3, PDGFRα, VEGFR-2 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 mM DTT, 1 mM $MgCl_2$, 1 mM $MnCl_2$, 0.1% NaN_3) was added to each well. Various concentrations of compounds were diluted in 10 μL of 1% DMSO (v/v), with blank DMSO solution 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. Reactions were incubated for 30 min at 25 °C and stopped by the addition of 5 μL Streptavidin-XL665 and 5 μL Tk Antibody Cryptate working solution to all of wells. The plate was read by Envision (Perkinelmer) at 320 nm and 615 nm. IC_{50} values were calculated from the inhibition curves.

4. Results and discussion

4.1. In vitro cytotoxic activities and structure activity relationships

The cytotoxic activities of the target compounds **25**–**59** were evaluated in H460 (human lung cancer), MKN-45 (human gastric cancer), HT-29 (human colon cancer), and MDA-MB-231 (human breast cancer) cell lines using the MTT assay. Foretinib was used as the positive control. The results were expressed as half-maximal inhibitory concentration (IC_{50}) values and were presented in Table 1, as mean values of experiments performed in triplicate.

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 the replacement of the cyclopropane-1,1-dicarboxamide framework of foretinib with the 4-oxo-3,4-dihydrophthalazine-1-carboxamide moiety maintained the potent cytotoxicity. The IC_{50} values of the most promising compound **33** were 0.055 μM, 0.071 μM, 0.13 μM, and 0.43 μM against H460, MKN-45, HT-29 and MDA-MB-231 cell lines, respectively. More importantly, most of the compounds were more potent against H460 and MKN-45 cell lines than HT-29 and MDA-MB-231 cell lines. These results revealed that this series of compounds possessed selectivity for H460 and MKN-45 cancer cell lines, and had the makings of good drugs for lung and gastric cancer.

Preliminary structure–activity relationships (SARs) indicated that the introduction of different water-soluble R_1 groups only slightly altered cytotoxicity, suggesting that the R_1 group contributed little to their potency. For example, compounds **41** (R_1 = 4-Methyl Piperazinyl, R_2 = 4-F), **48** (R_1 = Piperidinyl, R_2 = 4-F) and **54** (R_1 = 4-Methyl Piperidinyl, R_2 = 4-F) exhibited comparable cytotoxic activities against the different cancer cells. However, different biological properties were observed when various R_2 groups were introduced to the phenyl ring (moiety B). Compound **32** (R_1 = Pyrrolidinyl, R_2 = H), with no substituent on the phenyl ring, showed promising cytotoxicity against H460 and MKN-45 cell lines with IC_{50} values of 0.48 μM and 0.53 μM, respectively. The introduction of halogen groups, especially fluoro groups, **33**–**37** (R_2 = 4-F, 3-F, 2-F, 4-Br, 2-Br, respectively) led to an obvious improvement in antitumor activity than compound **32**, which could be further confirmed by compounds **40** and **41**–**44**. However, the introduction of nitro groups (**38**, IC_{50} = 1.24 μM against H460) or methoxy groups (**39**, R_2 = 4-OCH_3, IC_{50} = 1.65 μM against H460) caused the potency to be lowered by 2.6- and 3.4-fold, respectively. This could demonstrate that halogen groups had a positive effect on antitumor activity, but nitro groups and methoxy groups showed negative results.

Further analysis revealed that the position of R_2 group was closely related to antitumor activity as well. Compounds with 4-substituted phenyl group (**33**, R_2 = 4-F, IC_{50} = 0.055 μM and **36**, R_2 = 4-Br, IC_{50} = 0.18 μM against H460) displayed higher potency than those with 2-substituted phenyl group (**35**, R_2 = 2-F, IC_{50} = 0.23 μM and **37**, R_2 = 2-Br, IC_{50} = 0.32 μM against H460) or 3-substituted phenyl group (**34**, R_2 = 3-F, IC_{50} = 0.19 μM). Among them, 4-fluoro group on phenyl ring (moiety B) was the most favorable substituent for activity.

4.2. In vitro enzymatic assays

As shown in Table 2, the six tested compounds all exhibited excellent c-Met enzymatic potency, suggesting that the inhibition of c-Met is a candidate underlying mechanism for the antitumor effect. Compound **33** showed the most potent activity with an IC_{50} value of 1.63 nM, which was comparable to that of the positive control, foretinib (IC_{50} = 1.56 nM). Thus, compound **33** is worth further studying as new potential anticancer agent for the treatment of human cancers.

4.3. Enzymatic selectivity assays

To examine the selectivity of compound **33** on c-Met over other kinases, it was screened against 5 other tyrosine kinases (Table 3). Compared with its high potency against c-Met (IC_{50} = 1.63 nM), **33** also exhibited inhibitory effects against c-Kit, Flt-3, PDGFRα and VEGFR-2, although the potency was 1.3- to 43.2-fold lower than

Table 1
Structures and cytotoxicities of compounds **25**–**59** against H460, MKN-45, HT-29 and MDA-MB-231 cancer cell lines in vitro

Compd.	R_1	R_2	IC_{50}[a] (μmol/L) ±SD			
			H460	MKN-45	HT-29	MDA-MB-231
25	Morpholinyl	H	0.58 ± 0.038	0.43 ± 0.031	1.38 ± 0.14	1.23 ± 0.26
26	Morpholinyl	4-F	0.10 ± 0.012	0.09 ± 0.010	0.26 ± 0.027	0.67 ± 0.072
27	Morpholinyl	2-F	0.19 ± 0.024	0.15 ± 0.016	0.47 ± 0.033	0.70 ± 0.040
28	Morpholinyl	4-Br	0.29 ± 0.025	0.34 ± 0.038	0.71 ± 0.035	0.96 ± 0.10
29	Morpholinyl	2-Br	0.37 ± 0.037	0.45 ± 0.025	0.68 ± 0.041	1.56 ± 0.12
30	Morpholinyl	4-NO_2	1.89 ± 0.14	1.94 ± 0.20	2.52 ± 0.22	3.48 ± 0.21
31	Morpholinyl	4-OCH_3	1.24 ± 0.095	1.62 ± 0.13	3.36 ± 0.23	3.98 ± 0.24
32	Pyrrolidinyl	H	0.48 ± 0.026	0.53 ± 0.053	0.98 ± 0.055	1.13 ± 0.18
33	Pyrrolidinyl	4-F	0.055 ± 0.010	0.071 ± 0.011	0.13 ± 0.016	0.43 ± 0.050
34	Pyrrolidinyl	3-F	0.19 ± 0.013	0.16 ± 0.010	0.46 ± 0.063	0.88 ± 0.12
35	Pyrrolidinyl	2-F	0.23 ± 0.040	0.14 ± 0.012	0.40 ± 0.060	0.95 ± 0.055
36	Pyrrolidinyl	4-Br	0.18 ± 0.015	0.23 ± 0.012	0.67 ± 0.058	1.16 ± 0.19
37	Pyrrolidinyl	2-Br	0.32 ± 0.041	0.41 ± 0.050	0.85 ± 0.047	1.02 ± 0.27
38	Pyrrolidinyl	4-NO_2	1.24 ± 0.23	1.62 ± 0.22	1.76 ± 0.22	2.98 ± 0.33
39	Pyrrolidinyl	4-OCH_3	1.65 ± 0.37	1.32 ± 0.13	2.36 ± 0.20	3.45 ± 0.39
40	4-Methyl piperazinyl	H	0.45 ± 0.074	0.62 ± 0.10	1.14 ± 0.33	1.58 ± 0.18
41	4-Methyl piperazinyl	4-F	0.091 ± 0.011	0.15 ± 0.013	0.32 ± 0.019	0.46 ± 0.016
42	4-Methyl piperazinyl	2-F	0.23 ± 0.030	0.21 ± 0.015	0.48 ± 0.022	1.05 ± 0.11
43	4-Methyl piperazinyl	4-Br	0.25 ± 0.015	0.35 ± 0.020	0.85 ± 0.058	1.37 ± 0.15
44	4-Methyl piperazinyl	2-Br	0.29 ± 0.014	0.40 ± 0.031	1.19 ± 0.29	1.68 ± 0.20
45	4-Methyl piperazinyl	4-NO_2	0.98 ± 0.12	1.32 ± 0.29	2.56 ± 0.30	3.49 ± 0.26
46	4-Methyl piperazinyl	4-OCH_3	1.11 ± 0.20	1.32 ± 0.40	3.70 ± 0.60	3.98 ± 0.34
47	Piperidinyl	H	0.65 ± 0.10	0.59 ± 0.074	1.31 ± 0.25	1.88 ± 0.27
48	Piperidinyl	4-F	0.12 ± 0.017	0.18 ± 0.015	0.29 ± 0.021	0.55 ± 0.014
49	Piperidinyl	2-F	0.16 ± 0.020	0.35 ± 0.018	0.63 ± 0.026	0.91 ± 0.026
50	Piperidinyl	4-Br	0.41 ± 0.031	0.50 ± 0.031	0.77 ± 0.032	1.13 ± 0.15
51	Piperidinyl	4-NO_2	1.3 ± 0.26	1.14 ± 0.24	2.17 ± 0.35	2.62 ± 0.39
52	Piperidinyl	4-OCH_3	0.84 ± 0.095	0.95 ± 0.12	1.45 ± 0.21	2.01 ± 0.41
53	4-Methyl piperidinyl	H	0.55 ± 0.038	0.58 ± 0.073	1.04 ± 0.18	1.48 ± 0.29
54	4-Methyl piperidinyl	4-F	0.11 ± 0.011	0.13 ± 0.015	0.33 ± 0.049	0.66 ± 0.040
55	4-Methyl piperidinyl	3-F	0.19 ± 0.024	0.22 ± 0.019	0.50 ± 0.035	0.86 ± 0.071
56	4-Methyl piperidinyl	2-F	0.20 ± 0.017	0.26 ± 0.024	0.51 ± 0.062	0.67 ± 0.039
57	4-Methyl piperidinyl	4-Br	0.35 ± 0.022	0.33 ± 0.040	0.92 ± 0.10	1.16 ± 0.19
58	4-Methyl piperidinyl	2-Br	0.39 ± 0.045	0.51 ± 0.036	0.95 ± 0.14	1.24 ± 0.25
59	4-Methyl piperidinyl	4-NO_2	1.34 ± 0.29	1.15 ± 0.13	2.45 ± 0.38	4.01 ± 0.50
foretinib[b]			0.21 ± 0.03	0.032 ± 0.005	0.19 ± 0.01	0.54 ± 0.062

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

Table 2
c-Met kinase activity of selected compounds **32**, **33**, **34**, **35**, **41**, **48** and **foretinib** in vitro

Compd.	IC_{50}[a] on c-Met (nM)
32	13.57 ± 1.23
33	1.63 ± 0.12
34	4.31 ± 0.15
35	3.98 ± 0.35
41	1.98 ± 0.18
48	2.03 ± 0.22
foretinib[b]	1.56 ± 0.17

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

Table 3
Inhibition of tyrosine kinases by compound **33**

Kinase	Enzyme IC_{50} (nM)
c-kit	2.17
Flt-3	3.49
PDGFRα	15.73
VEGFR-2	70.41
EGFR	>10,000

that against c-Met. Moreover, this compound showed little or no kinase inhibition activity against EGFR kinase (IC_{50} >10 μM). These data suggested that compound **33** is a promising selective multi-target kinase inhibitor.

5. Binding model analysis

To further elucidate the binding mode of compounds, a docking analysis was performed. In our study, the co-crystal structure of foretinib (GSK1363089) with c-Met kinase was selected as the docking model (PDB ID: 3LQ8). The docking simulation was conducted with Glide XP (Schrödinger 2014), since Glide uses a hierarchical series of filters to search for possible locations of the ligand in the active-site region of the receptor. The shape and properties of the receptor were 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 by Accelrys DS visualizer 4.0 system. The binding model was exemplified by the interaction of compound **33** with c-Met. As shown in Figure 5, the nitrogen atom of pyrrolidine, the oxygen and fluorine atoms of 4-phenoxyquinoline in compound **33** formed three H-bond interactions with residue ASP1222. In the meantime, one Pi–Pi interaction between the phenyl ring (moiety B) and PHE1223, and one Pi–Sigma interaction between 3,4-dihydrophthalazine with ILE1084 had been formed. Both Pi–Pi and Pi–Sigma interactions played an important role in stabilizing the conformation of ligand–protein complex.

6. Conclusions

In summary, a series of 6,7-disubstituted-4-phenoxyquinoline derivatives bearing 4-oxo-3,4-dihydrophthalazine-1-carboxamide moieties were designed, synthesized and evaluated for their biological

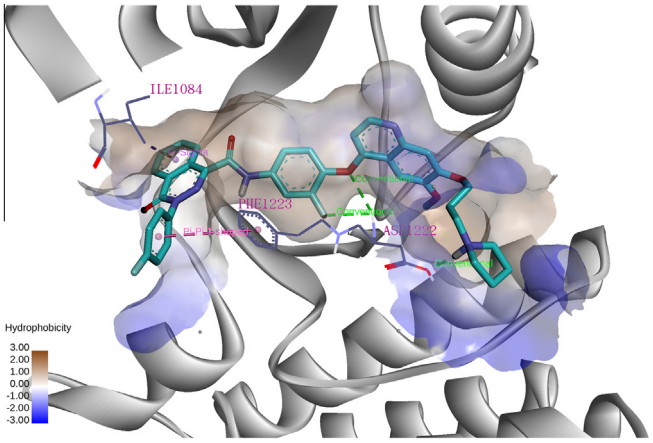


Figure 5. The c-Met active site in complex with compound **33** and its hydrophobic surface (brown: highly hydrophobic, blue: highly hydrophilic). The protein was displayed by secondary structure. Compound **33** was shown in colored sticks (cyan: carbon atom, blue: nitrogen atom, red: oxygen atom, white: hydrogen atom). The H-bond interaction was shown in green dotted lines, Pi–Pi interaction was shown in pink dotted lines, and Pi–Sigma interaction was shown in purple dotted lines.

activity. The preliminary investigation showed that most compounds displayed good to excellent potency against four tested cancer cell lines as compared with foretinib. In particular, the most promising compound **33** (c-Met IC_{50} = 1.63 nM, a multi-target tyrosine kinase inhibitor) showed the most potent antitumor activities with IC_{50} values of 0.055 μM, 0.071 μM, 0.13 μM, and 0.43 μM against H460, MKN-45, HT-29 and MDA-MB-231 cell lines, respectively. The SAR analyses indicated that the replacement of the cyclopropane-1,1-dicarboxamide framework of foretinib with the 4-oxo-3,4-dihydrophthalazine-1-carboxamide moiety maintained the potent cytotoxicity. Moreover, compounds with halogen groups, especially fluoro groups at 4-position on the phenyl ring (moiety B) were more active than those with nitro groups or methoxy groups. Further studies on SARs and mechanism of action of these compounds are in progress, and their results will be reported in the future.

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. 2-(Carboxycarbonyl)benzoic acid (22)

Naphthalene (16 g, 0.125 mol) was dissolved in 0.5 N NaOH (250 mL) under reflux to which 750 mL of boiling aqueous potassium permanganate (106 g, 0.67 mol) was added dropwise during an interval of 1.5 h under stirring. The reaction was continued to reflux for another 30 min to complete the oxidation. The reaction mixture was quenched by addition of 100 mL of ethanol, allowed to cool at room temperature and filtered. The resulting filtrate was acidified with 30% HCl and extracted with ethyl acetate (3 × 75 mL). The combined organic layer was dried over anhydrous Na_2SO_4, and concentrated under vacuum to afford 2-(carboxycarbonyl)benzoic acid **22** 8.5 g. White solid; yeild: 35%; mp: 142–144 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (dd, J = 7.6, 0.8 Hz, 1H), 7.77 (dd, J = 7.5, 1.1 Hz,1H), 7.68 (dd, J = 7.5, 1.0 Hz, 1H), 7.58 (dd, J = 7.6, 0.8 Hz, 1H); MS (ESI) m/z (%): 192.0 $[M-H]^+$.

7.2. General procedure for preparation of 4-oxo-3-substituted phenyl-3,4-dihydrophthalazine-1-carboxylic acid (23a–h)

To a solution of **22** (13 g, 0.067 mol) in water (100 mL), an appropriate phenyl hydrazine (0.067 mol) in ethanol (200 mL) was added. After stirring at room temperature for 15 h, the resultant precipitate was filtered, washed with dichloromethane and dried under vacuum to afford the title compounds **23a–h**.

7.2.1. 4-Oxo-3-phenyl-3,4-dihydrophthalazine-1-carboxylic acid (23a)

White solid; yield: 85%; mp: 217–218 °C; MS (ESI) m/z (%): 267.1 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO) δ 9.13 (d, J = 8.2 Hz, 1H), 8.48 (dd, J = 7.8, 0.8 Hz, 1H), 7.90 (dd, J = 7.6, 1.4 Hz, 1H), 7.83 (dd, J = 8.1, 1.1 Hz, 1H), 7.56–7.54 (m, 2H), 7.51–7.47 (m, 2H), 7.42–7.39 (m, 1H).

7.2.2. 3-(4-Fluorophenyl)-4-oxo-3,4-dihydrophthalazine-1-carboxylic acid (23b)

White solid; yield: 77%; mp: 215–217 °C; MS (ESI) m/z (%): 285.1 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO) δ 8.58 (d, J = 8.2 Hz, 1H), 8.38 (dd, J = 7.9, 0.8 Hz, 1H), 8.04 (dd, J = 7.4, 1.4 Hz, 1H), 7.96 (dd, J = 8.2, 1.2 Hz, 1H), 7.71–7.68 (m, 2H), 7.41–7.37 (m, 2H).

7.2.3. 3-(3-Fluorophenyl)-4-oxo-3,4-dihydrophthalazine-1-carboxylic acid (23c)

Yellow solid; yield: 75%; mp: 205–207 °C; MS (ESI) m/z (%): 285.5 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO) δ 8.55 (d, J = 8.5 Hz, 1H), 8.38 (d, J = 8.0 Hz, 1H), 8.10–8.06 (m, 2H) 8.05–8.01 (m, 2H), 7.76–7.72 (m, 1H), 7.33–7.30 (m, 1H).

7.2.4. 3-(2-Fluorophenyl)-4-oxo-3,4-dihydrophthalazine-1-carboxylic acid (23d)

Yellow solid; yield: 79%; mp: 214–217 °C; MS (ESI) m/z (%): 285.2 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO) δ 8.56 (d, J = 8.1 Hz, 1H), 8.37 (d, J = 8.5 Hz, 1H), 8.12–8.02 (m, 3H), 7.52–7.50 (m, 2H), 7.31–7.28 (m, 1H).

7.2.5. 3-(4-Bromophenyl)-4-oxo-3,4-dihydrophthalazine-1-carboxylic acid (23e)

Yellow solid; yield: 82%; mp: 202–205 °C; MS (ESI) m/z (%):345.0 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO) δ 8.58 (d, J = 8.4 Hz, 1H), 8.39 (dd, J = 8.8, 0.9 Hz, 1H), 8.04 (dd, J = 7.3, 1.4 Hz, 1H), 7.96 (dd, J = 8.0, 1.2 Hz, 1H), 7.72–7.69 (m, 2H), 7.74–7.61 (m, 2H).

7.2.6. 3-(2-Bromophenyl)-4-oxo-3,4-dihydrophthalazine-1-carboxylic acid (23f)

Yellow solid; yield: 81%; mp: 206–209 °C; MS (ESI) m/z (%):345.3 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO) δ 8.59 (d, J = 8.0 Hz, 1H), 8.38 (d, J = 7.2 Hz, 1H), 8.15–8.09 (m, 2H) 8.08–8.03 (m, 2H), 7.70–7.66 (m, 1H), 7.51–7.47 (m, 1H).

7.2.7. 3-(4-Nitrophenyl)-4-oxo-3,4-dihydrophthalazine-1-carboxylic acid (23g)

Yellow solid; yield: 81%; mp: 217–219 °C; MS (ESI) m/z (%):312.6 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO) δ 8.74–8.70 (m,

2H), 8.65–8.63 (m, 2H), 8.52 (d, *J* = 8.6 Hz, 1H), 8.41 (dd, *J* = 8.6, 1.0 Hz, 1H), 8.13 (dd, *J* = 7.5, 1.1 Hz, 1H), 7.98 (dd, *J* = 8.2, 1.2 Hz, 1H).

7.2.8. 3-(4-Methoxyphenyl)-4-oxo-3,4-dihydrophthalazine-1-carboxylic acid (23h)

White solid; yield: 87%; mp: 219–220 °C; MS (ESI) *m*/*z* (%): 297.2 $[M+H]^+$; ^1H NMR (400 MHz, DMSO) δ 8.57 (d, *J* = 8.0 Hz, 1H), 8.37 (dd, *J* = 7.8 and 0.7 Hz, 1H), 8.05–8.02 (m, 1H), 7.94 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.56–7.52 (m, 2H), 7.10–7.06 (m, 2H), 3.83 (s, 3H).

7.3. General procedure for preparation of 4-oxo-3-substituted phenyl-3,4-dihydrophthalazine-1-carbonyl chloride (24a–h)

An appropriate 4-oxo-3-substituted phenyl-3,4-dihydrophthalazine-1-carboxylic acid **23a**–**h** (0.01 mol) was added to thionyl chloride (15 mL), and refluxed for 5–7 h. The reaction mixture was evaporated to yield corresponding 4-oxo-3-phenyl-3,4-dihydrophthalazine-1-carbonyl chloride **24a**–**h**.

7.4. General procedure for preparation of the target compounds (25–59)

To a mixture of an appropriate aniline **21a**–**e** (0.48 mmol), triethylamine (0.58 mmol) and dichloromethane (10 mL) in an ice bath, an appropriate carbonyl chloride **24a**–**h** (0.52 mol) was dissolved in dried dichloromethane (10 mL) to add drop-wise. Upon the completion of addition, the reaction mixture was removed to room temperature for 10 h and monitored by TLC. The mixture was washed with 10% K_2CO_3 (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/Et_3N (40:1:1) to afford the target compounds **25**–**59**.

7.4.1. *N*-(3-Fluoro-4-((6-methoxy-7-(3-morpholinopropoxy) quinolin-4-yl)oxy)phenyl)-4-oxo-3-phenyl-3,4-dihydrophthalazine-1-carboxamide (25)

Yellow solid; yield: 62%; mp: 157–159 °C; MS (ESI) *m*/*z* (%): 676.5 $[M+H]^+$; ^1H NMR (400 MHz, DMSO) δ 11.24 (s, 1H), 8.64 (d, *J* = 5.5 Hz, 1H), 8.44 (d, *J* = 7.8 Hz, 2H), 8.16–7.97 (m, 3H), 7.84 (d, *J* = 7.7 Hz, 2H), 7.79 (d, *J* = 8.8 Hz, 1H), 7.66 (s, 1H), 7.59 (d, *J* = 7.8 Hz, 2H), 7.56 (s, 1H), 7.48 (t, *J* = 7.3 Hz, 1H), 6.70 (d, *J* = 5.3 Hz, 1H), 4.32 (s, 2H), 4.01 (s, 3H), 3.94 (d, *J* = 24.8 Hz, 4H), 3.50 (s, 2H), 3.13 (s, 2H), 2.51 (s, 2H), 2.37 (s, 2H); ^{13}C NMR (400 MHz, DMSO) δ 162.47, 161.58, 158.64, 154.90, 153.24, 152.46, 150.58, 147.27, 141.72, 140.24, 138.31, 138.21, 136.38, 136.26, 134.74, 133.22, 129.08 (2C), 128.44, 127.41, 127.29, 126.75, 126.69 (2C), 124.60, 117.74, 115.30, 109.71, 109.48, 102.93, 99.99, 66.85, 63.68 (2C), 56.59, 54.00, 51.57 (2C), 23.26. Anal. Calcd for $C_{38}H_{34}FN_5O_6$: C, 67.55; H, 5.07; N, 10.36. Found: C, 67.52; H, 5.10; N, 10.33.

7.4.2. *N*-(3-Fluoro-4-((6-methoxy-7-(3-morpholinopropoxy) quinolin-4-yl)oxy)phenyl)-3-(4-fluorophenyl)-4-oxo-3,4-dihydrophthalazine-1-carboxamide (26)

Yellow solid; yield: 65%; mp: 154–156 °C; MS (ESI) *m*/*z* (%): 694.3 $[M+H]^+$; ^1H NMR (400 MHz, DMSO) δ 11.04 (s, 1H), 8.53–8.40 (m, 3H), 8.11–7.97 (m, 3H), 7.86 (dd, *J* = 8.9, 5.0 Hz, 2H), 7.70 (d, *J* = 8.7 Hz, 1H), 7.59–7.48 (m, 2H), 7.47–7.36 (m, 3H), 6.48 (d, *J* = 5.1 Hz, 1H), 4.20 (t, *J* = 6.4 Hz, 2H), 3.95 (d, *J* = 7.5 Hz, 3H), 3.59 (t, *J* = 4.4 Hz, 4H), 2.47 (t, *J* = 7.1 Hz, 2H), 2.39 (s, 4H), 1.99 (dd, *J* = 13.4, 6.6 Hz, 2H); ^{13}C NMR (400 MHz, DMSO) δ162.73, 162.33, 160.43, 159.69, 158.69, 152.67, 152.43, 150.07, 149.31, 146.87, 140.20, 137.97, 137.67, 136.82, 134.78, 133.26, 128.88, 128.79, 128.41, 127.37, 126.87 (s, 1H), 124.68, 117.64, 116.02, 115.79, 114.92, 109.58, 109.01, 102.54, 99.48, 67.16, 66.70 (2C), 56.27, 55.29, 53.86 (2C), 26.17. Anal. Calcd for $C_{38}H_{33}F_2N_5O_6$: C, 65.79; H, 4.79; N, 10.10. Found: C, 65.81; H, 4.75; N, 10.08.

7.4.3. *N*-(3-Fluoro-4-((6-methoxy-7-(3-morpholinopropoxy) quinolin-4-yl)oxy)phenyl)-3-(2-fluorophenyl)-4-oxo-3,4-dihydrophthalazine-1-carboxamide (27)

Yellow solid; yield: 58%; mp: 158–160 °C; MS (ESI) *m*/*z* (%): 694.3 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 9.28 (d, *J* = 8.1 Hz, 1H), 9.17 (s, 1H), 8.56 (d, *J* = 7.8 Hz, 1H), 8.48 (dd, *J* = 9.1, 5.3 Hz, 1H), 8.02–7.96 (m, 1H), 7.94–7.91 (m, 1H), 7.89 (t, *J* = 3.9 Hz, 1H), 7.58 (d, *J* = 2.2 Hz, 1H), 7.57 (s, 1H), 7.56–7.49 (m, 1H), 7.48–7.27 (m, 4H), 7.09–6.95 (m, 1H), 6.60–6.45 (m, 1H), 6.41 (t, *J* = 4.6 Hz, 1H), 4.32–4.23 (m, 2H), 4.04 (s, 3H), 3.73 (t, *J* = 4.5 Hz, 4H), 2.59 (t, *J* = 7.1 Hz, 2H), 2.50 (s, 4H), 2.14 (p, *J* = 6.8 Hz, 2H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 160.90, 159.99, 158.86, 152.31, 149.90, 148.71, 146.89, 137.67, 136.75, 135.89, 134.40, 132.61, 131.00, 128.79, 128.24, 127.82, 127.56, 124.78, 123.88, 117.01, 116.81, 116.45, 115.44, 109.83, 109.60, 108.75, 102.20, 101.92, 99.51, 67.25, 66.99 (2C), 56.17, 55.40, 53.71 (2C), 25.97. Anal. Calcd for $C_{38}H_{33}F_2N_5O_6$: C, 65.79; H, 4.79; N, 10.10. Found: C, 65.77; H, 4.80; N, 10.07.

7.4.4. 3-(4-Bromophenyl)-*N*-(3-fluoro-4-((6-methoxy-7-(3-morpholinopropoxy)quinolin-4-yl)oxy)phenyl)-4-oxo-3,4-dihydrophthalazine-1-carboxamide (28)

Yellow solid; yield: 64%; mp: 154–157 °C; MS (ESI) *m*/*z* (%): 754.6 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 9.26 (d, *J* = 8.0 Hz, 1H), 9.18 (s, 1H), 8.59–8.52 (m, 1H), 8.49 (d, *J* = 5.3 Hz, 1H), 8.01–7.87 (m, 3H), 7.72–7.66 (m, 2H), 7.58 (dd, *J* = 5.9, 2.9 Hz, 3H), 7.45 (s, 1H), 7.40 (d, *J* = 10.0 Hz, 1H), 7.29 (d, *J* = 8.6 Hz, 1H), 6.42 (d, *J* = 5.3 Hz, 1H), 4.28 (t, *J* = 6.6 Hz, 2H), 4.05 (s, 3H), 3.75 (t, *J* = 4.4 Hz, 4H), 2.62 (t, *J* = 7.0 Hz, 2H), 2.53 (s, 4H), 2.22–2.11 (m, 2H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 160.98, 160.05, 158.93, 155.72, 153.23, 152.35, 149.92, 148.53, 146.71, 140.05, 137.64, 136.81, 136.00, 134.36, 132.60, 132.13 (2C), 128.38, 127.85–127.45 (2C), 127.30 (2C), 123.90, 122.23, 116.42, 115.45, 109.70, 108.59, 102.18, 99.53, 67.19, 66.85 (2C), 56.16, 55.38, 53.63 (2C), 25.87. Anal. Calcd for $C_{38}H_{33}BrFN_5O_6$: C, 60.48; H, 4.41; N, 9.28. Found: C, 60.51; H, 4.43; N, 9.30.

7.4.5. 3-(2-Bromophenyl)-*N*-(3-fluoro-4-((6-methoxy-7-(3-morpholinopropoxy)quinolin-4-yl)oxy)phenyl)-4-oxo-3,4-dihydrophthalazine-1-carboxamide (29)

Yellow solid; yield: 56%; mp: 149–152 °C; MS (ESI) *m*/*z* (%): 754.5 $[M+H]^+$; IR (KBr) cm^{-1}: 3384.3, 3066.0, 2927.2, 2851.5, 2811.6, 1725.7, 1682.3, 1620.7, 1598.6, 1578.7, 1508.0, 1478.6, 1430.6, 1384.0, 1348.4,1305.4, 1249.6, 1210.3, 1172.5, 1142.7, 1115.5, 1045.4, 1020.9, 971.8, 891.8, 853.0, 790.3, 750.2, 728.5, 686.3, 658.7, 618.7, 474.4; ^1H NMR (400 MHz, $CDCl_3$) δ 9.30 (d, *J* = 8.2 Hz, 1H), 9.21 (s, 1H), 8.56 (d, *J* = 7.3 Hz, 1H), 8.48 (d, *J* = 5.2 Hz, 1H), 7.98 (dd, *J* = 14.0, 6.7 Hz, 1H), 7.95–7.85 (m, 1H), 7.81 (d, *J* = 8.0 Hz, 1H), 7.61–7.48 (m, 3H), 7.48–7.36 (m, 3H), 7.25 (d, *J* = 8.7 Hz, 1H), 6.40 (d, *J* = 5.2 Hz, 1H), 4.28 (dd, *J* = 12.5, 6.0 Hz, 2H), 4.09–4.02 (m, 3H), 3.77–3.70 (m, 4H), 2.59 (dd, *J* = 14.0, 7.0 Hz, 2H), 2.49 (s, 4H), 2.13 (dd, *J* = 13.6, 6.8 Hz, 2H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 160.95, 159.96, 158.86, 152.28, 149.87, 148.75, 146.94, 140.05, 137.62, 136.39, 135.93, 134.42, 133.85, 132.54, 130.89, 129.46, 128.55, 128.42, 127.96, 127.82, 127.59, 123.86, 121.67, 116.44, 115.42, 109.80, 109.57, 108.79, 102.17, 99.50, 67.25, 67.03 (2C), 56.16, 55.39, 53.73 (2C), 26.01.

Anal. Calcd for $C_{38}H_{33}BrFN_5O_6$: C, 60.48; H, 4.41; N, 9.28. Found: C, 60.50; H, 4.39; N, 9.25.

7.4.6. *N*-(3-Fluoro-4-((6-methoxy-7-(3-morpholinopropoxy) quinolin-4-yl)oxy)phenyl)-3-(4-nitrophenyl)-4-oxo-3,4-dihydrophthalazine-1-carboxamide (30)

Yellow solid; yield: 58%; mp: 151–154 °C; MS (ESI) *m*/*z* (%): 721.3 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 9.29 (s, 1H), 9.21 (d, *J* = 8.0 Hz, 1H), 8.59 (d, *J* = 7.1 Hz, 1H), 8.51 (d, *J* = 5.3 Hz, 1H), 8.42 (d, *J* = 9.1 Hz, 2H), 8.05–7.98 (m, 4H), 7.94 (t, *J* = 7.6 Hz, 1H), 7.60 (s, 1H), 7.54 (d, *J* = 6.9 Hz, 1H), 7.48 (d, *J* = 8.3 Hz, 1H), 7.31 (dd, *J* = 16.0, 7.4 Hz, 1H), 6.49 (d, *J* = 5.4 Hz, 1H), 4.31 (dd, *J* = 10.7, 6.3 Hz, 2H), 4.06 (s, 3H), 3.91 (s, 4H), 3.12 (q, *J* = 7.3 Hz, 2H), 2.86 (d, *J* = 30.3 Hz, 4H), 2.33 (s, 2H). Anal. Calcd for $C_{38}H_{33}FN_6O_8$: C, 63.33; H, 4.62; N, 11.66. Found: C, 63.35; H, 4.59; N, 11.63.

7.4.7. *N*-(3-Fluoro-4-((6-methoxy-7-(3-morpholinopropoxy) quinolin-4-yl)oxy)phenyl)-3-(4-methoxyphenyl)-4-oxo-3,4-dihydrophthalazine-1-carboxamide (31)

Yellow solid; yield: 68%; mp: 153–156 °C; MS (ESI) *m*/*z* (%): 706.4 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 9.31–9.18 (m, 2H), 8.54 (d, *J* = 7.9 Hz, 1H), 8.49 (d, *J* = 5.3 Hz, 1H), 7.99–7.84 (m, 3H), 7.66 (dd, *J* = 14.3, 4.8 Hz, 1H), 7.60–7.51 (m, 2H), 7.45–7.38 (m, 2H), 7.29 (dd, *J* = 8.1, 4.7 Hz, 1H), 7.03 (t, *J* = 10.4 Hz, 1H), 6.42 (d, *J* = 5.3 Hz, 1H), 4.31–4.22 (m, 2H), 4.05 (s, 3H), 3.91 (t, *J* = 22.7 Hz, 3H), 3.78–3.67 (m, 4H), 2.58 (t, *J* = 7.1 Hz, 2H), 2.49 (s, 4H), 2.20–2.08 (m, 2H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 161.17, 160.98, 159.97, 159.50, 159.30, 159.26, 152.30, 149.88, 148.74, 146.94, 135.85, 134.31, 134.13, 132.47, 128.46, 127.85, 127.66, 127.56, 127.07, 126.43, 125.32, 123.91, 116.29, 115.43, 114.25, 111.69, 109.50, 108.78, 102.19, 99.50, 67.26, 67.04 (2C), 56.48, 56.17, 55.40, 53.73 (2C), 26.01. Anal. Calcd for $C_{39}H_{36}FN_5O_7$: C, 66.37; H, 5.14; N, 9.92. Found: C, 66.36; H, 5.12; N, 9.94.

7.4.8. *N*-(3-Fluoro-4-((6-methoxy-7-(3-(pyrrolidin-1-yl) propoxy)quinolin-4-yl)oxy)phenyl)-4-oxo-3-phenyl-3,4-dihydrophthalazine-1-carboxamide (32)

Yellow solid; yield: 68%; mp: 163–166 °C; MS (ESI) *m*/*z* (%): 660.2 $[M+H]^+$; ^1H NMR (400 MHz, DMSO) δ 11.18 (s, 1H), 8.67 (d, *J* = 5.8 Hz, 1H), 8.45 (d, *J* = 7.8 Hz, 2H), 8.14–7.98 (m, 3H), 7.82 (d, *J* = 7.7 Hz, 2H), 7.77 (d, *J* = 9.3 Hz, 1H), 7.68 (s, 1H), 7.58 (dd, *J* = 13.3, 7.3 Hz, 4H), 7.48 (t, *J* = 7.4 Hz, 1H), 6.75 (d, *J* = 5.3 Hz, 1H), 4.33 (t, *J* = 6.0 Hz, 2H), 4.02 (s, 3H), 3.60 (d, *J* = 5.0 Hz, 2H), 3.33 (dd, *J* = 14.1, 6.4 Hz, 2H), 3.11–2.98 (m, 2H), 2.37–2.24 (m, 2H), 2.03 (s, 2H), 1.97–1.83 (m, 2H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 167.24, 166.84, 163.39, 159.59, 158.35, 157.15, 155.52, 151.38, 146.48, 144.98, 143.14, 140.94, 139.41, 137.94, 133.88, 133.82 (2C), 133.18, 132.14, 132.03, 131.48, 131.45 (2C), 129.31, 122.51, 120.08, 114.35, 110.28, 107.75, 104.86, 71.55, 61.42, 58.10 (2C), 56.38, 30.18, 27.98 (2C). Anal. Calcd for $C_{38}H_{34}FN_5O_5$: C, 69.18; H, 5.19; N, 10.62. Found: C, 69.15; H, 5.18; N, 10.64.

7.4.9. *N*-(3-Fluoro-4-((6-methoxy-7-(3-(pyrrolidin-1-yl) propoxy)quinolin-4-yl)oxy)phenyl)-3-(4-fluorophenyl)-4-oxo-3,4-dihydrophthalazine-1-carboxamide (33)

Yellow solid; yield: 62%; mp: 160–163 °C; MS (ESI) *m*/*z* (%): 678.3 $[M+H]^+$; IR (KBr) cm^{-1}: 3377.7, 3075.1, 2956.2, 2877.0, 2794.1, 1677.1, 1620.7, 1604.5, 1579.9, 1508.0, 1430.6, 1384.5, 1349.6, 1329.9, 1305.8, 1250.4, 1210.9, 1172.4, 1139.5, 1077.6, 1020.8, 971.5, 852.8, 836.2, 789.4, 726.0, 685.9, 617.6, 590.7, 544.9, 525.7; ^1H NMR (400 MHz, DMSO) δ 11.37 (s, 1H), 8.49 (d, *J* = 5.2 Hz, 1H), 8.42 (d, *J* = 8.1 Hz, 2H), 8.15–7.96 (m, 3H), 7.92 (dd, *J* = 8.7, 5.0 Hz, 2H), 7.82–7.74 (m, 1H), 7.52 (dd, *J* = 16.6, 7.5 Hz, 2H), 7.40 (t, *J* = 8.8 Hz, 3H), 6.48 (d, *J* = 5.1 Hz, 1H), 4.21 (t, *J* = 6.3 Hz, 2H), 3.97 (s, 3H), 2.57 (t, *J* = 7.1 Hz, 2H), 2.46 (s, 4H), 2.05–1.93 (m, 2H), 1.69 (s, 4H); ^{13}C NMR (400 MHz, DMSO) δ 162.84, 162.41, 160.40, 159.71, 158.66, 155.07, 152.44, 150.05, 149.31, 146.88, 140.37, 137.96, 136.77, 134.73, 133.18, 128.94 (2C), 128.62, 128.38, 127.33, 126.77, 124.61, 117.64, 115.94, 115.71, 114.90, 109.54, 108.96, 102.49, 99.48, 67.21, 56.27, 54.11 (2C), 52.70, 28.52, 23.60 (2C). Anal. Calcd for $C_{38}H_{33}F_2N_5O_5$: C, 67.35; H, 4.91; N, 10.33. Found: C, 67.33; H, 4.93; N, 10.35.

7.4.10. *N*-(3-Fluoro-4-((6-methoxy-7-(3-(pyrrolidin-1-yl) propoxy)quinolin-4-yl)oxy)phenyl)-3-(3-fluorophenyl) -4-oxo-3,4-dihydrophthalazine-1-carboxamide (34)

Yellow solid; yield: 67%; mp: 157–160 °C; MS (ESI) *m*/*z* (%): 678.3 $[M+H]^+$; ^1H NMR (400 MHz, DMSO) δ 11.26 (s, 1H), 8.65 (d, *J* = 5.8 Hz, 1H), 8.45 (d, *J* = 8.0 Hz, 2H), 8.17–7.98 (m, 3H), 7.86–7.77 (m, 2H), 7.74 (d, *J* = 8.1 Hz, 1H), 7.67 (s, 1H), 7.65–7.54 (m, 3H), 7.33 (td, *J* = 8.4, 2.0 Hz, 1H), 6.72 (d, *J* = 5.6 Hz, 1H), 4.32 (s, 2H), 4.01 (s, 3H), 3.59 (d, *J* = 5.0 Hz, 2H), 3.36–3.31 (m, 3H), 3.06 (dd, *J* = 7.2, 4.7 Hz, 2H), 2.38–2.25 (m, 2H), 2.02 (s, 2H), 1.92 (dd, *J* = 13.1, 8.1 Hz, 2H). Anal. Calcd for $C_{38}H_{33}F_2N_5O_5$: C, 67.35; H, 4.91; N, 10.33. Found: C, 67.37; H, 4.90; N, 10.31.

7.4.11. *N*-(3-Fluoro-4-((6-methoxy-7-(3-(pyrrolidin-1-yl) propoxy)quinolin-4-yl)oxy)phenyl)-3-(2-fluorophenyl) -4-oxo-3,4-dihydrophthalazine-1-carboxamide (35)

Yellow solid; yield: 54%; mp: 166–168 °C; MS (ESI) *m*/*z* (%): 678.5 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 9.26 (d, *J* = 8.1 Hz, 1H), 9.22 (s, 1H), 8.55 (d, *J* = 8.0 Hz, 1H), 8.48 (d, *J* = 5.3 Hz, 1H), 8.01–7.95 (m, 1H), 7.90 (dt, *J* = 11.2, 5.2 Hz, 2H), 7.59–7.47 (m, 3H), 7.40 (d, *J* = 10.5 Hz, 2H), 7.37–7.28 (m, 2H), 7.25 (d, *J* = 8.7 Hz, 1H), 6.40 (d, *J* = 5.2 Hz, 1H), 4.26 (t, *J* = 6.6 Hz, 2H), 4.04 (s, 3H), 2.74 (t, *J* = 7.4 Hz, 2H), 2.62 (s, 4H), 2.24–2.15 (m, 2H), 1.84 (d, *J* = 13.9 Hz, 4H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 160.92, 159.94, 158.71, 156.07, 155.74, 152.27, 149.89, 148.72, 146.94, 137.68, 136.82, 135.90, 134.39, 132.59, 130.97, 128.91, 128.78, 128.21, 127.81, 127.54, 124.76, 123.87, 116.87, 116.43, 115.44, 109.82, 109.59, 108.82, 102.18, 99.50, 67.39, 56.16, 54.22 (2C), 53.01, 28.21, 23.50 (2C). Anal. Calcd for $C_{38}H_{33}F_2N_5O_5$: C, 67.35; H, 4.91; N, 10.33. Found: C, 67.38; H, 4.92; N, 10.29.

7.4.12. 3-(4-Bromophenyl)-*N*-(3-fluoro-4-((6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl) -4-oxo-3,4-dihydrophthalazine-1-carboxamide (36)

Yellow solid; yield: 57%; mp: 168–170 °C; MS (ESI) *m*/*z* (%): 638.2 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 9.27 (s, 1H), 9.23 (d, *J* = 8.1 Hz, 1H), 8.57–8.51 (m, 1H), 8.48 (d, *J* = 5.3 Hz, 1H), 7.93 (dtd, *J* = 15.2, 8.2, 1.1 Hz, 3H), 7.66 (d, *J* = 8.8 Hz, 2H), 7.56 (dd, *J* = 6.7, 2.1 Hz, 3H), 7.41 (d, *J* = 4.9 Hz, 2H), 7.29 (d, *J* = 9.1 Hz, 1H), 6.41 (d, *J* = 5.2 Hz, 1H), 4.30–4.22 (m, 2H), 4.04 (s, 3H), 2.90–2.81 (m, 2H), 2.76 (s, 4H), 2.31–2.21 (m, 2H), 1.89 (s, 4H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 160.94, 159.93, 158.98, 155.75, 153.27, 152.13, 149.84, 148.74, 146.87, 140.07, 137.70, 136.70, 135.90, 134.39, 132.63, 132.19, 128.41, 127.76 (2C), 127.35 (2C), 123.93, 122.30, 116.39, 115.51, 109.69, 108.88, 102.22, 99.55, 67.07, 56.15, 54.11 (2C), 53.01, 45.90, 27.68, 23.48 (2C). Anal. Calcd for $C_{38}H_{33}BrFN_5O_5$: C, 61.79; H, 4.50; N, 9.48. Found: C, 61.77; H, 4.55; N, 9.50.

7.4.13. 3-(2-Bromophenyl)-*N*-(3-fluoro-4-((6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl) -4-oxo-3,4-dihydrophthalazine-1-carboxamide (37)

Yellow solid; yield: 51%; mp: 162–164 °C; MS (ESI) *m*/*z* (%): 638.2 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 9.31 (d, *J* = 8.1 Hz, 1H), 9.23 (s, 1H), 8.57 (d, *J* = 6.5 Hz, 1H), 8.48 (t, *J* = 9.3 Hz, 1H), 8.04–7.97 (m, 1H), 7.96–7.86 (m, 2H), 7.82 (d, *J* = 7.6 Hz, 1H), 7.62–7.49 (m, 3H), 7.49–7.38 (m, 3H), 7.26 (d, *J* = 8.7 Hz, 1H), 6.41 (d, *J* = 5.1 Hz, 1H), 4.34–4.23 (m, 2H), 4.05 (s, 3H), 2.71 (t, *J* = 7.0 Hz, 2H), 2.58 (s, 4H), 2.18 (dd, *J* = 14.1, 7.0 Hz, 2H), 1.82 (s,

4H). Anal. Calcd for $C_{38}H_{33}BrFN_5O_5$: C, 61.79; H, 4.50; N, 9.48. Found: C, 61.73; H, 4.53; N, 9.53.

7.4.14. *N*-(3-Fluoro-4-((6-methoxy-7-(3-(pyrrolidin-1-yl) propoxy)quinolin-4-yl)oxy)phenyl)-3-(4-nitrophenyl)-4-oxo-3,4-dihydrophthalazine-1-carboxamide (38)

Yellow solid; yield: 56%; mp: 171–174 °C; MS (ESI) *m*/*z* (%): 705.2 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 9.24 (d, J = 8.1 Hz, 1H), 9.14 (s, 1H), 8.59 (d, J = 7.8 Hz, 1H), 8.50 (d, J = 5.2 Hz, 1H), 8.43 (d, J = 9.0 Hz, 2H), 8.04–7.90 (m, 5H), 7.58 (s, 1H), 7.41 (d, J = 9.4 Hz, 2H), 7.30 (t, J = 8.3 Hz, 1H), 6.43 (d, J = 5.2 Hz, 1H), 4.28 (dd, J = 13.8, 8.1 Hz, 2H), 4.04 (s, 3H), 3.18 (s, 4H), 3.08 (dd, J = 14.6, 7.2 Hz, 2H), 2.44 (s, 2H), 2.05 (d, J = 15.0 Hz, 4H). Anal. Calcd for $C_{38}H_{33}FN_6O_7$: C, 64.77; H, 4.72; N, 11.93. Found: C, 64.73; H, 4.75; N, 11.96.

7.4.15. *N*-(3-Fluoro-4-((6-methoxy-7-(3-(pyrrolidin-1-yl) propoxy)quinolin-4-yl)oxy)phenyl)-3-(4-methoxy phenyl)-4-oxo-3,4-dihydrophthalazine-1-carboxamide (39)

Yellow solid; yield: 59%; mp: 163–164 °C; MS (ESI) *m*/*z* (%): 705.2 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 9.31–9.17 (m, 2H), 8.54 (d, J = 7.9 Hz, 1H), 8.49 (d, J = 5.2 Hz, 1H), 8.01–7.84 (m, 3H), 7.71–7.65 (m, 1H), 7.60–7.51 (m, 2H), 7.41 (d, J = 11.5 Hz, 2H), 7.29 (dd, J = 8.2, 4.7 Hz, 1H), 7.25 (d, J = 3.3 Hz, 1H), 7.06 (dd, J = 9.0, 3.0 Hz, 1H), 6.42 (d, J = 5.2 Hz, 1H), 4.31–4.23 (m, 2H), 4.03 (d, J = 8.5 Hz, 3H), 3.94 (d, J = 37.8 Hz, 3H), 3.04 (s, 2H), 3.00 (d, J = 16.6 Hz, 4H), 2.42–2.28 (m, 2H), 1.99 (s, 4H). Anal. Calcd for $C_{39}H_{36}FN_5O_6$: C, 67.91; H, 5.26; N, 10.15. Found: C, 67.93; H, 5.25; N, 10.14.

7.4.16. *N*-(3-Fluoro-4-((6-methoxy-7-(3-(4-methylpiperazin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl)-4-oxo-3-phenyl-3,4-dihydrophthalazine-1-carboxamide (40)

Yellow solid; yield: 69%; mp: 137–140 °C; MS (ESI) *m*/*z* (%): 689.3 $[M+H]^+$; IR (KBr) cm^{-1}: 3418.3, 2345.9, 1639.7, 1532.9, 1506.3, 1437.8, 1384.0, 1099.6, 791.8, 710.5, 688.7, 617.4, 466.3; ^1H NMR (400 MHz, DMSO) δ 11.18 (s, 1H), 8.48 (d, J = 5.2 Hz, 1H), 8.44 (d, J = 8.2 Hz, 2H), 8.12–7.97 (m, 3H), 7.81 (d, J = 7.7 Hz, 2H), 7.73 (d, J = 8.8 Hz, 1H), 7.62–7.53 (m, 3H), 7.48 (dd, J = 15.2, 8.1 Hz, 2H), 7.40 (s, 1H), 6.48 (d, J = 5.1 Hz, 1H), 4.19 (t, J = 6.2 Hz, 2H), 3.96 (s, 3H), 2.46 (t, J = 7.1 Hz, 2H), 2.43 (dd, J = 32.0, 24.9 Hz, 8H), 2.15 (s, 3H), 2.02–1.92 (m, 2H). ^{13}C NMR (400 MHz, DMSO) δ 162.45, 159.70, 158.64, 155.10, 152.66, 152.44, 150.07, 149.31, 146.87, 141.72, 140.39, 137.88, 136.80, 134.73, 133.20, 129.09 (2C), 128.44, 127.40, 127.32, 126.81, 126.65 (2C), 124.63, 117.68, 114.92, 109.57, 108.98, 102.52, 99.49, 67.21, 56.27, 55.27 (2C), 54.83, 53.23 (2C), 46.24, 26.53. Anal. Calcd for $C_{39}H_{37}FN_6O_5$: C, 68.01; H, 5.41; N, 12.20. Found: C, 67.98; H, 5.44; N, 12.22.

7.4.17. *N*-(3-Fluoro-4-((6-methoxy-7-(3-(4-methylpiperazin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl)-3-(4-fluorophenyl)-4-oxo-3,4-dihydrophthalazine-1-carboxamide (41)

Yellow solid; yield: 64%; mp: 136–138 °C; MS (ESI) *m*/*z* (%): 707.5 $[M+H]^+$; ^1H NMR (400 MHz, DMSO) δ 11.27 (s, 1H), 8.63 (d, J = 44.5 Hz, 1H), 8.41 (t, J = 12.5 Hz, 2H), 8.24–7.97 (m, 3H), 7.87 (d, J = 28.6 Hz, 2H), 7.79 (s, 1H), 7.74–7.52 (m, 3H), 7.40 (s, 2H), 6.77 (s, 1H), 4.30 (s, 2H), 4.02 (s, 3H), 3.41 (s, 8H), 3.09 (s, 2H), 2.77 (s, 3H), 2.25 (s, 2H); ^{13}C NMR (400 MHz, DMSO) δ 162.85, 162.44, 160.41, 158.74, 154.80, 153.91, 152.35, 150.90, 146.20, 140.18, 138.46, 138.02, 136.09, 134.68, 133.20, 132.79, 128.94 (2C), 128.37, 127.33, 126.82, 124.53, 117.76, 116.01, 115.79 (2C), 115.31, 109.60, 103.01, 100.14, 67.08, 56.70, 53.36, 50.77 (2C), 48.86 (2C), 42.33, 24.52. Anal. Calcd for $C_{39}H_{36}F_2N_6O_5$: C, 66.28; H, 5.13; N, 11.89. Found: C, 66.25; H, 5.14; N, 11.91.

7.4.18. *N*-(3-Fluoro-4-((6-methoxy-7-(3-(4-methylpiperazin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl)-3-(2-fluorophenyl)-4-oxo-3,4-dihydrophthalazine-1-carboxamide (42)

Yellow solid; yield: 65%; mp: 141–143 °C; MS (ESI) *m*/*z* (%): 707.3 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 9.28 (d, J = 8.1 Hz, 1H), 9.17 (s, 1H), 8.55 (dd, J = 8.3, 7.4 Hz, 1H), 8.48 (d, J = 5.3 Hz, 1H), 8.03–7.95 (m, 1H), 7.91 (dt, J = 14.3, 5.0 Hz, 2H), 7.61–7.49 (m, 3H), 7.44–7.28 (m, 4H), 7.25 (d, J = 8.7 Hz, 1H), 6.41 (d, J = 5.3 Hz, 1H), 4.32–4.20 (m, 2H), 4.10–3.99 (m, 3H), 2.75–2.50 (m, 8H), 2.60 (d, J = 7.3 Hz, 2H), 2.35 (s, 3H), 2.19–2.09 (m, 2H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 160.90, 159.96, 158.85, 158.61, 156.09, 155.75, 153.26, 152.30, 149.89, 148.73, 146.93, 137.68, 136.76, 135.88, 134.40, 132.61, 130.99, 128.79, 128.23, 127.82, 127.56, 124.78, 123.89, 116.91, 116.44, 115.43, 109.71 108.78, 102.19, 99.50, 67.29, 56.17, 54.94 (2C), 54.82, 52.76 (2C), 45.75, 26.28. Anal. Calcd for $C_{39}H_{36}F_2N_6O_5$: C, 66.28; H, 5.13; N, 11.89. Found: C, 66.26; H, 5.13; N, 11.91.

7.4.19. 3-(4-Bromophenyl)-*N*-(3-fluoro-4-((6-methoxy-7-(3-(4-methylpiperazin-1-yl)propoxy)quinolin-4-yl) oxy)phenyl)-4-oxo-3,4-dihydrophthalazine-1-carboxamide (43)

Yellow solid; yield: 58%; mp: 143–145 °C; MS (ESI) *m*/*z* (%): 767.2 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 9.32 (s, 1H), 9.22 (d, J = 8.0 Hz, 1H), 8.53 (dd, J = 7.9, 0.8 Hz, 1H), 8.48 (d, J = 5.3 Hz, 1H), 8.00–7.91 (m, 2H), 7.91–7.84 (m, 1H), 7.68–7.60 (m, 2H), 7.60–7.53 (m, 3H), 7.46–7.39 (m, 2H), 7.29 (d, J = 7.2 Hz, 1H), 6.41 (d, J = 5.2 Hz, 1H), 4.25 (t, J = 6.7 Hz, 2H), 4.04 (s, 3H), 2.61 (d, J = 7.1 Hz, 2H), 2.59 (dd, J = 19.2, 11.9 Hz, 8H), 2.33 (s, 3H), 2.19–2.09 (m, 2H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 160.96, 159.93, 158.94, 155.73, 153.25, 152.31, 149.88, 148.67, 146.90, 140.04, 137.68, 136.78, 135.93, 134.37, 132.61, 132.14 (2C), 128.38, 127.72–127.45 (2C), 127.31 (2C), 123.92, 122.25, 116.40, 115.40, 109.68, 108.72, 102.15, 99.47, 67.31, 56.16, 55.01 (2C), 54.85, 52.91 (2C), 45.78, 26.29. Anal. Calcd for $C_{39}H_{36}BrFN_6O_5$: C, 61.02; H, 4.73; N, 10.95. Found: C, 61.04; H, 4.74; N, 10.92.

7.4.20. 3-(2-Bromophenyl)-*N*-(3-fluoro-4-((6-methoxy-7-(3-(piperidin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl) -4-oxo-3,4-dihydrophthalazine-1-carboxamide (44)

Yellow solid; yield: 55%; mp: 139–142 °C; MS (ESI) *m*/*z* (%): 767.2 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 9.32 (d, J = 8.1 Hz, 1H), 9.19 (s, 1H), 8.58 (d, J = 7.0 Hz, 1H), 8.50 (d, J = 5.2 Hz, 1H), 8.00 (t, J = 7.6 Hz, 1H), 7.92 (t, J = 7.8 Hz, 2H), 7.83 (d, J = 8.1 Hz, 1H), 7.62–7.52 (m, 3H), 7.52–7.38 (m, 3H), 7.30 (d, J = 12.0 Hz, 1H), 6.42 (d, J = 5.2 Hz, 1H), 4.27 (t, J = 6.3 Hz, 2H), 4.11–4.00 (m, 3H), 2.63 (d, J = 6.6 Hz, 2H), 2.74–2.44 (m, 8H), 2.37 (s, 3H), 2.21–2.08 (m, 2H). Anal. Calcd for $C_{39}H_{36}BrFN_6O_5$: C, 61.02; H, 4.73; N, 10.95. Found: C, 61.03; H, 4.74; N, 10.93.

7.4.21. *N*-(3-Fluoro-4-((6-methoxy-7-(3-(4-methylpiperazin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl)-3-(4-nitro phenyl)-4-oxo-3,4-dihydrophthalazine-1-carboxamide (45)

Yellow solid; yield: 58%; mp: 146–148 °C; MS (ESI) *m*/*z* (%): 734.1 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 9.24 (s, 1H), 9.21 (d, J = 8.1 Hz, 1H), 8.58 (d, J = 7.3 Hz, 1H), 8.49 (d, J = 5.2 Hz, 1H), 8.43 (t, J = 9.6 Hz, 2H), 8.06–7.89 (m, 4H), 7.58 (s, 1H), 7.47 (dd, J = 20.6, 14.2 Hz, 2H), 7.35–7.27 (m, 2H), 6.45 (t, J = 5.7 Hz, 1H), 4.28 (t, J = 6.2 Hz, 2H), 4.05 (s, 3H), 3.11 (q, J = 7.0 Hz, 2H), 2.87 (dd, J = 45.6, 38.7 Hz, 8H), 2.68 (s, 3H), 2.15 (d, J = 6.1 Hz, 2H). Anal. Calcd for $C_{39}H_{36}FN_7O_7$: C, 63.84; H, 4.95; N, 13.36. Found: C, 63.82; H, 4.96; N, 13.37.

7.4.22. *N*-(3-Fluoro-4-((6-methoxy-7-(3-(4-methylpiperazin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl)-3-(4-methoxyphenyl)-4-oxo-3,4-dihydrophthalazine-1-carboxamide (46)

Yellow solid; yield: 62%; mp: 147–148 °C; MS (ESI) *m*/*z* (%): 719.5 $[M+H]^+$; IR (KBr) cm^{-1}: 3380.0, 3071.5, 2934.6, 2794.2,

1676.5, 1620.6, 1605.7, 1579.5, 1509.2, 1479.3, 1430.3, 1384.1, 1348.8, 1304.8, 1251.0, 1211.0, 1168.4, 1139.5, 1021.3, 853.7, 832.5, 728.7, 686.3, 618.1, 555.7; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.42–9.30 (m, 1H), 9.30–9.14 (m, 1H), 8.52 (dd, J = 7.9, 1.6 Hz, 1H), 8.48 (d, J = 5.2 Hz, 1H), 8.02–7.91 (m, 2H), 7.91–7.82 (m, 1H), 7.68–7.63 (m, 1H), 7.60–7.54 (m, 2H), 7.54 (s, 1H), 7.47–7.39 (m, 2H), 7.31–7.28 (m, 1H), 7.06–6.98 (m, 1H), 6.42 (d, J = 5.2 Hz, 1H), 4.25 (t, J = 6.6 Hz, 2H), 4.04 (s, 3H), 3.99–3.84 (m, 3H), 2.62 (s, 2H), 2.71–2.48 (m, 8H), 2.37 (s, 3H), 2.18–2.10 (m, 2H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 161.12, 159.97, 158.99, 155.72, 154.97, 153.23, 152.28, 149.87, 148.69, 146.88, 135.96, 134.09, 132.43, 128.16, 127.74, 127.55 (2C), 127.02, 126.36, 125.27, 123.88, 122.65, 116.40, 115.42, 114.19, 111.62, 109.36, 108.71, 102.18, 99.50, 67.24, 56.15, 55.60, 54.90 (2C), 54.78, 52.67 (2C), 45.69, 26.26. Anal. Calcd for $C_{40}H_{39}FN_6O_6$: C, 66.84; H, 5.47; N, 11.69. Found: C, 66.85; H, 5.46; N, 11.67.

7.4.23. *N*-(3-Fluoro-4-((6-methoxy-7-(3-(piperidin-1-yl) propoxy)quinolin-4-yl)oxy)phenyl)-4-oxo-3-phenyl-3,4-dihydrophthalazine-1-carboxamide (47)

Yellow solid; yield: 61%; mp: 183–185 °C; MS (ESI) m/z (%): 674.1 $[M+H]^+$; IR (KBr) cm^{-1}: 3384.5, 3060.4, 2941.1, 2638.0, 2537.1, 1671.7, 1597.0, 1507.4, 1478.7, 1431.2, 1384.6, 1350.3, 1329.9, 1306.0, 1282.6, 1252.5, 1210.5, 1173.0, 1140.0, 1113.0, 1078.6, 1020.4, 971.8, 938.5, 852.8, 756.3, 687.6, 568.6; ^{1}H NMR (400 MHz, DMSO) δ 11.21 (s, 1H), 10.51 (s, 1H), 8.61 (d, J = 5.1 Hz, 1H), 8.44 (d, J = 6.9 Hz, 2H), 8.18–7.95 (m, 3H), 7.83 (d, J = 7.5 Hz, 2H), 7.77 (d, J = 8.8 Hz, 1H), 7.64 (s, 1H), 7.56 (d, J = 8.2 Hz, 3H), 7.48 (d, J = 7.1 Hz, 1H), 6.67 (d, J = 4.0 Hz, 1H), 4.30 (s, 2H), 4.00 (s, 3H), 3.49 (d, J = 10.6 Hz, 2H), 2.92 (s, 2H), 2.50 (s, 2H), 2.34 (s, 2H), 1.81 (s, 4H), 1.76–1.31 (m, 2H); ^{13}C NMR (400 MHz, DMSO) δ 162.47, 161.88–160.56 (m, 1H), 158.64, 155.05–154.78 (m, 0H), 153.29–152.82 (m, 1H), 152.60–152.36 (m, 0H), 150.51, 147.72–147.27 (m, 1H), 141.71, 140.25, 138.48–137.97 (m, 1H), 136.52–136.07 (m, 1H), 134.76, 133.23, 129.17, 129.09 (s, 2H), 128.44, 127.41, 127.29, 126.68 (s, 3H), 124.62, 117.71, 115.27, 109.95–109.58 (m, 0H), 109.58–109.20 (m, 0H), 102.90, 99.95, 66.84, 56.57, 53.89, 52.52 (s, 2H), 23.54, 22.85 (s, 3H), 21.85. Anal. Calcd for $C_{39}H_{36}FN_5O_5$: C, 69.53; H, 5.39; N, 10.39. Found: C, 69.50; H, 5.40; N, 10.40.

7.4.24. *N*-(3-Fluoro-4-((6-methoxy-7-(3-(piperidin-1-yl) propoxy)quinolin-4-yl)oxy)phenyl)-3-(4-fluorophenyl)-4-oxo-3,4-dihydrophthalazine-1-carboxamide (48)

Yellow solid; yield: 59%; mp: 187–190 °C; MS (ESI) m/z (%): 692.3 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO) δ 10.47 (s, 1H), 8.71 (d, J = 5.4 Hz, 1H), 8.44 (d, J = 7.8 Hz, 2H), 8.17–7.97 (m, 3H), 7.91 (dd, J = 19.2, 11.2 Hz, 2H), 7.79 (d, J = 8.3 Hz, 1H), 7.69 (d, J = 16.4 Hz, 2H), 7.61 (t, J = 8.8 Hz, 1H), 7.41 (t, J = 8.5 Hz, 2H), 6.81 (d, J = 4.9 Hz, 1H), 4.32 (s, 2H), 4.03 (s, 3H), 3.49 (d, J = 11.1 Hz, 2H), 3.22 (s, 2H), 2.92 (s, 2H), 2.36 (s, 2H), 1.82 (s, 4H), 1.76–1.33 (m, 2H); ^{13}C NMR (400 MHz, DMSO) δ 164.83, 162.46, 160.42, 158.74, 154.77, 154.00, 152.32, 150.98, 145.86, 140.19, 138.56, 138.06, 136.00, 134.68, 133.19, 132.79, 128.95 (2C), 128.37, 127.34, 126.73, 124.52, 117.79, 115.90, 116.01 (2C), 115.38, 109.60, 103.09, 100.23, 67.11, 56.75, 53.79, 52.49 (2C), 23.46, 22.79 (2C), 21.88. Anal. Calcd for $C_{39}H_{35}F_2N_5O_5$: C, 67.72; H, 5.10; N, 10.12. Found: C, 67.75; H, 5.12; N, 10.09.

7.4.25. *N*-(3-Fluoro-4-((6-methoxy-7-(3-(piperidin-1-yl) propoxy)quinolin-4-yl)oxy)phenyl)-3-(2-fluorophenyl)-4-oxo-3,4-dihydrophthalazine-1-carboxamide (49)

Yellow solid; yield: 63%; mp: 181–183 °C; MS (ESI) m/z (%): 692.3 $[M+H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.29 (d, J = 8.2 Hz, 1H), 9.18 (s, 1H), 8.56 (t, J = 8.5 Hz, 1H), 8.53–8.44 (m, 1H), 7.99 (t, J = 7.8 Hz, 1H), 7.96–7.87 (m, 2H), 7.62–7.49 (m, 3H), 7.41 (dd, J = 15.4, 6.6 Hz, 2H), 7.37–7.29 (m, 2H), 7.25 (s, 1H), 6.42 (d, J = 5.2 Hz, 1H), 4.26 (t, J = 6.7 Hz, 2H), 4.05 (s, 3H), 2.54 (t, J = 7.3 Hz, 2H), 2.43 (s, 4H), 2.20–2.11 (m, 2H), 1.60 (dd, J = 10.8, 5.3 Hz, 4H), 1.45 (s, 2H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 160.89, 159.94, 158.86, 158.62, 156.10, 155.76, 153.27, 152.38, 149.93, 148.71, 146.99, 137.72, 136.75, 135.84, 134.41, 132.61, 131.00, 128.79, 128.24, 127.84, 127.56, 124.78, 123.89, 116.91, 116.43, 115.39, 109.71, 108.79, 102.16, 99.45, 67.69, 56.17, 55.81, 54.63 (2C), 26.42, 26.05 (2C), 24.48. Anal. Calcd for $C_{39}H_{35}F_2N_5O_5$: C, 67.72; H, 5.10; N, 10.12. Found: C, 67.74; H, 5.11; N, 10.09.

7.4.26. 3-(4-Bromophenyl)-*N*-(3-fluoro-4-((6-methoxy-7-(3-(piperidin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl) -4-oxo-3,4-dihydrophthalazine-1-carboxamide (50)

Yellow solid; yield: 56%; mp: 178–180 °C; MS (ESI) m/z (%): 752.5 $[M+H]^+$; IR (KBr) cm^{-1}: 3379.4, 2931.8, 2851.1, 1677.0, 1620.4, 1597.5, 1578.5, 1508.2, 1479.3, 1430.2, 1384.1, 1348.7, 1326.0, 1305.7, 1249.8, 1210.6, 1171.4, 1138.9, 1078.6, 1011.5, 852.2, 828.4, 788.8, 751.6, 686.4, 616.3, 513.9; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.28 (s, 1H), 9.24 (d, J = 8.1 Hz, 1H), 8.59–8.52 (m, 1H), 8.49 (d, J = 5.3 Hz, 1H), 8.01–7.86 (m, 3H), 7.70–7.64 (m, 2H), 7.58 (dt, J = 6.7, 2.3 Hz, 3H), 7.42 (d, J = 7.2 Hz, 2H), 7.29 (d, J = 9.5 Hz, 1H), 6.42 (d, J = 5.2 Hz, 1H), 4.25 (t, J = 6.4 Hz, 2H), 4.04 (s, 3H), 2.72 (s, 2H), 2.62 (s, 4H), 2.32–2.18 (m, 2H), 1.72 (s, 4H), 1.51 (s, 2H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 161.05, 159.94, 158.91, 155.69, 153.21, 152.17, 149.84, 148.65, 146.81, 140.03, 137.62, 137.02, 136.07, 134.32, 132.56, 132.06 (2C), 128.34, 127.57, 127.47, 127.28 (2C), 123.88, 122.15, 116.46, 115.49, 109.70, 108.78, 102.20, 99.55, 67.21, 56.12, 55.59, 54.27 (2C), 25.68, 25.15 (2C), 23.86. Anal. Calcd for $C_{39}H_{35}BrFN_5O_5$: C, 62.24; H, 4.69; N, 9.31. Found: C, 62.22; H, 4.70; N, 9.33.

7.4.27. *N*-(3-Fluoro-4-((6-methoxy-7-(3-(piperidin-1-yl) propoxy)quinolin-4-yl)oxy)phenyl)-3-(4-nitrophenyl)-4-oxo-3,4-dihydrophthalazine-1-carboxamide (51)

Yellow solid; yield: 51%; mp: 187–190 °C; MS (ESI) m/z (%): 718.4 $[M+H]^+$; IR (KBr) cm^{-1}: 3418.4, 2935.3, 1679.9, 1621.1, 1596.0, 1509.7, 1432.2, 1384.4, 1349.2, 1323.8, 1307.1, 1252.3, 1211.4, 1172.6, 1139.5, 1114.8, 1022.0, 972.4, 941.0, 845.4, 750.7, 686.7, 617.9; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.34 (s, 1H), 9.20 (d, J = 8.1 Hz, 1H), 8.58 (d, J = 7.2 Hz, 1H), 8.49 (d, J = 4.6 Hz, 1H), 8.39 (t, J = 10.4 Hz, 2H), 8.05–7.97 (m, 4H), 7.94 (dd, J = 11.2, 4.0 Hz, 1H), 7.58 (s, 1H), 7.47 (d, J = 8.8 Hz, 1H), 7.38 (s, 1H), 7.31 (t, J = 7.1 Hz, 1H), 6.43 (d, J = 5.1 Hz, 1H), 4.26 (t, J = 5.6 Hz, 2H), 4.03 (s, 3H), 3.42–2.82 (m, 6H), 2.53 (d, J = 4.6 Hz, 2H), 2.03 (s, 4H), 1.69 (s, 2H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 160.77, 160.02, 158.92, 155.72, 153.24, 151.66, 149.71, 148.74, 146.64, 146.03, 137.99, 137.72, 135.96, 134.75, 133.01, 128.36, 127.82, 127.46, 126.31 (2C), 124.37 (2C), 123.97, 116.54, 115.84, 109.84, 109.05, 102.41, 99.76, 66.12, 56.09, 55.30, 53.58 (2C), 23.85, 22.93 (2C), 22.32. Anal. Calcd for $C_{39}H_{35}FN_6O_7$: C, 65.17; H, 4.91; N, 11.69. Found: C, 65.19; H, 4.90; N, 11.67.

7.4.28. *N*-(3-Fluoro-4-((6-methoxy-7-(3-(piperidin-1-yl) propoxy)quinolin-4-yl)oxy)phenyl)-3-(4-methoxy phenyl)-4-oxo-3,4-dihydrophthalazine-1-carboxamide (52)

Yellow solid; yield: 54%; mp: 183–185 °C; MS (ESI) m/z (%): 703.3 $[M+H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.25 (dt, J = 22.0, 11.7 Hz, 2H), 8.56 (d, J = 7.8 Hz, 1H), 8.50 (d, J = 5.3 Hz, 1H), 8.03–7.84 (m, 3H), 7.74–7.66 (m, 1H), 7.57 (dt, J = 8.8, 3.1 Hz, 2H), 7.44 (s, 1H), 7.41 (d, J = 6.8 Hz, 1H), 7.33–7.25 (m, 2H), 7.07 (dd, J = 9.0, 2.6 Hz, 1H), 6.43 (d, J = 5.3 Hz, 1H), 4.26 (t, J = 6.7 Hz, 2H), 4.06 (s, 3H), 4.03–3.86 (m, 3H), 2.57 (t, J = 7.1 Hz, 2H), 2.46 (s, 4H), 2.25–2.10 (m, 2H), 1.68–1.55 (m, 4H), 1.46 (s, 2H). Anal. Calcd for $C_{40}H_{38}FN_5O_6$: C, 68.27; H, 5.44; N, 9.95. Found: C, 68.24; H, 5.46; N, 9.97.

7.4.29. *N*-(3-Fluoro-4-((6-methoxy-7-(3-(4-methylpiperidin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl)-4-oxo-3-phenyl-3,4-dihydrophthalazine-1-carboxamide (53)

Yellow solid; yield: 57%; mp: 173–175 °C; MS (ESI) *m*/*z* (%): 688.6 $[M+H]^+$; IR (KBr) cm^{-1}: 3426.8, 3065.2, 2951.3, 2617.4, 2507.5, 1668.5, 1597.4, 1507.0, 1478.3, 1456.9, 1432.3, 1350.1, 1332.1, 1282.8, 1218.4, 1174.1, 1140.7, 1019.7, 857.1, 756.1, 688.7, 631.9, 573.1; ^1H NMR (400 MHz, DMSO) δ 11.20 (s, 1H), 8.65 (d, J = 5.4 Hz, 1H), 8.18–7.90 (m, 4H), 7.82 (d, J = 7.6 Hz, 2H), 7.77 (d, J = 8.8 Hz, 1H), 7.71–7.62 (m, 2H), 7.58 (dd, J = 12.8, 8.5 Hz, 4H), 7.47 (t, J = 7.1 Hz, 1H), 6.73 (d, J = 4.7 Hz, 1H), 4.30 (s, 2H), 4.01 (s, 3H), 3.51 (d, J = 10.9 Hz, 2H), 3.22 (s, 2H), 2.93 (d, J = 11.2 Hz, 2H), 2.35 (s, 2H), 1.90–1.71 (m, 2H), 1.62 (s, 1H), 1.59–1.40 (m, 2H), 0.97 (dd, J = 33.6, 5.7 Hz, 3H); ^{13}C NMR (400 MHz, DMSO) δ 164.91, 162.48, 161.87, 158.69, 154.85, 153.43, 152.41, 150.67, 146.82, 141.80, 140.21, 138.36, 137.30, 136.22, 134.64, 132.95, 129.15, 129.06 (2C), 128.42, 127.23, 126.70 (2C), 124.54, 117.74, 115.31, 109.59, 105.88, 102.95, 100.05, 66.96, 56.63, 53.91, 52.35 (2C), 31.15 (2C), 28.67, 23.58, 21.58. Anal. Calcd for $C_{40}H_{38}FN_5O_5$: C, 69.85; H, 5.57; N, 10.18. Found: C, 69.88; H, 5.55; N, 10.16.

7.4.30. *N*-(3-Fluoro-4-((6-methoxy-7-(3-(4-methylpiperidin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl)-3-(4-fluorophenyl)-4-oxo-3,4-dihydrophthalazine-1-carboxamide (54)

Yellow solid; yield: 62%; mp: 171–174 °C; MS (ESI) *m*/*z* (%): 706.3 $[M+H]^+$; IR (KBr) cm^{-1}: 3383.9, 3080.3, 3010.5, 2953.3, 2922.3, 2776.8, 1671.4, 1622.6, 1605.9, 1583.3, 1509.3, 1429.5, 1385.4, 1349.7, 1329.6, 1305.1, 1291.3, 1255.3, 1174.7, 1138.8, 1051.2, 1021.1, 974.9, 933.0, 851.6, 838.3, 726.1, 683.5, 617.9, 593.4, 526.3; ^1H NMR (400 MHz, DMSO) δ 11.37 (s, 1H), 8.48 (d, J = 5.2 Hz, 1H), 8.14–7.95 (m, 3H), 7.94–7.88 (m, 2H), 7.88–7.72 (m, 2H), 7.51 (dd, J = 17.0, 8.0 Hz, 2H), 7.43–7.35 (m, 3H), 7.31 (dd, J = 12.2, 5.5 Hz, 1H), 6.47 (d, J = 4.9 Hz, 1H), 4.18 (t, J = 6.4 Hz, 2H), 3.96 (s, 3H), 2.84 (d, J = 11.2 Hz, 2H), 2.43 (t, J = 7.1 Hz, 2H), 2.02–1.91 (m, 2H), 1.86 (t, J = 11.4 Hz, 2H), 1.56 (d, J = 11.5 Hz, 2H), 1.38–1.25 (m, 1H), 1.13 (qd, J = 12.2, 3.5 Hz, 2H), 0.86 (t, J = 11.6 Hz, 3H); ^{13}C NMR (400 MHz, DMSO) δ 166.71, 163.08, 162.39, 160.40, 159.70, 158.65, 152.54, 150.06, 149.29, 146.87, 140.31, 138.00, 137.83, 136.78, 134.72, 133.18, 128.92, 128.61, 128.36, 127.31, 124.61, 117.63, 115.94, 115.71, 115.53, 114.90, 109.41, 108.96, 99.47, 67.28, 56.26, 55.19, 53.98 (2C), 34.50 (2C), 30.90, 26.71, 22.32. Anal. Calcd for $C_{40}H_{37}F_2N_5O_5$: C, 68.07; H, 5.28; N, 9.92. Found: C, 68.04; H, 5.29; N, 9.90.

7.4.31. *N*-(3-Fluoro-4-((6-methoxy-7-(3-(4-methylpiperidin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl)-3-(3-fluorophenyl)-4-oxo-3,4-dihydrophthalazine-1-carboxamide (55)

Yellow solid; yield: 66%; mp: 165–168 °C; MS (ESI) *m*/*z* (%): 706.2 $[M+H]^+$; ^1H NMR (400 MHz, DMSO) δ 11.41 (s, 1H), 8.84 (s, 1H), 8.43 (d, J = 3.7 Hz, 2H), 8.17 (d, J = 12.6 Hz, 1H), 8.03 (dd, J = 17.5, 7.0 Hz, 2H), 7.94–7.80 (m, 3H), 7.78 (s, 1H), 7.75 (d, J = 7.7 Hz, 1H), 7.65 (dd, J = 15.3, 7.0 Hz, 1H), 7.60 (d, J = 6.8 Hz, 1H), 7.33 (d, J = 7.5 Hz, 1H), 7.00 (s, 1H), 4.34 (s, 2H), 4.06 (s, 3H), 3.50 (d, J = 9.4 Hz, 2H), 3.22 (s, 2H), 2.93 (d, J = 9.0 Hz, 2H), 2.39 (s, 2H), 1.78 (d, J = 11.9 Hz, 2H), 1.58 (d, J = 12.1 Hz, 2H), 1.54 (s, 1H), 0.92 (d, J = 4.2 Hz, 3H). Anal. Calcd for $C_{40}H_{37}F_2N_5O_5$: C, 68.07; H, 5.28; N, 9.92. Found: C, 68.05; H, 5.29; N, 9.90.

7.4.32. *N*-(3-Fluoro-4-((6-methoxy-7-(3-(4-methylpiperidin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl)-3-(2-fluorophenyl)-4-oxo-3,4-dihydrophthalazine-1-carboxamide (56)

Yellow solid; yield: 59%; mp: 174–176 °C; MS (ESI) *m*/*z* (%): 706.3 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 9.29 (d, J = 8.0 Hz, 1H), 9.17 (s, 1H), 8.57 (d, J = 7.1 Hz, 1H), 8.49 (dd, J = 9.3, 5.2 Hz, 1H), 8.05–7.96 (m, 1H), 7.92 (dt, J = 14.2, 4.9 Hz, 2H), 7.66–7.50 (m, 3H), 7.47–7.38 (m, 2H), 7.35 (dd, J = 8.7, 3.6 Hz, 1H), 7.33–7.25 (m, 2H), 6.41 (t, J = 5.5 Hz, 1H), 4.32–4.21 (m, 2H), 4.05 (s, 3H), 2.98 (d, J = 10.6 Hz, 2H), 2.63 (s, 2H), 2.20 (s, 2H), 2.05 (s, 2H), 1.67 (d, J = 11.2 Hz, 2H), 1.38 (s, 1H), 1.37–1.16 (m, 2H), 0.97 (dd, J = 13.3, 6.6 Hz, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 160.89, 159.94, 158.86, 156.11, 153.56–153.11, 152.28, 149.90, 148.75, 146.96, 137.66, 136.74, 135.90, 134.40, 132.61, 131.00, 128.80, 128.24, 127.84, 127.56, 124.78, 123.89, 117.02, 116.82, 116.40, 115.45, 109.82, 109.59, 108.86, 102.20, 99.50, 67.49, 56.16, 55.40, 53.93 (2C), 33.97 (2C), 30.66, 26.25, 21.79. Anal. Calcd for $C_{40}H_{37}F_2N_5O_5$: C, 68.07; H, 5.28; N, 9.92. Found: C, 68.05; H, 5.27; N, 9.95.

7.4.33. 3-(4-Bromophenyl)-*N*-(3-fluoro-4-((6-methoxy-7-(3-(4-methylpiperidin-1-yl)propoxy)quinolin-4-yl)oxy) phenyl)-4-oxo-3,4-dihydrophthalazine-1-carboxamide (57)

Yellow solid; yield: 55%; mp: 169–172 °C; MS (ESI) *m*/*z* (%): 766.2 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 9.33 (s, 1H), 9.22 (d, J = 8.1 Hz, 1H), 8.53 (d, J = 8.0 Hz, 1H), 8.48 (d, J = 5.3 Hz, 1H), 8.02–7.93 (m, 2H), 7.88 (dd, J = 11.1, 4.1 Hz, 1H), 7.71–7.62 (m, 2H), 7.62–7.52 (m, 3H), 7.47–7.38 (m, 2H), 7.29 (d, J = 8.0 Hz, 1H), 6.41 (d, J = 5.2 Hz, 1H), 4.24 (t, J = 6.3 Hz, 2H), 4.04 (s, 3H), 2.80 (s, 2H), 2.27 (d, J = 6.4 Hz, 4H), 1.71 (d, J = 9.1 Hz, 2H), 1.44 (d, J = 32.5 Hz, 3H), 1.38–1.29 (m, 2H), 0.97 (d, J = 4.6 Hz, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 160.99, 159.95, 158.96, 155.72, 153.24, 152.09, 149.82, 148.71, 146.81, 140.07, 137.65, 136.83, 135.97, 134.36, 132.61, 132.15 (2C), 128.39, 127.76 (2C), 127.35 (2C), 123.90, 122.25, 116.42, 115.53, 109.70, 108.86, 102.22, 99.56, 67.09, 56.12, 55.19, 53.58 (2C), 32.98 (2C), 30.24, 25.54, 21.50. Anal. Calcd for $C_{40}H_{37}BrFN_5O_5$: C, 62.67; H, 4.86; N, 9.13. Found: C, 62.64; H, 4.88; N, 9.12.

7.4.34. 3-(2-Bromophenyl)-*N*-(3-fluoro-4-((6-methoxy-7-(3-(4-methylpiperidin-1-yl)propoxy)quinolin-4-yl)oxy) phenyl)-4-oxo-3,4-dihydrophthalazine-1-carboxamide (58)

Yellow solid; yield: 57%; mp: 170–172 °C; MS (ESI) *m*/*z* (%): 766.2 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 9.31 (d, J = 8.2 Hz, 1H), 9.22 (s, 1H), 8.57 (d, J = 7.9 Hz, 1H), 8.48 (t, J = 6.6 Hz, 1H), 8.05–7.96 (m, 1H), 7.96–7.86 (m, 2H), 7.82 (d, J = 7.8 Hz, 1H), 7.60–7.53 (m, 3H), 7.46–7.39 (m, 3H), 7.25 (d, J = 8.7 Hz, 1H), 6.41 (d, J = 5.2 Hz, 1H), 4.25 (t, J = 6.5 Hz, 2H), 4.04 (s, 3H), 2.96 (d, J = 8.6 Hz, 2H), 2.59 (s, 2H), 2.15 (dd, J = 13.8, 6.8 Hz, 2H), 1.99 (s, 2H), 1.64 (d, J = 12.0 Hz, 2H), 1.40 (d, J = 31.8 Hz, 1H), 1.28 (d, J = 10.2 Hz, 2H), 0.94 (d, J = 6.2 Hz, 3H). Anal. Calcd for $C_{40}H_{37}BrFN_5O_5$: C, 62.67; H, 4.86; N, 9.13. Found: C, 62.65; H, 4.87; N, 9.12.

7.4.35. *N*-(3-Fluoro-4-((6-methoxy-7-(3-(4-methylpiperidin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl)-3-(4-nitro phenyl)-4-oxo-3,4-dihydrophthalazine-1-carboxamide (59)

Yellow solid; yield: 54%; mp: 175–177 °C; MS (ESI) *m*/*z* (%): 733.4 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 9.24 (d, J = 5.2 Hz, 1H), 9.23 (s, 1H), 8.59 (d, J = 7.5 Hz, 1H), 8.50 (d, J = 5.2 Hz, 1H), 8.43 (d, J = 9.0 Hz, 2H), 8.06–7.91 (m, 5H), 7.58 (s, 1H), 7.44 (d, J = 8.7 Hz, 1H), 7.40 (s, 1H), 7.32 (d, J = 8.6 Hz, 1H), 6.43 (d, J = 5.1 Hz, 1H), 4.26 (t, J = 5.9 Hz, 2H), 4.04 (s, 3H), 3.10–2.92 (m, 2H), 2.43 (s, 2H), 2.40 (s, 2H), 1.78 (s, 2H), 1.58 (s, 2H), 1.51–1.38 (m, 1H), 1.23 (dd, J = 15.8, 8.7 Hz, 2H), 1.02 (d, J = 6.0 Hz, 3H). Anal. Calcd for $C_{40}H_{37}FN_6O_7$: C, 65.56; H, 5.09; N, 11.47. Found: C, 65.54; H, 5.10; N, 11.49.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmc.2014.05.013.

References and notes

1. Giordano, S.; Ponzetto, C.; Di Renzo, M. F.; Cooper, C. S.; Comoglio, P. M. *Nature* **1989**, *339*, 155.
2. Lokker, N. A.; Mark, M. R.; Luis, E.; Bennett, G. L.; Robbins, K. A.; Baker, J. B.; Godowski, P. J. *EMBO J.* **1992**, *11*, 2503–2510.
3. Okigaki, M.; Komada, M.; Uehara, Y.; Miyazawa, K.; Kitamura, N. *Biochemistry* **1992**, *31*, 9555.
4. Aguirre Ghiso, J. A.; Alonso, J. A.; Farías, E. F.; Gomez, D. E.; de Kier Joffe, E. B. *Eur. J. Biochem.* **1999**, *263*, 295.
5. Parr, C.; Watkins, G.; Mansel, R. E.; Jiang, W. G. *Clin. Cancer Res.* **2004**, *10*, 202.
6. Rong, S.; Segal, S.; Anver, M.; Resau, J. H.; Vande Woude, G. F. *Proc. Natl. Acad. Sci. U.S.A.* **1994**, *91*, 4731.
7. Bellusci, S.; Moens, G.; Gaudino, G.; Comoglio, P.; Nakamura, T.; Thiery, J. P.; Jouanneau, J. *Oncogene* **1994**, *9*, 1091.
8. Jeffers, M.; Rong, S.; Anver, M.; Vande Woude, G. F. *Oncogene* **1996**, *13*, 853.
9. Takayama, H.; LaRochelle, W. J.; Sharp, R.; Otsuka, T.; Kriebel, P.; Anver, M.; Aaronson, S. A. *Proc. Natl. Acad. Sci. U.S.A.* **1997**, *94*, 701.
10. Otsuka, T.; Takayama, H.; Sharp, R.; Celli, G.; LaRochelle, W. J.; Bottaro, D. P.; Ellmore, N.; Vieira, W.; Owens, J. W.; Anver, M.; Merlino, G. *Cancer Res.* **1998**, *58*, 5157.
11. Nakagawa, T.; Tohyama, O.; Yamaguchi, A.; Matsushima, T.; Takahashi, K.; Funasaka, S.; Shirotori, S.; Asada, M.; Obaishi, H. *Cancer Sci.* **2010**, *101*, 210.
12. Bellon, S. F.; Kaplan-Lefko, P. J.; Yang, Y.; Zhang, Y.; Moriguchi, J.; Rex, K.; Johnson, C. W.; Rose, P. E.; Long, A. M.; O'Connor, A. B.; Gu, Y.; Coxon, A.; Kim, T. S.; Tasker, A.; Burgess, T. L.; Dussault, I. *J. Biol. Chem.* **2008**, *283*, 2675.
13. Saavedra, O.; Claridge, S.; Zhan, L.; Raeppel, F.; Granger, M. C.; Raeppel, S.; Mannion, M.; Gaudette, F.; Zhou, N.; Isakovic, L.; Bernstein, N.; Déziel, R.; Nguyen, H.; Normand, B.; Beaulieu, C.; Dupont, I.; Wang, J.; Macleod, R. A.; Besterman, M. J.; Vaisburg, A. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 6836.
14. Martens, T.; Schmidt, N. O.; Eckerich, C.; Fillbrandt, R.; Merchant, M.; Schwall, R.; Westphal, M.; Lamszus, K. *Clin. Cancer Res.* **2006**, *12*, 6144.
15. Caballero, J.; Quiliano, M.; Alzate-Morales, H. J.; Zimic, M.; Deharo, E. J. *Comput. Aided Mol. Des.* **2011**, *25*, 349.
16. Nishii, H.; Chiba, T.; Morikami, K.; Fukami, T. A.; Sakamoto, H.; Ko, K.; Koyano, H. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 1405.
17. Sun, Q.; Ng, C.; Guy, R. G.; Sivaraman, J. *FEBS Lett.* **2011**, *585*, 281.
18. Porter, J.; Lumb, S.; Franklin, R. J.; Gascon-Simorte, J. M.; Calmiano, M.; Riche, K. L.; Lallemand, B.; Keyaerts, J.; Edwards, H.; Maloney, A.; Delgado, J.; King, L.; Foley, A.; Lecomte, F.; Reuberson, J.; Meier, C.; Batchelor, M. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 2780.
19. Liu, X.; Yao, W.; Newton, R. C.; Scherle, P. A. *Expert Opin. Invest. Drugs* **2008**, *17*, 997.
20. Underiner, L. T.; Herbertz, T.; Miknyoczki, J. S. *Anticancer Agent Med.* **2010**, *10*, 7.
21. Yakes, F. M.; Chen, J.; Tan, J.; Yamaguchi, K.; Shi, Y. C.; Yu, P. W.; Qian, F.; Chu, F.; Bentzien, F.; Cancilla, B.; Orf, J.; You, A.; Laird, A. D.; Engst, S.; Lee, L.; Lesch, J.; Chou, Y. C.; Joly, A. H. *Mol. Cancer Ther.* **2011**, *10*, 2298.
22. Kim, K. S.; Zhang, L.; Schmidt, R.; Cai, Z. W.; Wei, D.; Williams, D. K.; Lombardo, L. J.; Trainor, G. L.; Xie, D.; Zhang, Y.; An, Y.; Sack, J. S.; Tokarski, J. S.; Darienzo, C.; Kamath, A.; Marathe, P.; Zhang, Y.; Lippy, J.; Jeyaseelan, R.; Wautlet, B.; Henley, B.; Gullo-Brown, J.; Manne, V.; Hunt, J. T.; Fargoli, J.; Borzilleri, R. M. *J. Med. Chem.* **2008**, *51*, 5330.
23. Norman, M. H.; Liu, L. B.; Lee, M.; Xi, N.; Fellows, I.; D'Angelo, N. D.; Dominguez, C.; Rex, K.; Bellon, S. F.; Kim, T. S.; Dussault, I. *J. Med. Chem.* **2012**, *55*, 1858.
24. Liu, L. B.; Norman, M. H.; Lee, M.; Xi, N.; Siegmund, A.; Boezio, A. A.; Booker, S.; Choquette, D.; D'Angelo, N. D.; Germain, J.; Yang, K.; Yang, Y. J.; Zhang, Y. H.; Bellon, S. F.; Whittington, D. A.; Harmange, J. C.; Dominguez, C.; Kim, T. S.; Dussault, I. *J. Med. Chem.* **2012**, *55*, 1868.
25. Albrecht, B. K.; Harmange, J. C.; Bauer, D.; Berry, L.; Bode, C.; Boezio, A. A.; Chen, A.; Choquette, D.; Dussault, I.; Fridrich, C.; Hirai, S.; Hoffman, D.; Larrow, J. F.; Kaplan-Lefko, P.; Lin, J.; Lohman, J.; Long, A. M.; Moriguchi, J.; O'Connor, A.; Potashman, M. H.; Reese, M.; Rex, K.; Siegmund, A.; Shah, K.; Shimanovich, R.; Springer, S. K.; Teffera, Y.; Yang, Y.; Zhang, Y.; Bellon, S. F. *J. Med. Chem.* **2008**, *51*, 2879.
26. D'Angelo, N. D.; Bellon, S. F.; Booker, S. K.; Cheng, Y.; Coxon, A.; Dominguez, C.; Fellows, I.; Hoffman, D.; Hungate, R.; Kaplan-Lefko, P.; Lee, M. R.; Li, C.; Liu, L.; Rainbeau, E.; Reider, P. J.; Rex, K.; Siegmund, A.; Sun, Y.; Tasker, A. S.; Xi, N.; Xu, S.; Yang, Y.; Zhang, Y.; Burgess, T. L.; Dussault, I.; Kim, T. S. *J. Med. Chem.* **2008**, *51*, 5766.
27. Mannion, M.; Raeppel, S.; Claridge, S.; Zhou, N.; Saavedra, O.; Isakovic, L.; Zhan, L.; Gaudette, F.; Reappel, F.; Déziel, R.; Beaulieu, N.; Nguyen, H.; Chute, I.; Beaulieu, C.; Dupont, I.; Robert, M. F.; Lefebvre, S.; Dubay, M.; Rahil, J.; Wang, J.; Ste-Croix, H.; Macleod, A. R. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 6552.
28. Qi, B. H.; Mi, B.; Zhai, X.; Xu, Z. Y.; Zhang, X. L.; Tian, Z. R.; Gong, P. *Bioorg. Med. Chem.* **2013**, *21*, 5246.
29. Qi, B. H.; Tao, H. Y.; Wu, D.; Bai, J. Y.; Shi, Y. D.; Gong, P. *Arch. Pharm. Chem. Life Sci.* **2013**, *346*, 596.
30. Li, S.; Huang, Q.; Liu, Y. J.; Zhang, X. L.; Liu, S.; He, C.; Gong, P. *Eur. J. Med. Chem.* **2013**, *64*, 62.
31. Li, S.; Zhao, Y. F.; Wang, K. W.; Gao, Y. L.; Han, J. M.; Cui, B. B.; Gong, P. *Bioorg. Med. Chem.* **2013**, *21*, 2843.
32. Li, S.; Jiang, R.; Qin, M. Z.; Liu, H. C.; Zhang, G. Y.; Gong, P. *Arch. Pharm. Chem. Life Sci.* **2013**, *346*, 521.
33. Tang, Q. D.; Zhao, Y. F.; Du, X. M.; Chong, L. E.; Gong, P.; Guo, C. *Eur. J. Med. Chem.* **2013**, *69*, 77.
34. Tang, Q. D.; Zhang, G. G.; Du, X. M.; Zhu, W. F.; Li, R. J.; Lin, H. F.; Li, P. C.; Cheng, M. S.; Gong, P.; Zhao, Y. F. *Bioorg. Med. Chem.* **2014**, *22*, 1236.
35. Vlaar, T.; Ruijter, E.; Znabet, A.; Janssen, E.; de Kanter, F. J. J.; Maes, B. U. W.; Orru, R. V. A. *Org. Lett.* **2011**, *13*, 6496.
36. Prime, M. E.; Courtney, S. M.; Brookfield, F. A.; Marston, R. W.; Walker, V.; Warne, J.; Boyd, A. E.; Kairies, N. A.; von der Saal, W.; Limberg, A.; Georges, G.; Engh, R. A.; Goller, B.; Rueger, P.; Rueth, M. *J. Med. Chem.* **2011**, *54*, 312.
37. Goldstein, D.M.; Rueth, M. *From U.S. Pat. Appl. Publ.* 2007, US 20070219195.
38. Poli, D.; Catarzi, D.; Colotta, V.; Varano, F.; Filacchioni, G.; Daniele, S.; Trincavelli, L.; Martini, C.; Paoletta, S.; Moro, S. *J. Med. Chem.* **2011**, *54*, 2102.
39. Gagan, K.; Samiron, P.; Jawahar, K.; Maruti, M. D.; Vilas, U. M.; Venkata, P.; Kumar, K. R. *From PCT Int. Appl.* WO 2013005157.
40. Koza, G.; Keskin, S.; Özer, M. S.; Cengiz, B.; Şahin, E.; Balci, M. *Tetrahedron* **2013**, *69*, 395.
41. Tiedt, R.; Degenkolbe, E.; Furet, P.; Appleton, B. A.; Wagner, S.; Schoepfer, J.; Buck, E.; Ruddy, D. A.; Monahan, J. E.; Jones, M. D.; Blank, J.; Haasen, D.; Drueckes, P.; Wartmann, M.; McCarthy, C.; Sellers, W. R.; Hofmann, F. *Cancer Res.* **2011**, *71*, 5255.
42. Zhang, Z.; Lee, J. C.; Olivas, V.; Au, V.; Laframboise, T.; Abdel-Rahman, M.; Wang, X.; Levine, A. D.; Rho, J. K.; Choi, Y. J.; Choi, C. M.; Kim, S. W.; Jang, S. J.; Park, Y. S.; Kim, W. S.; Lee, D. H.; Lee, J. S.; Miller, V. A.; Arcila, M.; Ladanyi, M.; Moonsamy, P.; Sawyers, C.; Boggon, T. J.; Ma, P. C.; Costa, C.; Taron, M.; Rosell, R.; Halmos, B.; Bivona, T. G. *Nat. Genet.* **2012**, *44*, 852.
43. Liu, L. B.; Siegmund, A.; Xi, N.; Kaplan-Lefko, P.; Rex, K.; Chen, A.; Lin, J.; Moriguchi, J.; Berry, L.; Huang, L. Y.; Teffera, Y.; Yang, Y. J.; Zhang, Y. H.; Bellon, S. F.; Lee, M.; Shimanovich, R.; Bak, A.; Dominguez, C.; Norman, M. H.; Harmange, J. C.; Dussault, I.; Kim, T. S. *J. Med. Chem.* **2008**, *51*, 3688.
44. Peach, M. L.; Tan, N.; Tan, N.; Choyke, S. J.; Giubellino, A.; Athauda, G.; Burke, T. R.; Nicklaus, M. C.; Bottaro, D. P. *J. Med. Chem.* **2009**, *52*, 943.