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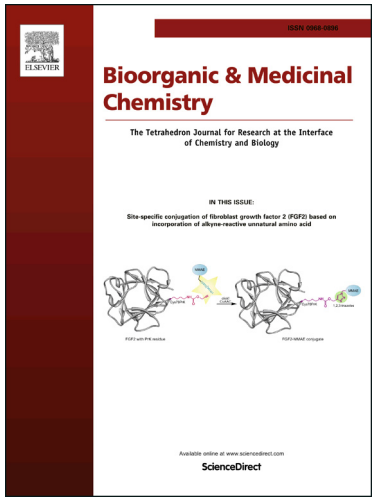

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Design, synthesis and biological evaluation of novel 4-phenoxyquinoline derivatives containing 3-oxo-3,4-dihydroquinoxaline moiety as c-Met kinase inhibitors

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Abstract

A series of novel 4-phenoxyquinoline derivatives containing 3-oxo-3,4-dihydroquinoxaline moiety were synthesized and evaluated for their c-Met kinase inhibitory activity and antiproliferative activity against five cancer cell lines (HT-29, H460, A549, MKN-45 and U87MG) *in vitro*. Most of the compounds exhibited moderate-to-significant cytotoxicity as compared with foretinib. The most promising compound **41** (with c-Met IC_{50} value of 0.90 nM) showed remarkable cytotoxicity against HT-29, H460, A549, MKN-45 and U87MG cell lines with IC_{50} values of 0.06μM, 0.05μM, 0.18μM, 0.023μM and 0.66 μM, respectively, and thus it was 1.22- to 3.50- fold more potent than foretinib. Their preliminary structure-activity relationships (SARs) studies indicate that electron-withdrawing groups on the terminal phenyl rings are beneficial for improving the antitumor activity.

Keywords: Synthesis; 4-phenoxyquinoline derivatives; c-Met inhibitors; Antitumor activity.

1. Introduction

Receptor tyrosine kinases (RTKs) play crucial roles in numerous signal transduction pathways and cellular processes. Many are implicated in cancer,[1] including the Hepatocyte Growth Factor Receptor (HGFR) c-Met,[2] which is over-expressed and/or mutated in various human tumor types. Dysregulation of c-Met/HGF signaling pathway affects cell proliferation, survival and motility, leading to tumor growth, angiogenesis, and metastasis. Therefore, c-Met has become an attractive target for cancer therapy.[3, 4]

Recently, a series of 4-phenoxyquinoline derivatives have been reported as class II c-Met inhibitors, such as Cabozantinib (1), Foretinib (2), Kirin (3), AM7 (4), MG10 (5) and Amgen (6)(Fig. 1).[5-10] Among them, Cabozantinib was approved as a novel oral multi-kinase inhibitor for the treatment of patients with progressive metastatic medullary thyroid cancer (MTC).[11] Foretinib (Fig. 1) which is currently undergoing phase III studies for different cancer types, is also a multikinase inhibitor targeting c-Met, VEGFR-2, RON and Flt-1.[12] Meanwhile, other derivatives have been progressed into clinical or preclinical studies as c-Met kinase inhibitors. However, it was reported that the more potent VEGFR activity in some class II c-Met inhibitors may lead to suboptimal dosing for c-Met inhibition in clinical applications because of VEGFR-related side effects.[13, 14] Moreover，it is important that compounds designed as kinase inhibitors have a good kinase selectivity profile because inhibiting particular kinases carries the risk of adverse effects.[15] Thus far, a majority of the class II c-Met molecules are multikinase inhibitors. Above all, improving the selectivity of class II c-Met inhibitors has been a significant challenge.

During the course of analyzing the SAR of these analogues (Fig. 1),[16-18] most of them may be disconnected

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into three units according to their structures and subunit functions. We found that modification of moiety A usually occurs at position 7 of quinoline, where the side chain is replaced by different water-soluble fragment, such as 3-morpholinopropoxy, 3-piperidinylpropoxy and 3-(4-methylpiperazinyl) propoxy group. Furthermore, there is little change to B moiety except for a phenyl ring or a substituted phenyl ring. We found that moiety A and moiety B appears to be critical for kinase activity. In contrast, the structure of moiety C is alterable, and various linear chains and heterocyclic rings can be introduced to the main chain of 5-atom linker (i.e., six chemical bonds distance between moiety A and B, as summarized recently by our team.[19]), containing hydrogen-bond donors and acceptors. These structural characteristics suggest that exploring a satisfactory linker is a practicable way of designing this series of quinoline derivatives and could improve the kinase selectivity of the molecules. In the light of the results mentioned above, our research group has introduced different 5-atom linkers such as imidazole, pyrimidine-2,4,6-trione and 1,2,4-triazolone into the moiety C and the resulting derivatives 7-9 (Fig. 1) showed excellent potency and kinase selectivity. [20-22]

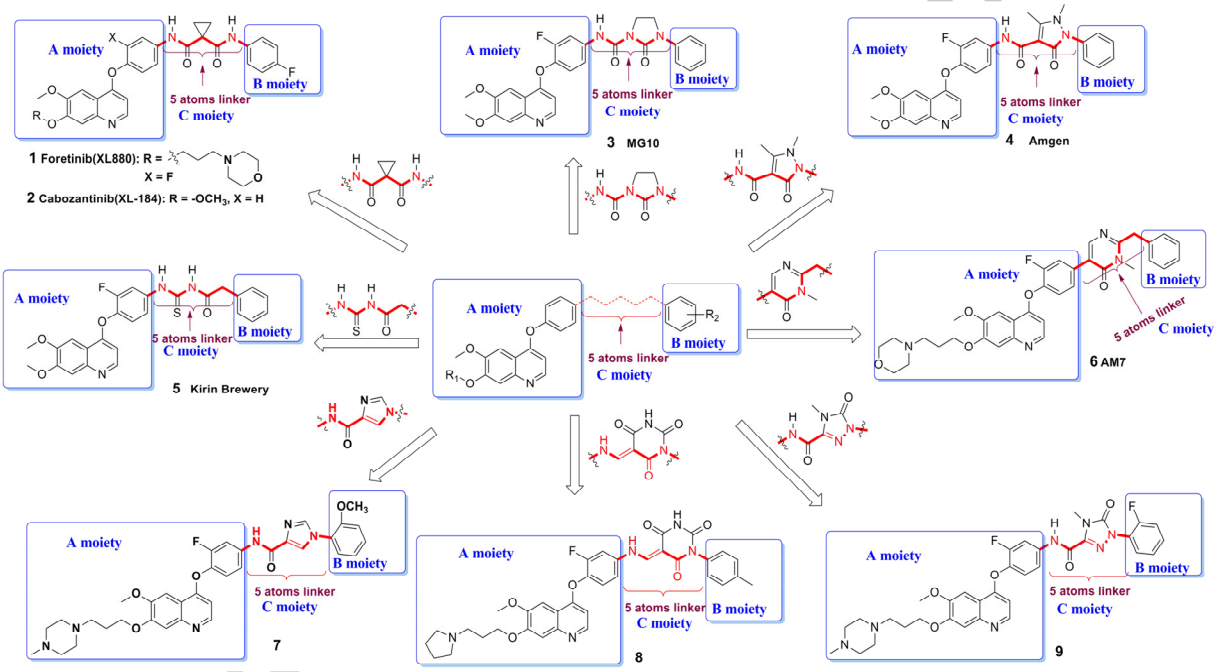


Figure 1. Structures of small-molecule c-Met inhibitors

To our knowledge, compounds bearing quinoxalinone fragment have been reported to exhibit a large field of biological activities, including antitumor, antibacterial, and anti-inflammatory activities, etc (**10-13**, Fig. 2).[23-26] Remarkably, the 3-oxo-3,4-dihydroquinoxaline-2-carboxamide framework conforms to "5 atoms regulation", and contains both hydrogen-bond donor and acceptor, which makes it a satisfactory linker. So we replaced the cyclopropane-1,1-dicarboxamide fragment of foretinib with 3-oxo-3,4-dihydroquinoxaline-2-carboxamide scaffold to obtain a series of novel 4-(2-fluorophenoxy)quinoline derivatives (Fig. 3). Meanwhile, the morpholinyl group at 7-position of quinoline scaffold was replaced by several water-soluble groups including piperidinyl, pyrrolidinyl and 4-methyl piperidinyl groups. Additionally, various substituents (R_2) were introduced into the terminal phenyl ring (moiety B) to investigate their effects on activity.

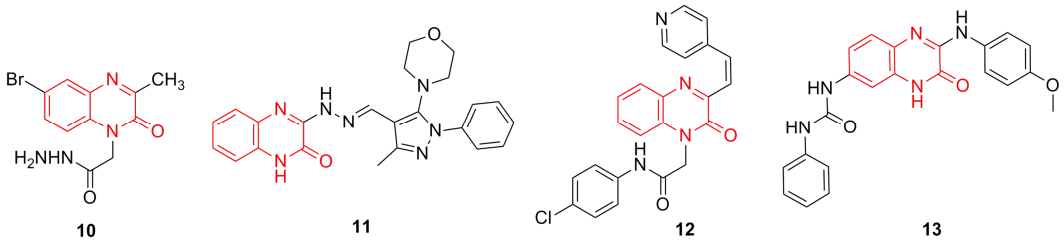


Figure 2. Anticancer agents bearing quinoxalinone moiety

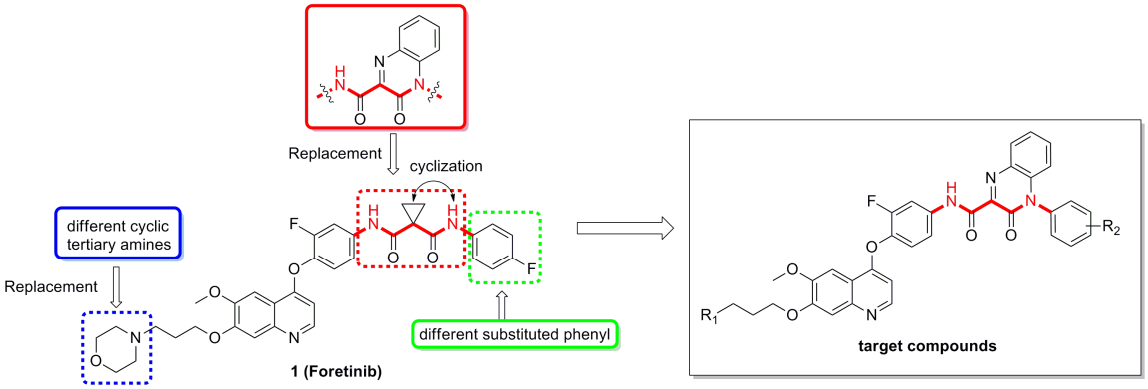
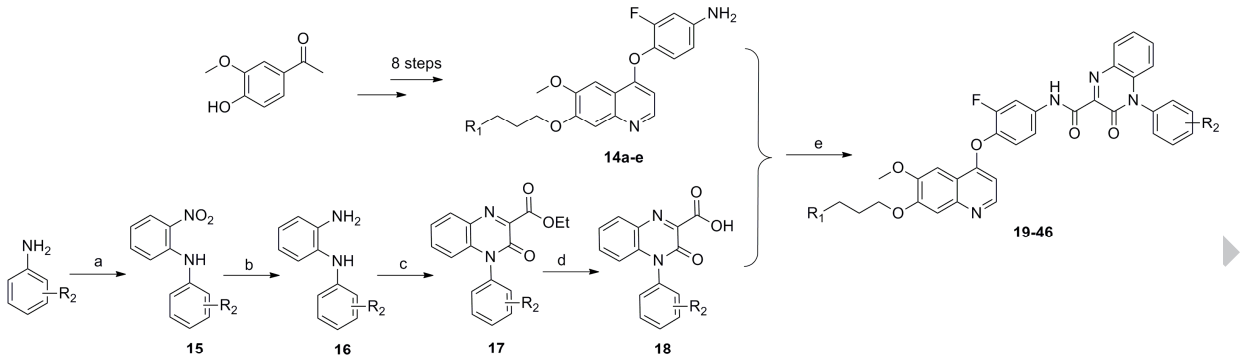


Figure 3. Design strategy and general structure of the target compounds

In the current study, all target compounds were evaluated for their antiproliferative activity in vitro against five cancer cell lines: human colon cancer cell line (HT-29), human lung cancer cell lines (H460), human lung adenocarcinoma cell line (A549), human gastric cancer cell line (MKN-45) and human glioblastoma cell line (U87MG), and their structure-activity relationships (SARs) were further explored. Additionally, to determine c-Met kinase inhibition, the enzymatic assays of several potent compounds were evaluated, and most of them showed promising inhibition. Furthermore, the inhibitory activities of the most potent compound **41** against seven other RTK kinases were also investigated, and a docking analysis was also performed to elucidate the binding mode of the target compound **41** with c-Met kinase.

2. Chemistry

The synthesis of target compounds **19–46** is described in Scheme 1. The key intermediates 6,7-disubstituted-4-phenoxyquinolines **14a–14e** were synthesized using a convenient eight-step procedure starting from 1-(4-hydroxy-3-methoxyphenyl)ethanone, which was illustrated in detail in our previous study.[19,27] The condensation of commercially available 1-fluoro-2-nitrobenzene with different substituted amines in the presence of sodium hydride in *N,N*-dimethylformamide afforded intermediates diphenyl amines **15** as yellow solids. Reduction of the nitro group of **15** with iron powder provided compounds **16**. The cyclization of **16** with diethyl ketomalonate afforded 3-oxo-3,4-dihydroquinoxaline-2-carboxylic acid esters **17**, which were converted to acids **18** using lithium hydroxide monohydrate in THF/water at RT for 2 hours. Finally, acids **18** were refluxed in toluene and $SOCl_2$ for 5 h to afford acyl chlorides which were condensed with intermediates **14a–14e** in the presence of sodium carbonate in dichloromethane at room temperature overnight to afford the target compounds **19–46** having a 3-oxo-4-aryl -3,4-dihydroquinoxaline-2-carboxamide group.



14a: R_1 = morpholinyl; 14b: R1 = piperidinyl; 14c: R_1 = 4-methyl piperidinyl; 14d: R_1 = 4-methyl piperazinyl; 14e: R_1 = pyrrolidiny.

15a-18a: R_2 = H; 15b-18b: R_2 = 4-OCH_3; 15c-18c: R_2 = 4-CH_3; 15d-18d: R_2 = 2,4-diOCH_3; 15e-18e: R_2 = 4-OCF_3;

15f-18f: R_2 = 2-CF_3; 15g-18g: R_2 = 4-F; 15h-18h: R_2 = 4-Cl; 15i-18i: R_2 = 4-Br; 15j-18j: R_2 = 2-F;

15k-18k: R_2 = 2-Cl; 15l-18l: R_2 = 3-F; 15m-18m: R_2 = 3-Cl; 15n-18n: R_2 = 2,4-diCl.

Scheme 1. Reagents and conditions: (a) amines, NaH, DMF, RT, 16 h; (b) Fe powder, HOAc, CH_3COOEt/H_2O, reflux, 6 h; (c) diethyl ketomalonate, toluene, reflux, 12 h; (d) LiOH, THF/ H_2O, RT, 1.5 h, then 6 N HCl; (e) toluene, $SOCl_2$, reflux, 5 h; Na_2CO_3, CH_2Cl_2, 25 °C, 3 h.

3. Results and discussion

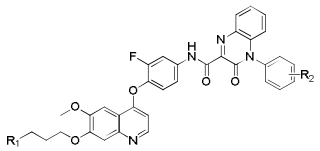
3.1. *In vitro cytotoxicity and structure–activity relationships*

All the 28 newly synthesized compounds (**19-46**) were screened for their in vitro cytotoxic activity by the MTT-based assay using Foretinib as a positive control. They were tested against five c-Met overexpresed human cancer cell lines, namely human colon cancer cell line (HT-29), human lung cancer cell lines (H460), human lung adenocarcinoma cell line (A549), human gastric cancer cell line (MKN-45) and human glioblastoma cell line (U87MG). The results were expressed as IC_{50} values and summarized in Table 1. The IC_{50} values were the average of at least three independent experiments.

As illustrated in Table 1, all the target compounds showed excellent cytotoxic activity against different cancer cells and some exhibited more or similar potent activities against certain cancer lines in comparison with foretinib, which suggested that replacement of cyclopropane-1,1-dicarboxamide framework of foretinib with 3-oxo-4-aryl-3, 4-dihydroquinoxaline-2-carboxamide moiety as the linker maintained the potent cytotoxic activity. It is worth pointing out that 23 compounds were more potent than foretinib against one or more cell lines. The most significant cytotoxic activity was achieved for compounds **25**, **41** and **44** with IC_{50} values ranging from 0.023 μM to 0.94 μM against all tested cell lines, which were better than that of foretinib (IC_{50} = 0.030 to 0.96 μM). More importantly, most of the compounds were more potent against A549 and MKN-45 cell lines with potencies in the double-digit nM range than other three cell lines. These results revealed that this series of compounds possessed selectivity for A549 and MKN-45 cancer cell lines, and had the makings of good drugs for lung and gastric cancer.

Table 1

Structures and cytotoxicity of compounds 19-46.



Compd.	R_1	R_2	IC_{50} (μmol/L) ± SD[a]				
			HT-29	A549	H460	MKN-45	U87MG
19	Morpholinyl	H	**0.20 ± 0.03**	0.41± 0.05	1.04± 0.01	0.082± 0.008	1.72± 0.07
20	Morpholinyl	4-OCH_3	0.69 ± 0.01	1.72± 0.02	1.85± 0.03	0.66± 0.05	>32± 0.07

21	Morpholinyl	4-CH_3	1.03 ± 0.01	2.16± 0.01	1.12± 0.07	0.58± 0.02	4.17± 0.01
22	Morpholinyl	2,4-$(OCH_3)_2$	1.29± 0.03	5.11± 0.03	2.05± 0.03	0.86± 0.07	16.25± 0.07
23	Morpholinyl	4-OCF_3	**0.20± 0.003**	0.33± 0.05	0.29± 0.002	0.26± 0.01	1.22± 0.09
24	Morpholinyl	2-CF_3	**0.19± 0.003**	0.22± 0.003	0.28± 0.002	0.56± 0.001	1.78± 0.07
25	Morpholinyl	4-F	**0.11 ± 0.01**	**0.030± 0.05**	**0.14± 0.05**	**0.026± 0.03**	**0.81± 0.21**
26	Morpholinyl	4-Cl	**0.16 ± 0.003**	**0.042± 0.04**	0.28± 0.06	**0.029± 0.08**	1.06± 0.02
27	Morpholinyl	4-Br	**0.17± 0.04**	0.32± 0.002	**0.21± 0.01**	0.11± 0.03	1.17± 0.02
28	Morpholinyl	2-F	**0.17 ± 0.012**	**0.033± 0.03**	0.23± 0.002	**0.029± 0.01**	**0.65± 0.02**
29	Morpholinyl	2-Cl	**0.15 ± 0.004**	**0.050± 0.03**	**0.14± 0.002**	**0.025± 0.01**	1.50± 0.02
30	Morpholinyl	3-F	**0.20 ± 0.09**	0.31± 0.01	0.40± 0.01	0.39± 0.03	1.85± 0.31
31	Morpholinyl	3-Cl	0.33 ± 0.04	0.24± 0.05	0.53± 0.02	0.34± 0.02	0.98± 0.05
32	Morpholinyl	2,4-$(Cl)_2$	0.59 ± 0.01	0.17± 0.06	0.64± 0.08	0.075± 0.02	5.04± 0.21
33	Piperidinyl	4-F	**0.16± 0.04**	**0.055± 0.02**	0.23± 0.03	**0.020± 0.08**	1.61± 0.02
34	Piperidinyl	4-Cl	0.24± 0.04	**0.09± 0.02**	0.31± 0.03	0.053± 0.08	1.31± 0.02
35	Piperidinyl	2-F	0.22± 0.01	**0.084± 0.02**	**0.14± 0.01**	0.034± 0.05	1.17± 0.22
36	Piperidinyl	2-Cl	**0.15± 0.03**	0.20± 0.01	0.35± 0.12	0.060± 0.11	1.23± 0.01
37	4-Methylpiperidinyl	4-F	**0.16± 0.01**	**0.052± 0.08**	0.31± 0.22	**0.028± 0.08**	**0.87± 0.22**
38	4-Methylpiperidinyl	4-Cl	0.24± 0.05	**0.14± 0.012**	0.28± 0.06	0.098± 0.07	1.41± 0.04
39	4-Methylpiperidinyl	2-F	**0.19± 0.03**	**0.10± 0.01**	**0.16± 0.03**	0.040± 0.01	1.12± 0.01
40	4-Methylpiperidinyl	2-Cl	**0.17± 0.04**	0.39± 0.002	0.53± 0.01	0.075± 0.03	2.17± 0.02
41	4-Methylpiperazinyl	4-F	**0.06± 0.03**	**0.050± 0.20**	**0.18± 0.01**	**0.023± 0.02**	**0.66± 0.22**
42	4-Methylpiperazinyl	4-Cl	**0.20± 0.08**	**0.11± 0.09**	0.25± 0.02	0.043± 0.07	1.21± 0.04
43	4-Methylpiperazinyl	2-F	**0.16± 0.01**	**0.049± 0.03**	0.25± 0.05	0.039± 0.02	1.10± 0.01
44	4-Methylpiperazinyl	2-Cl	**0.13± 0.03**	**0.025± 0.20**	**0.12± 0.01**	**0.024± 0.02**	**0.94± 0.22**
45	Pyrrolidinyl	4-F	0.25± 0.11	**0.090± 0.02**	**0.21± 0.21**	0.056± 0.14	1.52± 0.21
46	Pyrrolidinyl	2-Cl	0.35± 0.03	**0.12± 0.01**	**0.19± 0.09**	0.048± 0.11	1.03± 0.10
Foretinib[b]			0.21 ± 0.01	0.15 ± 0.03	0.22 ± 0.01	0.030 ± 0.005	0.96 ± 0.12

Bold values show the IC_{50} values of target compounds lower than the values of the positive control.
[a] IC_{50}: concentration of the compound (mM) producing 50% cell growth inhibition after 72 h of drug exposure, as determined by the MTT assay. Each experiment was carried out in triplicate.
[b] Used as a positive control.

As show in Table 1, the SARs based on IC_{50} values of cytotoxic activity revealed that variations in the R_2 groups on the phenyl ring (moiety B) markedly affect their activities. Primarily, mono-electron-donating groups (mono-EDGs) such as 4-methoxy and 4-methyl analogues (**20, 21**) exhibited a negative effect compared to no substituent on the phenyl ring (**19**: R_2 = H). A dramatic drop in antiproliferative activity was seen as we introduced double-EDGs (**22**: R_2 = 2, 4-dimethoxy) at this region of the molecule. Gratifyingly, the introduction of mono-electron-withdrawing groups (mono-EWGs) and double-EWGs exhibited a positive effect on the cytotoxic activity. In particular, incorporation of the halogen atom (R_2 = F, Cl, Br, respectively) to the 2- or 4- position of phenyl ring showed a higher potency, such as compound **25** (R_2 = 4-F, IC_{50} = 0.026 to 0.81 μM against all tested cell lines). However, moving the halogen atom from 2-or 4-position to 3-position (**30**, **31**) led to decrease in cytotoxicity against all cancer cells. Moreover, incorporation of another halogen atom in the form of 2, 4-dichloro compound (**32:** R_2 = 2, 4-dichloro, IC_{50} = 0.59 μM against HT-29) showed somewhat a decreased cellular activity compared with 4-chloro analogue (**26:** R_2 = 4-Cl, IC_{50} = 0.16 μM against HT-29) and 2-chloro analogue (**29:** R_2 = 2-Cl, IC_{50} = 0.15 μM against HT-29), which indicates monosubstitution of phenyl is more preferred. Meanwhile, compared with halogen analogs **28** (R_2 = 2-F) and **29** (R_2 = 2-Cl), incorporation of strong electron-withdrawing groups (EWGs) such as trifluoromethyl group (**24**) on the phenyl ring (moiety B) reduced the antitumor activity

slightly against HT-29, H460 and U87MG, but lowered the efficiency even further against A549 and MKN-45. It suggested that the moiety B probably need medium electron density. Accordingly, compounds possessing chloro and fluoro groups at the 2- and 4-position of phenyl ring were further studied in our work.

To understanding the SAR deeply, we examined the effects of the R_1 substituent on the three carbon ether connected to the quinoline at the 7-position by replacing the morpholinyl group with piperidinyl, 4-methylpiperidinyl, 4-methylpiperazinyl and pyrrolidinyl groups. As show in Table 1, the results indicated that the introduction of different water-soluble R_1 groups had a slight influence on activity.Taking R_2=2-Cl series compounds for example, compounds **29** (R_1 = Morpholinyl), **36** (R_1 = Piperidinyl), **40** (4-Methylpiperidinyl), **44** (4-Methylpiperazinyl) and **46** (R_1 = Pyrrolidinyl), exhibited comparable cytotoxic activities against the different cancer cells.

3.2. *In vitro enzymatic assays*

Based on the cellular assay results, we selected nine compounds which were more potent than foretinib against three or more cell lines for c-Met kinase activity determination using homogenous time-resolved fluorescence (HTRF) assays and the results were outlined in Table 2. As shown in Table 2, all the ten tested compounds exhibited excellent c-Met enzymatic potency with IC_{50} values ranging from 0.90 to 13.14 nM. These data suggest that c-Met inhibition may be a mechanism for the antitumor effect of these derivatives. Compounds **41** and **44** showed the most potent activity with an IC_{50} values of 0.90 nM and 1.22 nM, respectively, which were better than that of foretinib (IC_{50} = 1.41 nM), indicating that these compounds deserve further study with regard to its application in the treatment of cancer.

Table 2

c-Met kinase activity of selected compounds **25, 26, 28, 29, 33, 37, 39, 41, 44** and **Foretinib** *in vitro*.

Compd.	IC_{50} on c-Met (nM)[a]
25	2.35
26	6.76
28	4.52
29	3.23
33	8.03
37	3.57
39	13.14
41	**0.90**
44	**1.22**
Foretinib[b]	1.41

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

The inhibitory activity of the most potent compound **41** against c-Kit, PDGFRα, Ron, VEGFR-2, Flt-3, EGFR and ALK kinase was also assayed using HTRF method (Table 3). In contrast to its high potency against c-Met (IC_{50} = 0.90 nM), **41** also exhibited high inhibitory effects against c-Kit (IC_{50}= 2.45 nM) and PDGFRα (IC_{50}= 19.13 nM). Moreover, **41** demonstrated moderate-to-excellent selectivity against Ron, VEGFR-2, Flt-3, EGFR and ALK kinase with IC_{50} values of 82.56 nM, 151.47 nM, 268.81 nM, 980.83 nM and 2840.72 nM, respectively.

Table 3

Inhibition of tyrosine kinases by compound **41** and foretinib

Kinase	IC_{50}(nM)	
	41	foretinib
c-Kit	2.45	6.83
PDGFRα	19.13	6.82
Ron	82.56	3.48
VEGFR-2	151.52	4.79
Flt-3	268.81	5.58
EGFR	980.83	2990
ALK	2840.72	>3000

4. Binding model analysis

To further elucidate the binding mode of compounds, a detail docking analysis was performed. In our study, the co-crystal structure of foretinib (GSK1363089) with c-Met was selected as the docking model (PDB ID code: 3LQ8). The docking simulation was conducted using Glide XP (Schrödinger 2014), since Glide uses a hierarchical series of filters to search for possible locations of the ligand in the active-site region of the receptor. The shape and properties of the receptor are represented on a grid by several different sets of fields that provide progressively more accurate scoring of the ligand poses. The image files were generated using Accelrys DS visualizer 4.0 system. The binding model was exemplified by the interaction of compound **41** with c-Met. As shown in Figure 4A, the nitrogen atom of the quinoline, the NH and the oxygen of amide formed three hydrogen-bonding interactions with Met1160, Asp1222 and Lys1110, respectively. In the meantime, two Pi-Sigma interaction between quinoline with ILE1084 and MET1211 had beenformed. All these interactions played an important role in stabilizing the conformation of ligand-protein complex. Docking structure of compound **41** overlayed with foretinib in c-Met showed that the conformation and binding mode of compound **41** were well consistent with foretinib, which suggested that a 3-oxo-3,4-dihydroquinoxaline-2-carboxamide moiety could serve as a scaffold from which to build a novel series of c-Met inhibitors (Figure 4B).

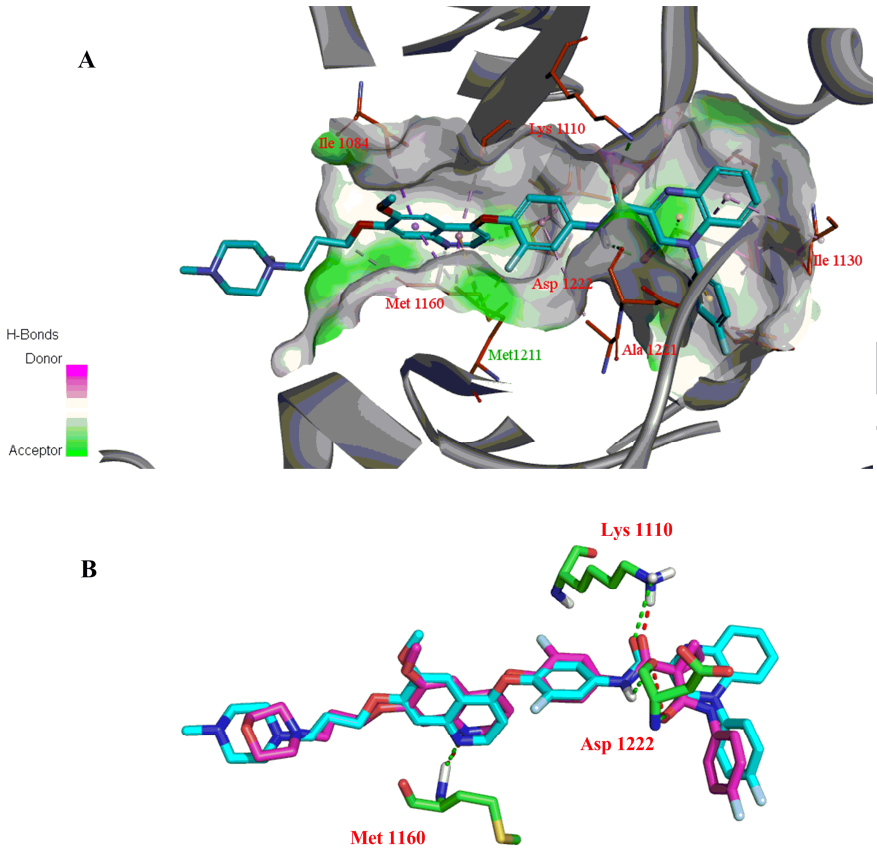


Figure 4. A: The c-Met active site in complex with compound **41**, the proteins were displayed by silver ribbon. Compound 41 was shown in colored sticks (cyan:carbon atom, blue: nitrogen atom, red: oxygen atom, light cyan: fluorine atom). H-bonding interactions between the 41 and c-Met were indicated with dotted lines in green, and Pi-Sigma interaction was shown in purple dotted lines. B : Superposed docking poses of foretinib (purple) and compound **41** (blue) in c-Met.

5. Conclusion

In summary, on the basis of our previous work, a series of 6, 7-disubstituted-4-phenoxyquinoline derivatives bearing 3-oxo-3,4-dihydroquinoxaline moiety scaffold were designed and synthesized. The entire target compounds were investigated for their in vitro antiproliferative activity using the MTT-based assay against five human cancer cell lines (HT-29, H460, A549, MKN-45 and U87MG). Most compounds showed significant antiproliferative activities against all cancer cell lines. In particular, the most promising compound **41** (c-Met IC_{50}= 0.90 nM) showed antitumor activities with IC_{50} values of 0.06μM, 0.05μM, 0.18μM, 0.023μM and 0.66 μM against HT-29, H460, A549, MKN-45 and U87MG cell lines, respectively. The preliminary studies on enzymatic selectivity also revealed that compound **41** showed moderate-to-excellent selectivity against Ron, VEGFR-2, Flt-3, EGFR and ALK kinase, but it is still a multitarget inhibitor of tyrosine kinases. The structure-activity relationships (SARs) analyses indicated that the replacement of the cyclopropane-1,1-dicarboxamide framework of foretinib with the 3-oxo-3,4-dihydroquinoxaline moiety maintained the potent cytotoxicity. Meanwhile, compounds with mono-EWGs, especially chloro, fluoro group at 2- or 4-position on the phenyl ring (moiety B) were more active than those without substituents, double-EWGs or EDGs. Further studies on structural optimization and biological activities about these derivatives are still underway in our laboratory and will be reported in the future.

6. Experimental

6.1. Chemistry

Unless otherwise specified, 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, U.S.A.). ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker ARX-400, 400MHz or Bruker ARX-600, 600MHz spectrometers (Bruker Bioscience, Billerica, MA, USA) with TMS as an internal standard. All materials were obtained from commercial suppliers and were used without further purification. 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). The IR spectra were recorded by means of the KBr pellet technique on a Bruker FTS 135 spectrometer. The elemental analysis of the compounds was performed on a Perkin Elmer 2400 Elemental Analyser (In the mode of measurement C, H, and N, the sample into the combustion tube in pure oxygen atmosphere static combustion and products by a specific reagent after formation of CO_2, H_2O, N_2 and nitrogen oxides, uniform mixing under the atmospheric pressure. The thermal conductivity detector is used for determining the content of C, H and N from mixed gases.).

6.2. General procedure for preparation intermediates of N-substituted-2-nitroanilines (**15a–15n**)

To the suspension of NaH (75 mol) in DMF (60 mL), substituted amines (50 mmol) was added at 0 °C. The mixture was stirred for 30 min at the same temperature, and then 2-fluoronitrobenzene (60 mmol) diluted in DMF (30 mL) was added slowly. The mixture was warmed to room temperature and stirred for 16 hours. The reaction mixture was carefully poured into stirring saturated NH_4Cl (500 mL), then filtered. The filter cake was washed with water, and recrystallized from methanol to afford corresponding N-aryl-2-nitroanilines **15a–15n**.

6.2.1. 2-nitro-N-phenylaniline (**15a**)

Red solid; Yield: 79.4%; M.p.: 74.2–76.1 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.52 (s, 1H), 8.23 (dd, J = 8.4 Hz, 1.6 Hz, 1H), 7.43 (m, 3H), 7.30 (m, 2H), 7.25 (m, 2H), 6.79 (m, 1H); MS (ESI) m/z(%): 213.3 $[M-H]^-$.

6.2.2. N-(4-methoxyphenyl)-2-nitroaniline (**15b**)

Red solid; Yield: 79.7%; M.p.: 88.1–89.7 °C; MS (ESI) m/z(%): 243.3 $[M-H]^-$.

6.2.3. 2-nitro-N-(p-tolyl)aniline (**15c**)

Orange solid; Yield: 81.0%; M.p.: 69.3–70.9 °C; MS (ESI) m/z(%): 227.2 $[M-H]^-$.

6.2.4. 2,4-dimethoxy-N-(2-nitrophenyl)aniline (**15d**)

Red solid; Yield: 81.7%; M.p.: 100.0–101.8 °C; MS (ESI) m/z(%): 273.3 $[M-H]^-$.

6.2.5. 2-nitro-N-(4-(trifluoromethoxy)phenyl)aniline (**15e**)

Red solid; Yield: 65.9%; M.p.: 67.8–69.6 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.34 (s, 1H), 8.12 (d, J = 8.4, 1H), 7.54(t, J = 8.0 Hz, 1H), 7.42 (m, 4H), 7.24 (d, J = 8.4 Hz, 1H), 6.95 (t, J = 8.0 Hz, 1H); MS (ESI) m/z(%): 297.0 $[M-H]^-$.

6.2.6. 2-nitro-N-(2-(trifluoromethyl)phenyl)aniline (**15f**)

Red solid; Yield: 61.6%; M.p.: 98.1–99.7 °C; MS (ESI) m/z(%): 281.1 $[M-H]^-$.

6.2.7. N-(4-fluorophenyl)-2-nitroaniline (**15g**)

Red solid; Yield: 71.4%; M.p.: 82.5–83.8 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.42 (s, 1H), 8.23 (dd, J = 8.4 Hz, 1.6 Hz, 1H), 7.38 (m, 1H), 7.28 (m, 2H), 7.15 (m, 2H), 7.07 (m, 1H), 6.79 (m, 1H); MS (ESI) m/z(%): 230.8 $[M-H]^-$.

6.2.8. N-(4-chlorophenyl)-2-nitroaniline (**15h**)

Orange solid; Yield: 72.3%; M.p.: 135.1–137.0 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.31 (s, 1H), 8.12 (d, J = 8.0, 1H), 7.53(t, J = 7.6 Hz, 1H), 7.44 (d, J = 8.8 Hz, 2H), 7.34 (d, J = 8.8 Hz, 2H), 7.22 (d, J = 8.4 Hz, 1H), 6.93 (t,

J = 7.6 Hz, 1H); MS (ESI) m/z(%): 247.2 $[M-H]^-$.

6.2.9. N-(4-bromophenyl)-2-nitroaniline (**15i**)

Orange solid; Yield: 74.8%; M.p.: 168.7–170.2 °C; MS (ESI) m/z(%): 292.1$[M-H]^-$.

6.2.10. 2-fluoro-N-(2-nitrophenyl)aniline (**15j**)

Red solid; Yield: 74.1%; M.p.: 74.4–75.8 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.28 (s, 1H), 8.14 (d, J = 8.0 Hz, 1H), 7.51 (m, 2H), 7.35 (m, 3H), 6.90 (m, 2H); MS (ESI) m/z(%): 231.1 $[M-H]^-$.

6.2.11. 2-chloro-N-(2-nitrophenyl)aniline (**15k**)

Red solid; Yield: 77.3%; M.p.: 110.1–111.8 °C; MS (ESI) m/z(%):247.2 $[M-H]^-$.

6.2.12. N-(3-fluorophenyl)-2-nitroaniline (**15l**)

Red solid; Yield: 72.2%; M.p.: 63.5–65.1 °C; MS (ESI) m/z(%):230.8 $[M-H]^-$.

6.2.13. N-(3-chlorophenyl)-2-nitroaniline (**15m**)

Red solid; Yield: 74.5%; M.p.: 93.5–95.2 °C; MS (ESI) m/z(%):247.1 $[M-H]^-$.

6.2.14. 2,4-dichloro-N-(2-nitrophenyl)aniline (**15n**)

Red solid; Yield: 69.5%; M.p.: 137.7–138.8 °C; MS (ESI) m/z(%): 282.0 $[M-H]^-$.

6.3. General procedure for preparation of N^1- substituted-benzene-1,2-diamine (**16a–16n**)

A mixture of N-substituted-2-nitroanilines (50 mmol), iron powder (250 mmol), acetic acid (500 mmol), water (35 ml) and ethyl acetate (80 ml) was heated to reflux for 6 hours. After completion of the reaction as indicated by TLC, the mixture was filtered immediately. The organic layer of the filtrate was separated, washed with water, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain diamines(**16a–16n**) as a brown solid.

6.4. General procedure for preparation of ethyl 4-substituted-3-oxo-3,4-dihydroquinoxaline-2-carboxylate (**17a–17n**)

21 mmol of corresponding diamine and 23 mmol of diethyl ketomalonate were dissolved in toluene (60 ml) and the solution was heated to reflux for 12 hours while removing water using a Dean-Stark apparatus. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure and then partitioned between water (50 mL) and ethyl acetate (50 mL). The organic layer was separated and the aqueous layer was then extracted with ethyl acetate (50 mL × 3). The combined organic extracts were sequentially washed with water (50 mL × 3), brine (80 mL × 3) and dried over anhydrous Na_2SO_4. After evaporation of the organic solvent, the residue was purified by column chromatography to afford **17a–17n**.

6.4.1. Ethyl 3-oxo-4-phenyl-3,4-dihydroquinoxaline-2-carboxylate (**17a**)

White solid; Yield: 78.2%; M.p.: 146.0–147.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (dd, J = 7.6 Hz, 1.6 Hz, 1H), 7.63 (m, 3H), 7.46 (m, 1H), 7.38 (m, 1H), 7.34 (m, 2H), 6.75 (m, 1H), 4.53 (q, J = 6.8 Hz, 2H), 1.46 (t, J = 6.8 Hz, 3H); MS (ESI) m/z(%): 295.0 $[M+H]^+$.

6.4.2. Ethyl 4-(4-methoxyphenyl)-3-oxo-3,4-dihydroquinoxaline-2-carboxylate (**17b**)

Light yellow solid; Yield: 82.1%; M.p.: 140.8–142.3 °C; MS (ESI) m/z(%): 325.0 $[M+H]^+$, 347.1 $[M+Na]^+$.

6.4.3. Ethyl 3-oxo-4-(p-tolyl)-3,4-dihydroquinoxaline-2-carboxylate (**17c**)

White solid; Yield: 80.1%; M.p.: 98.8–100.9 °C; MS (ESI) m/z(%): 309.2 $[M+H]^+$.

6.4.4. Ethyl 4-(2,4-dimethoxyphenyl)-3-oxo-3,4-dihydroquinoxaline-2-carboxylate (**17d**)

Yellow solid; Yield: 79.5%; M.p.: 87.0–89.3 °C; MS (ESI) m/z(%): 355.1 $[M+H]^+$.

6.4.5. Ethyl 3-oxo-4-(4-(trifluoromethoxy)phenyl)-3,4-dihydroquinoxaline-2-carboxylate (**17e**)

White solid;Yield: 69.6%; M.p.: 135.3–137.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, J = 8.0 Hz, 1H), 7.51 (m, 3H), 7.41 (m, 3H), 7.41 (m, 1H), 6.75 (d, J = 8.0 Hz, 1H), 4.53 (q, J = 6.8 Hz, 2H), 1.46 (t, J = 6.8 Hz, 3H); MS (ESI) m/z(%): 379.1 $[M+H]^+$.

6.4.6. Ethyl 3-oxo-4-(2-(trifluoromethyl)phenyl)-3,4-dihydroquinoxaline-2-carboxylate (**17f**)

White solid; Yield: 61.5%; M.p.: 107.0–108.8 °C; MS (ESI) m/z(%): 363.1 $[M+H]^+$.

6.4.7. Ethyl 4-(4-fluorophenyl)-3-oxo-3,4-dihydroquinoxaline-2-carboxylate (**17g**)

White solid; Yield: 69.2%; M.p.: 132–133.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, *J* = 7.6 Hz, 1H), 7.40 (m, 6H), 6.75 (d, *J* = 8.0 Hz, 1H), 4.53 (q, *J* = 6.8 Hz, 2H), 1.46 (t, *J* = 6.8 Hz, 3H); MS (ESI) m/z(%): 313.1 $[M+H]^+$, 647.1 $[2M+Na]^+$.

6.4.8. Ethyl 4-(4-chlorophenyl)-3-oxo-3,4-dihydroquinoxaline-2-carboxylate (**17h**)

White solid; Yield: 69.6%; M.p.: 124.7–125.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (dd, *J* = 8.0 Hz, 1.6 Hz, 1H), 7.62 (m, 2H), 7.48 (m, 1H), 7.41 (m, 1H), 7.29 (m, 2H), 6.75 (dd, *J* = 8.0 Hz, 1.6 Hz, 1H), 4.53 (q, *J* = 6.8 Hz, 2H), 1.46 (t, *J* = 6.8 Hz, 3H); MS (ESI) m/z(%): 329.1 $[M+H]^+$.

6.4.9. Ethyl 4-(4-bromophenyl)-3-oxo-3,4-dihydroquinoxaline-2-carboxylate (**17i**)

Light yellow solid; Yield: 61.3%; M.p.: 140–142 °C; MS (ESI) m/z(%): 373.0 $[M+H]^+$.

6.4.10. Ethyl 4-(2-fluorophenyl)-3-oxo-3,4-dihydroquinoxaline-2-carboxylate (**17j**)

White solid; Yield: 62.5%; M.p.: 143.3–145 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, *J* = 8.0 Hz, 1H), 7.61 (m, 1H), 7.51 (m, 1H), 7.40 (m, 4H), 4.53 (q, *J* = 7.2 Hz, 2H), 1.46 (t, *J* = 7.2 Hz, 3H); MS (ESI) m/z(%): 313.0 $[M+H]^+$;

6.4.11. Ethyl 4-(2-chlorophenyl)-3-oxo-3,4-dihydroquinoxaline-2-carboxylate (**17k**)

White solid; Yield: 68.5%; M.p.: 132.4–134.8 °C; MS (ESI) m/z(%): 329.1 $[M+H]^+$.

6.4.12. Ethyl 4-(3-fluorophenyl)-3-oxo-3,4-dihydroquinoxaline-2-carboxylate (**17l**)

White solid; Yield: 60.9%; M.p.: 128.8–130.9 °C; MS (ESI) m/z(%): 313.1 $[M+H]^+$.

6.4.13. Ethyl 4-(3-chlorophenyl)-3-oxo-3,4-dihydroquinoxaline-2-carboxylate (**17m**)

White solid; Yield: 59.6%; M.p.: 114.1–115.9 °C; MS (ESI) m/z(%): 329.1 $[M+H]^+$.

6.4.14. Ethyl 4-(2,4-dichlorophenyl)-3-oxo-3,4-dihydroquinoxaline-2-carboxylate (**17n**)

Yellow solid; Yield: 63.4%; M.p.: 144.0–145.8 °C; MS (ESI) m/z(%): 363.1 $[M+H]^+$.

6.5. General procedure for preparation of 4-subistituted-3-oxo-3,4-dihydroquinoxaline-2-carboxylic acid(**18a–18n**)

To a solution of an appropriate intermediate (**17a–17n**) (7.56 mmol) dissolved in THF/H_2O (40 mL, 4:1), was added 2 eq of lithium hydroxide monohydrate, and the resulting suspension was stirred for 2 h at room temperature. Then, most of the solvent was evaporated, and the residue was poured into H_2O (50 mL) and acidified by addition of 6 N HCl solution until pH 2. A solid precipitated therefrom was separated by filtration, washed with water and then dried to obtain substituted acids (**18a–18n**) as pale yellow powder.

6.5.1. 3-oxo-4-phenyl-3,4-dihydroquinoxaline-2-carboxylic acid (**18a**)

Yield: 88.1%; M.p.: 172–174 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 14.08 (br, 1H), 7.95 (dd, *J* = 8.0 Hz, 1.2 Hz, 1H), 7.62 (m, 4H), 7.47 (m, 3H), 6.62 (m, 1H); MS (ESI) m/z(%): 265.1 $[M-H]^-$.

6.5.2. 4-(4-methoxyphenyl)-3-oxo-3,4-dihydroquinoxaline-2-carboxylic acid (**18b**)

Yield: 83.8%; M.p.: 194.5–195.8 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 14.05 (br, 1H), 7.93 (d, *J* = 7.2 Hz, 1H), 7.56 (t, *J* = 7.6 Hz, 1H), 7.41 (m, 3H), 7.19 (d, *J* = 8.8 Hz, 2H), 6.69 (d, *J* = 8.8 Hz, 1H), 3.87 (s, 3H); MS (ESI) m/z(%): 295.1 $[M-H]^-$.

6.5.3. 3-oxo-4-(p-tolyl)-3,4-dihydroquinoxaline-2-carboxylic acid (**18c)**

Yield: 80.9%; M.p.: 177.4–179 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 14.03 (br, 1H), 7.94 (dd, *J* = 8.0 Hz, 1.2 Hz, 1H), 7.55 (m, 1H), 7.46 (m, 3H), 7.33 (d, *J* = 8.4 Hz, 2H), 6.65 (d, *J* = 8.4 Hz, 1H), 2.45(s, 3H); MS (ESI) m/z(%): 281.4 $[M+H]^+$.

6.5.4. 4-(2,4-dimethoxyphenyl)-3-oxo-3,4-dihydroquinoxaline-2-carboxylic acid (**18d**)

Yield: 81.2%; M.p.: 180.4–182 °C; MS (ESI) m/z(%): 325.0 $[M-H]^-$.

6.5.5. 3-oxo-4-(4-(trifluoromethoxy)phenyl)-3,4-dihydroquinoxaline-2-carboxylic acid (**18e)**

Yield: 91.3%; M.p.: 184–186 °C; MS (ESI) m/z(%): 349.0 $[M-H]^-$.

6.5.6. 3-oxo-4-(2-(trifluoromethyl)phenyl)-3,4-dihydroquinoxaline-2-carboxylic acid (**18f**)

Yield: 93.1%; M.p.: 189–190.2 °C; MS (ESI) m/z(%): 335.4 $[M+H]^+$.

6.5.7. 4-(4-fluorophenyl)-3-oxo-3,4-dihydroquinoxaline-2-carboxylic acid (**18g**)

Yield: 86.4%; M.p.:288–290 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.74 (dd, J = 7.6 Hz, 1.6 Hz, 1H), 7.45 (m, 4H), 7.33 (m, 2H), 6.53 (d, J = 7.2 Hz, 1H); MS (ESI) m/z(%): 282.7 $[M-H]^-$.

6.5.8. 4-(4-chlorophenyl)-3-oxo-3,4-dihydroquinoxaline-2-carboxylic acid (**18h**)

Yield: 89.9%; M.p.: 186.7–188.6 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 14.01 (br, 1H), 7.94 (d, J = 7.2 Hz, 1H), 7.50 (d, J = 8.4 Hz, 2H), 7.54 (m, 3H), 7.44 (t, J = 7.2 Hz, 1H), 6.67 (d, J = 8.0 Hz, 1H); MS (ESI) m/z(%): 299.0$[M-H]^-$.

6.5.9. 4-(4-bromophenyl)-3-oxo-3,4-dihydroquinoxaline-2-carboxylic acid (**18i**)

Yield: 88.6%; M.p.: 190–192 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 14.04 (br, 1H), 7.95 (dd, J = 8.0 Hz, 1.2 Hz, 1H), 7.88 (d, J = 8.4 Hz, 2H), 7.56 (m, 1H), 7.56 (m, 3H), 6.67 (d, J = 7.6 Hz, 1H); MS (ESI) m/z(%): 345.3 $[M+H]^+$.

6.5.10. 4-(2-fluorophenyl)-3-oxo-3,4-dihydroquinoxaline-2-carboxylic acid (**18j**)

Yield: 89.8%; M.p.: 184.4–186.5 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 14.14 (br, 1H), 7.98 (d, J = 7.6 Hz, 1H), 7.67 (m, 4H), 7.50 (m, 2H), 6.72 (d, J = 8.8 Hz, 1H); MS (ESI) m/z(%):283.1 $[M-H]^-$.

6.5.11. 4-(2-chlorophenyl)-3-oxo-3,4-dihydroquinoxaline-2-carboxylic acid (**18k**)

Yield: 90.4%; M.p.: 155.4–157 °C; MS (ESI) m/z(%): 298.9$[M-H]^-$.

6.5.12. 4-(3-fluorophenyl)-3-oxo-3,4-dihydroquinoxaline-2-carboxylic acid (**18l**)

Yield: 87.9%; M.p.: 146.4–149 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 14.03 (br, 1H), 7.95 (dd, J = 8.0 Hz, 1.2 Hz, 1H), 7.73 (m, 1H), 7.52 (m, 4H), 7.36 (d, J = 7.6 Hz, 1H), 6.67 (d, J = 7.6 Hz, 1H); MS (ESI) m/z(%): 283.2 $[M-H]^-$.

6.5.13. 4-(3-chlorophenyl)-3-oxo-3,4-dihydroquinoxaline-2-carboxylic acid (**18m**)

Yield: 88.4%; M.p.: 174.5–175.8 °C; MS (ESI) m/z(%): 299.1$[M-H]^-$.

6.5.14. 4-(2,4-dichlorophenyl)-3-oxo-3,4-dihydroquinoxaline-2-carboxylic acid (**18n**)

Yield: 89.8%; M.p.: 154.8–157 °C; MS (ESI) m/z(%): 334.1 $[M-H]^-$.

6.6. General procedure for Preparation of the target Compounds (**19–46**)

A mixture of the corresponding acids (**18a–18n**) (1.30 mmol), toluene (10 mL), and $SOCl_2$ (8 mL) was heated at 85 °C for 5 h. Upon cooling to room temperature, the solvent was evaporated in vacuum. The residue was dissolved in dried CH_2Cl_2 (10 mL) and drop-wise added to a mixture of the corresponding anilines (**14a–14e**) (1.00 mmol), Na_2CO_3 (3.90 mmol) and CH_2Cl_2 (10 mL) in an ice bath, which was then removed to raise the temperature to room temperature and stirred for 3 h. The resulting mixture was sequentially washed with 20% K_2CO_3 (20 mL × 3) and brine (20 mL × 3), and the organic phase was separated, dried, and evaporated. The crude product obtained was purified by silica gel chromatography to afford **19–46** as white solids.

6.6.1. *N-(3-fluoro-4-((6-methoxy-7-(3-morpholinopropoxy)quinolin-4-yl)oxy)phenyl)-3-oxo-4-phenyl-3,4-dihydroquinoxaline-2-carboxamide* (**19**)

Yield: 72.1%; M.p.: 205.3–207.2 °C; IR (KBr) cm^{-1}: 3434.6, 2956.1, 2917.6, 2846.2, 1703.7, 1637.9, 1597.0, 1554.9, 1508.2, 1477.8, 1430.0, 1349.5, 1304.8, 1247.9, 1212.2, 1166.0, 1113.2, 852.4, 743.1; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.06 (s, 1H), 8.49 (d, J = 5.2 Hz, 1H), 8.31 (dd, J = 8.0 Hz, 1.2 Hz, 1H), 8.03 (dd, J = 12.0 Hz, 2.4 Hz, 1H), 7.70 (m, 3H), 7.52 (m, 5H), 7.36 (d, J = 7.2 Hz, 2H), 7.23 (d, J = 8.4 Hz, 1H), 6.80 (d, J = 8.4 Hz, 1H), 6.44 (d, J = 5.2 Hz, 1H), 4.27 (t, J = 6.4 Hz, 2H), 4.03 (s, 3H), 3.73 (t, J = 4.4 Hz, 4H), 2.59 (t, J = 6.8 Hz, 2H), 2.51 (br, 4H), 2.14 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.16, 158.96, 155.68, 153.14, 152.32, 149.89, 148.53, 146.52, 144.28, 137.57, 136.63, 134.92, 134.47, 133.55, 133.05, 132.21, 130.77, 130.36, 127.72, 125.51, 123.74, 116.72, 115.88, 115.54, 109.92, 108.52, 102.36, 99.60, 67.14, 66.70, 56.16, 55.42, 53.57, 25.75; MS (ESI) m/z(%): 676.3 $[M+H]^+$; Anal. calcd. for $C_{38}H_{34}FN_5O_6$ (%): C, 67.55; H, 5.07; N, 10.36. Found (%): C, 67.74; H, 5.00; N, 10.43.

6.6.2. *N-(3-fluoro-4-((6-methoxy-7-(3-morpholinopropoxy)quinolin-4-yl)oxy)phenyl)-4-(4-methoxyphenyl)-3-oxo-3,4-dihydroquinoxaline-2-carboxamide* (**20**)

Yield: 74.5%; M.p.: 164.3–165.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.17 (s, 1H), 8.51 (d, *J* = 5.4 Hz, 1H), 8.32 (dd, *J* = 8.0 Hz, 1.2 Hz, 1H), 8.08 (dd, *J* = 12.0 Hz, 2.4 Hz, 1H), 7.58 (m, 5H), 7.29 (m, 3H), 7.22 (m, 2H), 6.89 (d, *J* = 7.6 Hz, 1H), 6.56 (d, *J* = 5.6 Hz, 1H), 4.34 (t, *J* = 6.4 Hz, 2H), 4.06 (s, 3H), 3.99 (br, 4H), 3.95 (s, 3H), 2.97 (m, 6H), 2.43 (m, 2H); MS (ESI) m/z(%): 704.9 $[M-H]^-$; Anal. calcd. for $C_{39}H_{36}FN_5O_7$ (%): C, 66.37; H, 5.14; N, 9.92. Found (%): C, 66.59; H, 5.28; N, 10.02.

6.6.3. *N-(3-fluoro-4-((6-methoxy-7-(3-morpholinopropoxy)quinolin-4-yl)oxy)phenyl)-3-oxo-4-(p-tolyl)-3,4-dihydroquinoxaline-2-carboxamide* (**21**)

Yield: 70.3%; M.p.: 122.5–124.1 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.13 (s, 1H), 8.50 (d, *J* = 5.6 Hz, 1H), 8.32 (dd, *J* = 8.0 Hz, 1.2 Hz, 1H), 8.05 (dd, *J* = 12.0 Hz, 2.4 Hz, 1H), 7.54 (m, 7H), 7.26 (m, 3H), 6.86 (d, *J* = 8.4 Hz, 1H), 6.48 (d, *J* = 5.2 Hz, 1H), 4.30 (t, *J* = 6.4 Hz, 2H), 4.05 (s, 3H), 3.82 (t, *J* = 4.4 Hz, 4H), 2.72 (t, *J* = 7.2 Hz, 2H), 2.63 (br, 4H), 2.54 (s, 3H), 2.23 (m, 2H); MS (ESI) m/z(%): 690.1 $[M+H]^+$; Anal. calcd. for $C_{39}H_{36}FN_5O_6$ (%): C, 67.91; H, 5.26; N, 10.15. Found (%): C, 68.12; H, 5.38; N, 10.00.

6.6.4. *4-(2,4-dimethoxyphenyl)-N-(3-fluoro-4-((6-methoxy-7-(3-morpholinopropoxy)quinolin-4-yl)oxy)phenyl)-3-oxo-3,4-dihydroquinoxaline-2-carboxamide* (**22**)

Yield: 66.3%; M.p.: 149.7–151.4 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.21 (s, 1H), 8.51 (d, *J* = 5.2 Hz, 1H), 8.31 (d, *J* = 7.6 Hz, 1H), 8.07 (dd, *J* = 12.0 Hz, 2.4 Hz, 1H), 7.55(m, 5H), 7.22 (m, 2H), 6.86 (d, *J* = 8.4 Hz, 1H), 6.76 (m, 2H), 6.50 (d, *J* = 5.2 Hz, 1H), 4.31 (t, *J* = 6.8 Hz, 2H), 4.06 (s, 3H), 3.95 (s, 3H), 3.86 (br, 4H), 3.77 (s, 3H), 2.75 (m, 6H), 2.28 (m, 2H); MS (ESI) m/z(%): 736.4 $[M+H]^+$, 758.9 $[M+Na]^+$; Anal. calcd. for $C_{40}H_{38}FN_5O_8$ (%): C, 65.30; H, 5.21; N, 9.52. Found (%): C, 65.51; H, 5.31; N, 9.63.

6.6.5. *N-(3-fluoro-4-((6-methoxy-7-(3-morpholinopropoxy)quinolin-4-yl)oxy)phenyl)-3-oxo-4-(4-(trifluoromethoxy)phenyl)-3,4-dihydroquinoxaline-2-carboxamide* (**23**)

Yield: 88.9%; M.p.: 202.5–204.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.96 (s, 1H), 8.51 (br, 1H), 8.34 (d, *J* = 8.0 Hz, 1H), 8.06 (dd, *J* = 12.0 Hz, 2.0Hz, 1H), 7.55 (m, 9H), 7.28 (t, 1H), 6.82 (d, *J* = 8.0 Hz, 1H), 6.52 (d, *J* = 5.2 Hz, 1H), 4.32 (t, *J* = 6.4 Hz, 2H), 4.06 (s, 3H), 3.92 (m, 4H), 2.84 (m, 6H), 2.34 (m, 2H); MS (ESI) m/z(%): 760.20$[M+H]^+$; Anal. calcd. for $C_{39}H_{33}F_4N_5O_7$ (%): C, 61.66; H, 4.38; N, 9.22. Found (%): C, 61.93; H, 4.45; N, 9.41.

6.6.6. *N-(3-fluoro-4-((6-methoxy-7-(3-morpholinopropoxy)quinolin-4-yl)oxy)phenyl)-3-oxo-4-(2-(trifluoromethyl)phenyl)-3,4-dihydroquinoxaline-2-carboxamide* (**24**)

Yield: 79.9%; M.p.: 131.1–132.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.91 (s, 1H), 8.51 (d, *J* = 5.4 Hz, 1H), 8.33 (d, *J* = 8.0 Hz, 1H), 8.06 (m, 2H), 7.95 (m, 1H), 7.86 (m, 1H), 7.70 (br, 1H), 7.53 (m, 5H), 7.28 (t, *J* = 8.8 Hz, 1H), 6.62 (d, *J* = 8.0 Hz, 1H), 6.56 (d, *J* = 5.4 Hz, 1H), 4.34 (t, *J* = 5.6 Hz, 2H), 4.06 (s, 3H), 4.02 (m, 4H), 3.02 (m, 6H), 2.45 (br, 2H); MS (ESI) m/z(%): 744.9 $[M+H]^+$, 766.4 $[M+Na]^+$; Anal. calcd. for $C_{39}H_{33}F_4N_5O_6$ (%): C, 62.98; H, 4.47; N, 9.42. Found (%): C, 62.81; H, 4.59; N, 9.66.

6.6.7. *N-(3-fluoro-4-((6-methoxy-7-(3-morpholinopropoxy)quinolin-4-yl)oxy)phenyl)-4-(4-fluorophenyl)-3-oxo-3,4-dihydroquinoxaline-2-carboxamide* (**25**)

Yield: 66.2%; M.p.: 202.1–203.1 °C; IR (KBr) cm^{-1}: 3428.5, 3065.9, 2950.5, 2851.6, 1698.1, 1618.7, 1596.9, 1542.6, 1507.0, 1479.2, 1430.6, 1349.9, 1305.7, 1251.9, 1208.9, 1171.6, 1116.1, 846.0, 761.1; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.98 (s, 1H), 8.50 (d, *J* = 5.2 Hz, 1H), 8.32 (d, *J* = 7.6 Hz, 1H), 8.04 (dd, *J* = 12.0 Hz, 2.4 Hz, 1H), 7.57 (m, 3H), 7.42 (m, 6H), 7.26 (t, *J* = 8.8 Hz, 1H), 6.82 (d, *J* = 8.4 Hz, 1H), 6.46 (d, *J* = 5.2 Hz, 1H), 4.29 (t, *J* = 6.4 Hz, 2H), 4.05 (s, 3H), 3.78 (t, *J* = 4.4 Hz, 4H), 2.66 (t, *J* = 7.2 Hz, 2H), 2.57 (br, 4H), 2.19 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.52, 162.02, 160.13, 158.81, 155.65, 153.14, 152.34, 149.92, 148.50, 146.56, 144.30, 137.70, 136.50, 134.45, 133.63, 133.00, 132.30, 130.68, 129.82, 125.61, 123.75, 117.94, 116.69, 115.60, 109.99, 108.56,

102.36, 99.60, 67.14, 66.69, 56.16, 55.41, 53.57, 25.76; MS (ESI) m/z(%): 694.4 $[M+H]^+$; Anal. calcd. for $C_{38}H_{33}F_2N_5O_6$ (%): C, 65.79; H, 4.79; N, 10.10. Found (%): C, 65.68; H, 4.82; N, 10.20.

6.6.8. *4-(4-chlorophenyl)-N-(3-fluoro-4-((6-methoxy-7-(3-morpholinopropoxy)quinolin-4-yl)oxy)phenyl)-3-oxo-3,4-dihydroquinoxaline-2-carboxamide* (**26**)

Yield: 82.6%; M.p.: 136.5–138.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.98 (s, 1H), 8.51 (br, 1H), 8.32 (d, *J* = 8.0 Hz, 1H), 8.05 (dd, *J* = 12.0 Hz, 2.0 Hz, 1H), 7.71 (d, *J* = 8.4 Hz, 2H), 7.53 (m, 5H), 7.34 (d, *J* = 8.4 Hz, 2H), 7.27 (t, *J* = 8.8 Hz, 1H), 6.83 (d, *J* = 8.4 Hz, 1H), 6.49 (d, *J* = 4.8 Hz, 1H), 4.30 (t, *J* = 6.4 Hz, 2H), 4.05 (s, 3H), 3.85 (m, 4H), 2.74 (m, 6H), 2.27 (m, 2H); MS (ESI) m/z(%): 710.1 $[M+H]^+$; Anal. calcd. for $C_{38}H_{33}ClFN_5O_6$ (%): C, 64.27; H, 4.68; N, 9.86. Found (%): C, 64.49; H, 4.79; N, 9.76.

6.6.9. *4-(4-bromophenyl)-N-(3-fluoro-4-((6-methoxy-7-(3-morpholinopropoxy)quinolin-4-yl)oxy)phenyl)-3-oxo-3,4-dihydroquinoxaline-2-carboxamide* (**27**)

Yield: 85.9%; M.p.: 159.0–161.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.00 (s, 1H), 8.51 (br, 1H), 8.32 (d, *J* = 8.0 Hz, 1H), 8.06 (d, *J* = 12.0 Hz, 1H), 7.87 (d, *J* = 8.0 Hz, 2H), 7.57 (m, 5H), 7.27 (m, 3H), 6.83 (d, *J* = 8.4 Hz, 1H), 6.56 (br, 1H), 4.33 (t, *J* = 6.4 Hz, 2H), 4.05 (s, 3H), 3.98 (m, 4H), 2.96 (m, 6H), 2.41 (m, 2H); MS (ESI) m/z(%): 754.3 $[M+H]^+$, 776.2 $[M+Na]^+$; Anal. calcd. for $C_{38}H_{33}BrFN_5O_6$ (%): C, 60.48; H, 4.41; N, 9.28. Found (%): C, 60.32; H, 4.60; N, 9.34.

6.6.10. *N-(3-fluoro-4-((6-methoxy-7-(3-morpholinopropoxy)quinolin-4-yl)oxy)phenyl)-4-(2-fluorophenyl)-3-oxo-3,4-dihydroquinoxaline-2-carboxamide* (**28**)

Yield: 77.8%; M.p.: 120.3–121.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.91 (s, 1H), 8.49 (d, *J* = 5.2 Hz, 1H), 8.33 (d, *J* = 6.8 Hz, 1H), 8.03 (dd, *J* = 12.0 Hz, 2.4 Hz, 1H), 7.52 (m, 9H), 7.23 (t, *J* = 8.8 Hz, 1H), 6.83 (d, *J* = 8.4 Hz, 1H), 6.44 (d, *J* = 5.2 Hz, 1H), 4.27 (t, *J* = 6.4 Hz, 2H), 4.04 (s, 3H), 3.73 (t, *J* = 4.4 Hz, 4H), 2.58 (t, *J* = 7.2 Hz, 2H), 2.49 (br, 4H), 2.14 (m, 2H); MS (ESI) m/z(%): 695.1 $[M+H]^+$; Anal. calcd. for $C_{38}H_{33}F_2N_5O_6$ (%): C, 65.79; H, 4.79; N, 10.10. Found (%): C, 65.93; H, 4.85; N, 10.03.

6.6.11. *4-(2-chlorophenyl)-N-(3-fluoro-4-((6-methoxy-7-(3-morpholinopropoxy)quinolin-4-yl)oxy)phenyl)-3-oxo-3,4-dihydroquinoxaline-2-carboxamide* (**29**)

Yield: 80.2%; M.p.: 192.3–193.9 °C; IR (KBr) cm^{-1}: 3434.7, 2926.7, 1698.2, 1621.2, 1599.5, 1508.0, 1479.7, 1431.1, 1349.6, 1305.9, 1251.2, 1210.8, 1168.8, 1115.3, 855.1, 749.9; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.03 (s, 1H), 8.51 (d, *J* = 6.0 Hz, 1H), 8.35 (dd, *J* = 8.0 Hz, 1.2 Hz, 1H), 8.11 (dd, *J* = 12.0 Hz, 2.4 Hz, 1H), 7.91 (br, 1H), 7.78 (m, 1H), 7.65 (m, 4H), 7.55 (m, 2H), 7.44 (m, 1H), 7.32 (t, *J* = 8.8 Hz, 1H), 6.72 (d, *J* = 8.0 Hz, 1H), 6.64 (d, *J* = 6.0 Hz, 1H), 4.38 (t, *J* = 6.0 Hz, 2H), 4.08 (m, 7H), 3.14 (m, 6H), 2.54 (br, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.77, 158.86, 155.51, 154.97, 153.03, 152.61, 150.11, 147.53, 145.33, 144.34, 137.43, 136.72, 133.53, 133.06, 132.56, 132.39, 132.33, 131.85, 131.46, 129.55, 129.02, 125.77, 123.69, 116.84, 115.67, 115.11, 109.99, 107.67, 102.36, 99.71, 66.88, 65.79, 56.19, 55.42, 53.13, 24.97; MS (ESI) m/z(%): 710.1 $[M+H]^+$; Anal. calcd. for $C_{38}H_{33}ClFN_5O_6$ (%): C, 64.27; H, 4.68; N, 9.86. Found (%): C, 64.46; H, 4.81; N, 9.78.

6.6.12. *N-(3-fluoro-4-((6-methoxy-7-(3-morpholinopropoxy)quinolin-4-yl)oxy)phenyl)-4-(3-fluorophenyl)-3-oxo-3,4-dihydroquinoxaline-2-carboxamide* (**30**)

Yield: 65.4%; M.p.: 214.2–215.4 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.96 (s, 1H), 8.51 (d, *J* = 5.6 Hz, 1H), 8.34 (d, *J* = 6.8 Hz, 1H), 8.05 (dd, *J* = 12.0 Hz, 2.4Hz, 1H), 7.72 (m, 1H), 7.55 (m, 5H), 7.42 (m, 1H), 7.27 (d, *J* = 8.8 Hz, 1H), 7.27 (d, *J* = 8.0 Hz, 1H), 7.15 (m, 1H), 6.83 (d, *J* = 8.0 Hz, 1H), 6.49 (d, *J* = 5.2 Hz, 1H), 4.31 (t, *J* = 6.4 Hz, 2H), 4.06 (s, 3H), 3.85 (m, 4H), 2.70 (m, 6H), 2.27 (m, 2H); MS (ESI) m/z(%): 694.3 $[M+H]^+$; Anal. calcd. for $C_{38}H_{33}F_2N_5O_6$ (%): C, 65.79; H, 4.79; N, 10.10. Found (%): C, 65.91; H, 4.88; N, 10.35.

6.6.13. *4-(3-chlorophenyl)-N-(3-fluoro-4-((6-methoxy-7-(3-morpholinopropoxy)quinolin-4-yl)oxy)phenyl)-3-oxo-3,4-dihydroquinoxaline-2-carboxamide* (**31**)

Yield: 76.8%; M.p.: 135.2–136.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.96 (s, 1H), 8.51 (d, *J* = 5.2 Hz, 1H),

8.34 (dd, *J* = 8.0 Hz, 1.2 Hz, 1H), 8.06 (dd, *J* = 12.0 Hz, 2.0Hz, 1H), 7.60 (m, 6H), 7.49 (d, *J* = 9.6 Hz, 1H), 7.42 (m, 1H), 7.29 (m, 2H), 6.83 (d, *J* = 8.0 Hz, 1H), 6.51 (d, *J* = 5.2 Hz, 1H), 4.31 (t, *J* = 6.4 Hz, 2H), 4.06 (s, 3H), 3.89 (m, 4H), 2.77 (m, 6H), 2.32 (m, 2H); MS (ESI) m/z(%): 710.4 $[M+H]^+$; Anal. calcd. for $C_{38}H_{33}ClFN_5O_6$ (%): C, 64.27; H, 4.68; N, 9.86. Found (%): C, 64.44; H, 4.81; N, 10.02.

6.6.14. *4-(2,4-dichlorophenyl)-N-(3-fluoro-4-((6-methoxy-7-(3-morpholinopropoxy)quinolin-4-yl)oxy)phenyl)-3-oxo-3,4-dihydroquinoxaline-2-carboxamide* (**32**)

Yield: 67.9%; M.p.: 140.1–141.3 °C; IR (KBr) cm^{-1}: 3429.9, 2921.9, 2846.2, 1695.5, 1618.7, 1598.3, 1508.1, 1479.7, 1431.3, 1384.3, 1350.1, 1251.9, 1211.2, 1113.9, 855.0, 761.4; ^1H NMR (400 MHz, $CDCl_3$) δ 11.85 (s, 1H), 8.51 (d, *J* = 5.2 Hz, 1H), 8.35 (d, *J* = 8.0 Hz, 1H), 8.05 (dd, *J* = 12.0 Hz, 2.0 Hz, 1H), 7.79 (d, *J* = 2.0 Hz, 1H), 7.61 (m, 4H), 7.48 (m, 2H), 7.39 (d, *J* = 8.4 Hz, 1H), 7.26 (t, *J* = 8.8 Hz, 1H), 6.72 (d, *J* = 8.4 Hz, 1H), 6.46 (d, *J* = 5.2 Hz, 1H), 4.29 (t, *J* = 6.4 Hz, 2H), 4.06 (s, 3H), 3.77 (t, *J* = 4.4 Hz, 4H), 2.65 (t, *J* = 7.2 Hz, 2H), 2.56 (br, 4H), 2.18 (m, 2H); MS (ESI) m/z(%): 741.7 $[M-H]^-$, 778.4 $[M+Cl]^-$; Anal. calcd. for $C_{38}H_{32}Cl_2FN_5O_6$ (%): C, 61.30; H, 4.33; N, 9.41. Found (%): C, 61.01; H, 4.41; N, 9.56.

6.6.15. *N-(3-fluoro-4-((6-methoxy-7-(3-(piperidin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl)-4-(4-fluorophenyl)-3-oxo-3,4-dihydroquinoxaline-2-carboxamide* (**33**)

Yield: 62.2%; M.p.: 234.9–236.8 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 11.98 (s, 1H), 8.50 (d, *J* = 5.2 Hz, 1H), 8.33 (dd, *J* = 8.0 Hz, 1.2 Hz, 1H), 8.04 (dd, *J* = 12.0 Hz, 2.4 Hz, 1H), 7.58(m, 3H), 7.42 (m, 6H), 7.26 (t, *J* = 8.8 Hz, 1H), 6.83 (d, *J* = 8.4 Hz, 1H), 6.45 (d, *J* = 5.2 Hz, 1H), 4.27 (t, *J* = 6.8 Hz, 2H), 4.05 (s, 3H) , 2.54 (m, 6H), 2.16 (m, 2H), 1.61 (m, 4H), 1.46 (br, 2H); MS (ESI) m/z(%): 692.4 $[M+H]^+$; Anal. calcd. for $C_{39}H_{35}F_2N_5O_5$ (%): C, 67.72; H, 5.10; N, 10.12. Found (%): C, 67.51; H, 5.02; N, 10.24.

6.6.16. *4-(4-chlorophenyl)-N-(3-fluoro-4-((6-methoxy-7-(3-(piperidin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl)-3-oxo-3,4-dihydroquinoxaline-2-carboxamide* (**34**)

Yield: 84.1%; M.p.: 149.3–151.4 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 11.96 (s, 1H), 8.51 (d, *J* = 4.8 Hz, 1H), 8.32 (d, *J* = 8.0 Hz, 1H), 8.04 (d, *J* = 12.0 Hz, 1H), 7.71 (d, *J* = 8.4 Hz, 2H), 7.56 (m, 3H), 7.45 (m, 2H), 7.34 (d, *J* = 8.4 Hz, 2H), 7.26 (t, *J* = 8.8 Hz, 1H), 6.83 (d, *J* = 8.4 Hz, 1H), 6.45 (d, *J* = 4.8 Hz, 1H), 4.27 (t, *J* = 6.0 Hz, 2H), 4.05 (s, 3H), 2.66 (m, 6H), 2.29 (m, 2H), 1.77 (m, 4H), 1.53 (m, 2H); MS (ESI) m/z(%): 708.3 $[M+H]^+$; Anal. calcd. for $C_{39}H_{35}ClFN_5O_5$ (%): C, 66.14; H, 4.98; N, 9.89. Found (%): C, 66.38; H, 5.09; N, 9.79.

6.6.17. *N-(3-fluoro-4-((6-methoxy-7-(3-(piperidin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl)-4-(2-fluorophenyl)-3-oxo-3,4-dihydroquinoxaline-2-carboxamide* (**35**)

Yield: 73.7%; M.p.: 131.2–132.1 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 11.91 (s, 1H), 8.50 (d, *J* = 5.2 Hz, 1H), 8.33 (dd, *J* = 8.0 Hz, 1.2 Hz, 1H), 8.03 (dd, *J* = 12.0 Hz, 2.4 Hz, 1H), 7.54(m, 9H), 7.23 (t, *J* = 8.4 Hz, 1H), 6.83 (d, *J* = 8.4 Hz, 1H), 6.44 (d, *J* = 5.2 Hz, 1H), 4.26 (t, *J* = 6.8 Hz, 2H), 4.02 (s, 3H), 2.89 (m, 6H), 2.42 (m, 2H), 1.91 (m, 4H), 1.60 (br, 2H); MS (ESI) m/z(%): 692.1 $[M+H]^+$; Anal. calcd. for $C_{39}H_{35}F_2N_5O_5$ (%): C, 67.72; H, 5.10; N, 10.12. Found (%): C, 67.88; H, 5.21; N, 10.26.

6.6.18. *4-(2-chlorophenyl)-N-(3-fluoro-4-((6-methoxy-7-(3-(piperidin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl)-3-oxo-3,4-dihydroquinoxaline-2-carboxamide* (**36**)

Yield: 77.5%; M.p.: 165.0–166.7 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 12.08 (s, 1H), 8.51 (d, *J* = 6.4 Hz, 1H), 8.34 (d, *J* = 8.0 Hz, 1H), 8.29 (br, 1H), 8.15 (d, *J* = 12.4 Hz, 1H), 7.79 (m, 1H), 7.62 (m, 6H), 7.45 (m, 1H), 7.34 (t, *J* = 8.4 Hz, 1H), 6.78 (d, *J* = 6.4 Hz, 1H), 6.72 (d, *J* = 8.0 Hz, 1H), 4.44 (t, *J* = 6.4 Hz, 2H), 4.10 (s, 3H), 3.62 (br, 2H), 3.31 (br, 2H), 2.84 (br, 2H), 2.63 (br, 2H), 2.33 (br, 3H), 1.89 (br, 3H); MS (ESI) m/z(%): 708.5 $[M+H]^+$; Anal. calcd. for $C_{39}H_{35}ClFN_5O_5$ (%): C, 66.14; H, 4.98; N, 9.89. Found (%): C, 66.25; H, 5.06; N, 9.94.

6.6.19. *N-(3-fluoro-4-((6-methoxy-7-(3-(4-methylpiperidin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl)-4-(4-fluorophenyl)-3-oxo-3,4-dihydroquinoxaline-2-carboxamide* (**37**)

Yield: 65.4%; M.p.: 232.7–233.8 °C; IR (KBr) cm^{-1}: 3433.9, 3071.4, 2923.4, 1702.1, 1597.2, 1552.4, 1508.2,

1476.2, 1430.5, 1349.7, 1307.2, 1252.2, 1209.6, 1175.9, 1091.7, 853.5, 766.0; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.98 (s, 1H), 8.50 (d, *J* = 5.2 Hz, 1H), 8.33 (dd, *J* = 8.0 Hz, 1.2 Hz, 1H), 8.04 (dd, *J* = 12.0 Hz, 2.4 Hz, 1H), 7.59 (m, 3H), 7.41 (m, 6H), 7.26 (t, *J* = 8.8 Hz, 1H), 6.83 (d, *J* = 8.4 Hz, 1H), 6.46 (d, *J* = 5.2 Hz, 1H), 4.27 (t, *J* = 6.4 Hz, 2H), 4.05 (s, 3H), 3.14 (br, 2H), 2.82 (br, 2H), 2.25 (m, 4H), 1.72 (br, 2H), 1.48 (br, 3H), 0.98 (d, *J* = 5.6 Hz, 3H); MS (ESI) m/z(%): 706.4 $[M+H]^+$; Anal. calcd. for $C_{40}H_{37}F_2N_5O_5$ (%): C, 68.07; H, 5.28; N, 9.92. Found (%): C, 68.18; H, 5.22; N, 9.99.

6.6.20. *4-(4-chlorophenyl)-N-(3-fluoro-4-((6-methoxy-7-(3-(4-methylpiperidin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl)-3-oxo-3,4-dihydroquinoxaline-2-carboxamide* (**38**)

Yield: 83.8%; M.p.: 194.5–195.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.96 (s, 1H), 8.51 (d, *J* = 4.8 Hz, 1H), 8.33 (d, *J* = 8.0 Hz, 1H), 8.04 (dd, *J* = 12.0 Hz, 2.4 Hz, 1H), 7.71 (d, *J* = 8.4 Hz, 2H), 7.58 (m, 3H), 7.46 (m, 2H), 7.34 (d, *J* = 8.4 Hz, 2H), 7.26 (t, *J* = 8.8 Hz, 1H), 6.83 (d, *J* = 8.4 Hz, 1H), 6.45 (d, *J* = 4.8 Hz, 1H), 4.27 (t, *J* = 6.4 Hz, 2H), 4.06 (s, 3H), 2.94 (m, 2H), 2.57 (m, 2H), 2.16 (m, 2H), 1.98 (m, 2H), 1.65 (m, 2H), 1.27 (m, 3H), 0.94 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.93, 158.74, 155.51, 153.17, 152.33, 149.89, 148.72, 146.93, 144.28, 137.90, 137.77, 136.58, 136.42, 136.33, 134.21, 133.66, 133.26, 132.99, 132.34, 131.07, 129.26, 125.67, 123.79, 116.66, 115.59, 110.10, 109.87, 108.77, 102.33, 99.53, 67.62, 56.15, 55.44, 54.02, 34.31, 30.81, 26.51, 21.89; MS (ESI) m/z(%): 722.4 $[M+H]^+$; Anal. calcd. for $C_{40}H_{37}ClFN_5O_5$ (%): C, 66.52; H, 5.16; N, 9.70. Found (%): C, 66.78; H, 5.29; N, 9.89.

6.6.21. *N-(3-fluoro-4-((6-methoxy-7-(3-(4-methylpiperidin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl)-4-(2-fluorophenyl)-3-oxo-3,4-dihydroquinoxaline-2-carboxamide* (**39**)

Yield: 64.9%; M.p.: 131.5–132.6 °C; IR (KBr) cm^{-1}: 3409.3, 2917.6, 2796.7, 1704.9, 1625.7, 1557.6, 1499.2, 1476.8, 1432.1, 1349.9, 1307.0, 1248.2, 1214.7, 1175.9, 1089.2, 849.9, 762.9; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.91 (s, 1H), 8.50 (d, *J* = 5.2 Hz, 1H), 8.32 (d, *J* = 8.0 Hz, 1H), 8.03 (dd, *J* = 12.0 Hz, 2.4 Hz, 1H), 7.54 (m, 9H), 7.23 (t, *J* = 8.8 Hz, 1H), 6.83 (d, *J* = 8.0 Hz, 1H), 6.46 (d, *J* = 5.2 Hz, 1H), 4.26 (t, *J* = 6.4 Hz, 2H), 4.02 (s, 3H), 3.36 (br, 2H), 3.02 (br, 2H), 2.44 (m, 4H), 1.65 (m, 5H), 1.01 (d, *J* = 6.0 Hz, 3H); MS (ESI) m/z(%): 706.2 $[M+H]^+$; Anal. calcd. for $C_{40}H_{37}F_2N_5O_5$ (%): C, 68.07; H, 5.28; N, 9.92. Found (%): C, 68.29; H, 5.35; N, 10.03.

6.6.22. *4-(2-chlorophenyl)-N-(3-fluoro-4-((6-methoxy-7-(3-(4-methylpiperidin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl)-3-oxo-3,4-dihydroquinoxaline-2-carboxamide* (**40**)

Yield: 71.2%; M.p.: 162.2–163.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.96 (s, 1H), 8.52 (d, *J* = 5.2 Hz, 1H), 8.35 (d, *J* = 8.0 Hz, 1H), 8.06 (dd, *J* = 12.0 Hz, 2.0 Hz, 1H), 7.79 (m, 1H), 7.54 (m, 8H), 7.26 (t, *J* = 8.4 Hz, 1H), 6.71 (d, *J* = 8.4 Hz, 1H), 6.48 (d, *J* = 5.2 Hz, 1H), 4.29 (t, *J* = 6.8 Hz, 2H), 4.04 (s, 3H), 3.60 (br, 2H), 3.26 (m, 2H), 2.60 (m, 4H), 1.91 (br, 5H), 1.07 (d, *J* = 6.4 Hz, 3H); MS (ESI) m/z(%): 722.4 $[M+H]^+$; Anal. calcd. for $C_{40}H_{37}ClFN_5O_5$ (%): C, 66.52; H, 5.16; N, 9.70. Found (%): C, 66.75; H, 5.26; N, 9.82.

6.6.23. *N-(3-fluoro-4-((6-methoxy-7-(3-(4-methylpiperazin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl)-4-(4-fluorophenyl)-3-oxo-3,4-dihydroquinoxaline-2-carboxamide* (**41**)

Yield: 68.1%; M.p.: 125.0–126.8 °C; IR (KBr) cm^{-1}: 3418.1, 2926.8, 1695.5, 1621.4, 1541.9, 1507.8, 1479.3, 1432.0, 1349.8, 1305.9, 1250.3, 1209.7, 1169.8, 1091.9, 854.3, 762.7; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.99 (s, 1H), 8.50 (d, *J* = 5.2 Hz, 1H), 8.33 (d, *J* = 8.0 Hz, 1H), 8.05 (dd, *J* = 12.0 Hz, 2.0 Hz, 1H), 7.59 (m, 3H), 7.43 (m, 6H), 7.26 (t, *J* = 8.8 Hz, 1H), 6.83 (d, *J* = 8.4 Hz, 1H), 6.46 (d, *J* = 5.2 Hz, 1H), 4.28 (t, *J* = 6.4 Hz, 2H), 4.05 (s, 3H), 3.20-2.61 (m, 10H), 2.54 (s, 3H), 2.17 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.51, 162.01, 160.00, 158.83, 155.65, 153.15, 152.22, 149.83, 148.72, 146.78, 144.28, 137.81, 136.48, 134.44, 133.66, 133.01, 132.31, 130.67, 129.84, 125.64, 123.78, 118.06, 117.83, 116.70, 115.65, 110.13, 109.90, 108.67, 102.35, 99.58, 67.01, 56.14, 54.55, 54.50, 51.94, 45.17, 26.13; MS (ESI) m/z(%): 707.2 $[M+H]^+$; Anal. calcd. for $C_{39}H_{36}F_2N_6O_5$ (%): C, 66.28; H, 5.13; N, 11.89. Found (%): C, 66.48; H, 5.23; N, 11.80.

6.6.24. *4-(4-chlorophenyl)-N-(3-fluoro-4-((6-methoxy-7-(3-(4-methylpiperazin-1-yl)propoxy)quinolin-4-yl)oxy)p*

henyl)-3-oxo-3,4-dihydroquinoxaline-2-carboxamide (**42**)

Yield: 78.9%; M.p.: 216.1–217.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.96 (s, 1H), 8.50 (d, *J* = 5.2 Hz, 1H), 8.33 (dd, *J* = 8.0 Hz, 1.2 Hz, 1H), 8.04 (dd, *J* = 12.0 Hz, 2.0 Hz, 1H), 7.71 (d, *J* = 8.8 Hz, 2H), 7.59 (m, 3H), 7.46 (m, 2H), 7.34 (d, *J* = 8.8 Hz, 2H), 7.26 (t, *J* = 8.8 Hz, 1H), 6.83 (d, *J* = 8.4 Hz, 1H), 6.46 (d, *J* = 5.2 Hz, 1H), 4.28 (t, *J* = 6.4 Hz, 2H), 4.05 (s, 3H), 3.23-2.55 (m, 10H), 2.51 (s, 3H), 2.17 (m, 2H); MS (ESI) m/z(%): 723.4 $[M+H]^+$; Anal. calcd. for $C_{39}H_{36}ClFN_6O_5$ (%): C, 64.77; H, 5.02; N, 11.62. Found (%): C, 64.98; H, 4.89; N, 11.78.

6.6.25. *N-(3-fluoro-4-((6-methoxy-7-(3-(4-methylpiperazin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl)-4-(2-fluorophenyl)-3-oxo-3,4-dihydroquinoxaline-2-carboxamide* (**43**)

Yield: 71.6%; M.p.: 123.9–125.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.91 (s, 1H), 8.49 (d, *J* = 5.2 Hz, 1H), 8.33 (d, *J* = 8.0 Hz, 1H), 8.03 (dd, *J* = 12.0 Hz, 2.4 Hz, 1H), 7.54 (m, 9H), 7.24 (t, *J* = 8.8 Hz, 1H), 6.83 (d, *J* = 8.4 Hz, 1H), 6.44 (d, *J* = 5.2 Hz, 1H), 4.26 (t, *J* = 6.4 Hz, 2H), 4.03 (s, 3H), 3.20-2.41 (m, 10H), 2.38 (s, 3H), 2.13 (m, 2H); MS (ESI) m/z(%): 707.8 $[M+H]^+$; Anal. calcd. for $C_{39}H_{36}F_2N_6O_5$ (%): C, 66.28; H, 5.13; N, 11.89. Found (%): C, 66.15; H, 5.04; N, 11.70.

6.6.26. *4-(2-chlorophenyl)-N-(3-fluoro-4-((6-methoxy-7-(3-(4-methylpiperazin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl)-3-oxo-3,4-dihydroquinoxaline-2-carboxamide* (**44**)

Yield: 63.3%; M.p.: 170.5–171.8 °C; IR (KBr) cm^{-1}: 3412.9, 2923.1, 2846.2, 1695.5, 1618.7, 1596.7, 1479.9, 1429.4, 1382.7, 1349.8, 1305.9, 1251.2, 1211.0; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.96 (s, 1H), 8.51 (d, *J* = 5.2 Hz, 1H), 8.35 (d, *J* = 8.0 Hz, 1H), 8.06 (dd, *J* = 12.0 Hz, 2.4 Hz, 1H), 7.79 (m, 1H), 7.63 (m, 5H), 7.45 (m, 3H), 7.26 (t, *J* = 8.8 Hz, 1H), 6.71 (d, *J* = 8.4 Hz, 1H), 6.46 (d, *J* = 5.2 Hz, 1H), 4.29 (t, *J* = 6.4 Hz, 2H), 4.06 (s, 3H), 3.30-2.60 (m, 10H), 2.57 (s, 3H), 2.17 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.00, 158.82, 155.63, 154.96, 153.15, 152.23, 149.83, 148.76, 146.81, 144.39, 137.80, 136.51, 133.52, 133.05, 132.58, 132.39, 132.35, 131.83, 131.45, 129.56, 129.01, 125.74, 123.75, 116.77, 115.51, 115.09, 109.95, 108.70, 102.35, 99.58, 67.08, 56.15, 54.63, 52.18, 45.34, 29.69, 26.17; MS (ESI) m/z(%): 724.3 $[M+H]^+$; Anal. calcd. for $C_{39}H_{36}ClFN_6O_5$ (%): C, 64.77; H, 5.02; N, 11.62. Found (%): C, 64.91; H, 5.21; N, 11.78.

6.6.27. *N-(3-fluoro-4-((6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl)-4-(4-fluorophenyl)-3-oxo-3,4-dihydroquinoxaline-2-carboxamide* (**45**)

Yield: 59.3%; M.p.: 218.2–219.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.98 (s, 1H), 8.51 (d, *J* = 5.2 Hz, 1H), 8.33 (dd, *J* = 8.0 Hz, 1.2 Hz, 1H), 8.04 (dd, *J* = 12.0 Hz, 2.0Hz, 1H), 7.58 (m, 3H), 7.43 (m, 6H), 7.26 (t, *J* = 8.8 Hz, 1H), 6.82 (d, *J* = 8.4 Hz, 1H), 6.45 (d, *J* = 5.2 Hz, 1H), 4.29 (t, *J* = 6.4 Hz, 2H), 4.06 (s, 3H), 2.72 (t, *J* = 7.2 Hz, 2H), 2.60 (m, 4H), 2.20 (m, 2H), 1.83 (m, 4H); MS (ESI) m/z(%): 678.8 $[M+H]^+$; Anal. calcd. for $C_{38}H_{33}F_2N_5O_5$ (%): C, 67.35; H, 4.91; N, 10.33. Found (%): C, 67.22; H, 4.98; N, 10.44.

6.6.28. *4-(2-chlorophenyl)-N-(3-fluoro-4-((6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl)-3-oxo-3,4-dihydroquinoxaline-2-carboxamide* (**46**)

Yield: 61.3%; M.p.: 197.3–197.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.87 (s, 1H), 8.42 (d, *J* = 5.2 Hz, 1H), 8.27 (dd, *J* = 8.0 Hz, 1.6 Hz, 1H), 7.97 (dd, *J* = 12.0 Hz, 2.4 Hz, 1H), 7.69 (m, 1H), 7.52 (m, 5H), 7.37 (m, 3H), 7.17 (t, *J* = 8.8 Hz, 1H), 6.62 (d, *J* = 7.2 Hz, 1H), 6.38 (d, *J* = 5.2 Hz, 1H), 4.20 (t, *J* = 6.0 Hz, 2H), 3.96 (s, 3H), 3.02 (m, 6H), 2.31 (m, 2H), 1.95 (m, 4H); MS (ESI) m/z(%): 694.4 $[M+H]^+$; Anal. calcd. for $C_{38}H_{33}ClFN_5O_5$ (%): C, 65.75; H, 4.79; N, 10.09; Found (%): C, 65.89; H, 4.88; N, 9.02.

6.7. *Pharmacology*

6.7.1. MTT assay in vitro

The anti-proliferative activities of compounds **19–46** were evaluated against HT-29, H460, A549 and MKN-45 cell lines using the standard MTT assay *in vitro*, with Foretinib as the positive control. The cancer cell lines were cultured in minimum essential medium (MEM) supplement with 10% fetal bovine serum (FBS). Approximate 4 × 10^3 cells, suspended in MEM medium, were plated onto each well of a 96-well plate and incubated in 5% CO_2 at 37

°C for 24 h. The tested compounds at the indicated final concentrations were added to the culture medium and the cell cultures were continued for 72 h. Fresh MTT was added to each well at a terminal concentration of 5 μg/mL, and incubated with cells at 37 °C for 4 h. The formazan crystals were dissolved in 100 mL DMSO each well, and the absorbency at 492 nm (for absorbance of MTT formazan) and 630 nm (for the reference wavelength) was measured with an ELISA reader. All compounds were tested three times in each of the cell lines. The results expressed as IC_{50} (inhibitory concentration 50%) were the averages of three determinations and calculated by using the Bacus Laboratories Incorporated Slide Scanner (Bliss) software.

6.7.2. HTRF kinase assay

The c-Met kinase activity was evaluated using homogeneous time-resolved fluorescence (HTRF) assays as previously reported protocol.[28,29] In addition, the most promising compound **41** was further evaluated against other five tyrosine kinase (c-Kit, PDGFRα, Ron, VEGFR-2, Flt-3, EGFR and ALK) using the same screening method. Briefly, 20 μg/mL poly (Glu, Tyr) 4:1 (Sigma) was preloaded as a substrate in 384-well plates. Then 50 μL of 10 mM ATP (Invitrogen) solution diluted in kinase reaction buffer (50 mM HEPES, Ph 7.0, 1 M DTT, 1 M $MgCl_2$, 1 M $MnCl_2$, and 0.1% NaN_3) was added to each well. Various concentrations of compounds diluted in 10 μL of 1% DMSO (v/v) used as the negative control. The kinase reaction was initiated by the addition of purified tyrosine kinase proteins diluted in 39 μL of kinase reaction buffer solution. The incubation time for the reactions was 30 min at 25 °C and the reactions were stopped by the addition of 5 μL of Streptavidin-XL665 and 5 μL Tk Antibody Cryptate working solution to all of wells. The plate was read using Envision (Perkin Elmer) at 320 nm and 615 nm. The inhibition rate (%) was calculated using the following equation: % inhibition = 100 – [(Activity of enzyme with tested compounds – Min)/(Max – Min)] × 100 (Max: the observed enzyme activity measured in the presence of enzyme, substrates, and cofactors; Min: the observed enzyme activity in the presence of substrates, cofactors and in the absence of enzyme). IC_{50} values were calculated from the inhibition curves.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found in the online version,

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Legends

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

Figure 2. Anticancer agents bearing quinoxalinone moiety

Figure 3. Design strategy and general structure of the target compounds

Scheme 1. Reagents and conditions: (a) amines, NaH, DMF, RT, 16 h; (b) Fe powder, HOAc, CH_3COOEt/H_2O, reflux, 6 h; (c) diethyl ketomalonate, toluene, reflux, 12 h; (d) LiOH, THF/ H_2O, RT, 1.5 h, then 6 N HCl; (e) toluene, $SOCl_2$, reflux, 5 h; Na_2CO_3, CH_2Cl_2, 25 °C, 3 h.

Table 1
Structures and cytotoxicity of compounds 19-46

Table 2
c-Met kinase activity of selected compounds **25, 26, 28, 29, 33, 37, 39, 41, 44** and **Foretinib** *in vitro*.

Table 3
Inhibition of tyrosine kinases by compound **41**

Figure 4. A: The c-Met active site in complex with compound **41**, the proteins were displayed by silver ribbon. Compound 41 was shown in colored sticks (cyan:carbon atom, blue: nitrogen atom, red: oxygen atom, light cyan: fluorine atom). H-bonding interactions between the 41 and c-Met were indicated with dotted lines in green, and Pi-Sigma interaction was shown in purple dotted lines. B : Superposed docking poses of foretinib (purple) and compound **41** (blue) in c-Met.

- ►A series of 4-phenoxyquinoline derivatives bearing an 3-oxo-3,4-dihydroquinoxaline moiety were designed and synthesized.
- ►The target compounds showed potent antitumor activity.
- ►Compound **41** showed more potent against five cell lines than foretinib.
- ►Compound **41** showed an IC_{50} value of 0.90 nM against c-Met kinase.
- ►Compound **41** showed moderate-to-excellent selectivity against 5 other RTK kinases.

Graphical abstract

A series of novel 4-(2-fluorophenoxy)quinoline derivatives containing 3-oxo-3,4-dihydroquinoxaline moiety were designed, synthesized and evaluated for their cytotoxicity, enzymatic assays and docking analysis.