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Original article

Design, synthesis and structure–activity relationships of novel 4-phenoxyquinoline derivatives containing pyridazinone moiety as potential antitumor agents

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ABSTRACT

A series of novel 4-phenoxyquinoline derivatives containing pyridazinone moiety were synthesized and evaluated for their *in vitro* cytotoxic activity against five cancer cell lines (HT-29, H460, A549, MKN-45, and U87MG). Most of the compounds exhibited moderate-to-significant cytotoxicity and high selectivity against one or more cell lines. Compounds **15a**, **20a**, **15b**, **15c**, **20d**, and **16e** were further examined for their inhibitory activity against c-Met kinase. The most promising compound **15a** (c-Met half-maximal inhibitory concentration [IC_{50}] = 2.15 nM) showed remarkable cytotoxicity against HT-29, H460, and A549 cell lines with IC_{50} values of 0.10 μM, 0.13 μM, and 0.05 μM, respectively, and thus it was 1.5- to 2.3-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.

1. Introduction

Cancer, also known as malignancy, is a life-threatening disease and the leading cause of death worldwide [1]. Although cancer chemotherapy has entered a new field of molecularly targeted therapeutics, drug resistance and adverse side effects are still vital problems [2,3]. Therefore, the search for highly efficient and safe antitumor agents has become more urgent than ever before [4,5].

The receptor, tyrosine kinase c-Met, is expressed by binding to its natural ligand hepatocyte growth factor, also known as the scatter factor (HGF/SF). One mechanism for c-Met deregulation leading to cancer involves gain-of-function mutations [6]. Therefore, the development of small molecules targeting these mutations is beneficial for affected patients. Recently, considerable efforts have been made for the synthesis of novel 6,7-disubstituted-4-phenoxyquinolines because of their reported antitumor activity [7–13]. Many of these derivatives have been approved as drugs or in clinical/preclinical development, such as foretinib, cabozantinib, Amgen, AM 7, and MG10 (**1**–**5**, Fig. 1). The main modification of these quinoline derivatives was focused on the 5-atom linker containing hydrogen-bond donors and acceptors between moiety A and moiety B, which is known as "**5 atoms regulation**" in our previous study [14]. Moreover, the modifications of the A moiety usually focused on the 7-position of quinoline, where the methoxy group was replaced by a water-soluble fragment, such as a 3-morpholinopropoxy group, while slight change was made to moiety B except the phenyl ring or substituted phenyl ring. Therefore, these structural characteristics indicated that a new linker should be developed for this series of quinoline derivatives. In our previous study, we introduced 1,4-dihydrocinnoline-3-carboxamide, *N*-acyl hydrazine, and pyridine/pyrimidine-based scaffolds as a part of the 5-atom linker, and the resulting derivatives (**6**–**8**, Fig. 1) showed excellent antitumor activity [15–17].

To our knowledge, as an extension of our work on the development of novel potent c-Met inhibitors, we noticed that compound **1** (Fig. 2), which contain pyridazinone moiety displayed a multitude of biological activities, including antitumor, antibacterial, antihypertensive, antiplatelet, and anti-inflammatory activities [18–22]. Recently, some pyridazinone derivatives have been reported as the core skeleton for the design of potent and inhibitors for Vascular adhesion protein-1 (VAP-1), especially 6-oxo-1,6-

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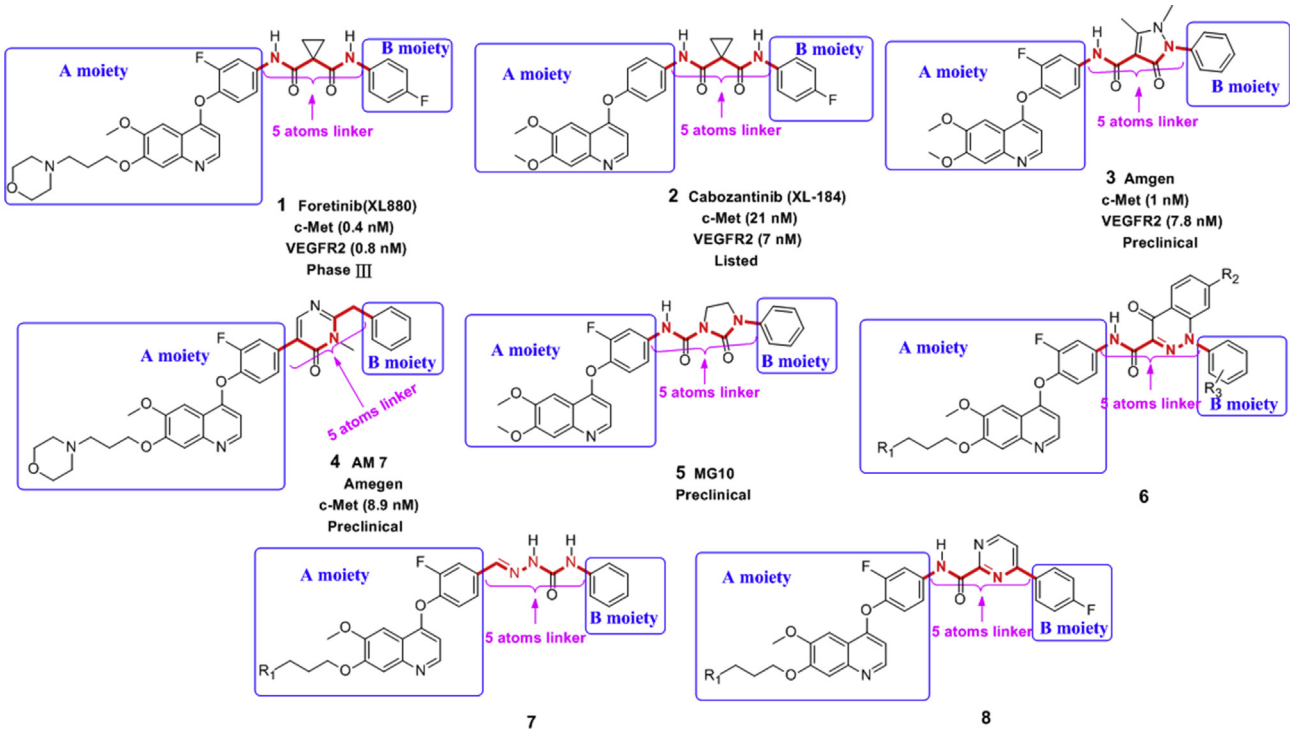


Fig. 1. Structures of small-molecule c-Met inhibitors based on the 6,7-disubstituted-4-phenoxyquinoline scaffold.

dihydropyridazinone being the most potent and against human VAP-1 enzyme activity with IC_{50} values from 290 to 20 nM. However, 1403985-31-8 (**compound 2**, Fig. 2), a potent small-molecule-selective c-Met inhibitor, was reported to be highly active against NIH3T3/TPR-Met cancer cells with IC_{50} values of 1–5 μM *in vitro* [23–25]. This pyridazinone-3-carboxamide framework conforms to **"5 atoms regulation"**, and contains both hydrogen-bond donor and acceptor, thus making it a satisfactory linker. So we introduced 6-oxo-1,6-dihydropyridazinone-3-carboxamide framework as a part of the 5-atom linker to the 4-phenoxyquinoline moiety via an amide bond.

Using foretinib as the leading compound, a series of 4-phenoxyquinoline derivatives were designed and synthesized (**I**, Fig. 2), in which the 6-oxo-1,6-dihydropyridazinone-3-carboxamide framework attached to the C-4′ position of the moiety A acted as the 5-atom linker. Meanwhile, the morpholinyl group at the 7-position of quinoline scaffold was replaced by several water-soluble groups including pyrrolidinyl, piperidinyl, 4-methyl piperazinyl and 4-methyl piperidinyl groups. In addition, various substituents (R_2), particularly mono-electron-withdrawing groups (mono-EWGs) were introduced into the phenyl ring (B moiety) to investigate their effect on activity. In this paper, we report the synthesis of these quinoline derivatives and evaluate their *in vitro* antitumor activities against five human cancer cell lines and c-Met kinase.

2. Chemistry

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

The key intermediates 6,7-disubstituted-4-phenoxyquinolines **8a**–**e** were synthesized using a convenient eight-step procedure starting from 1-(4-hydroxy-3-methoxyphenyl)ethanone (Scheme 1), which was illustrated in detail in our previous study [14,26].

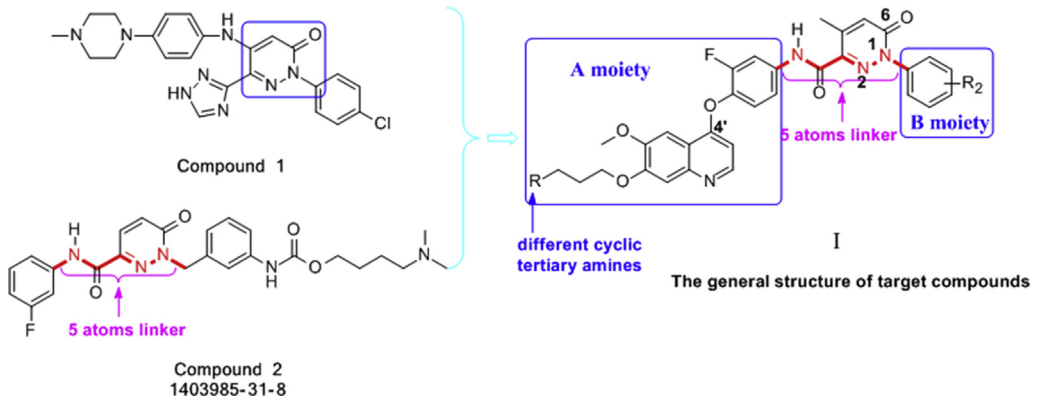
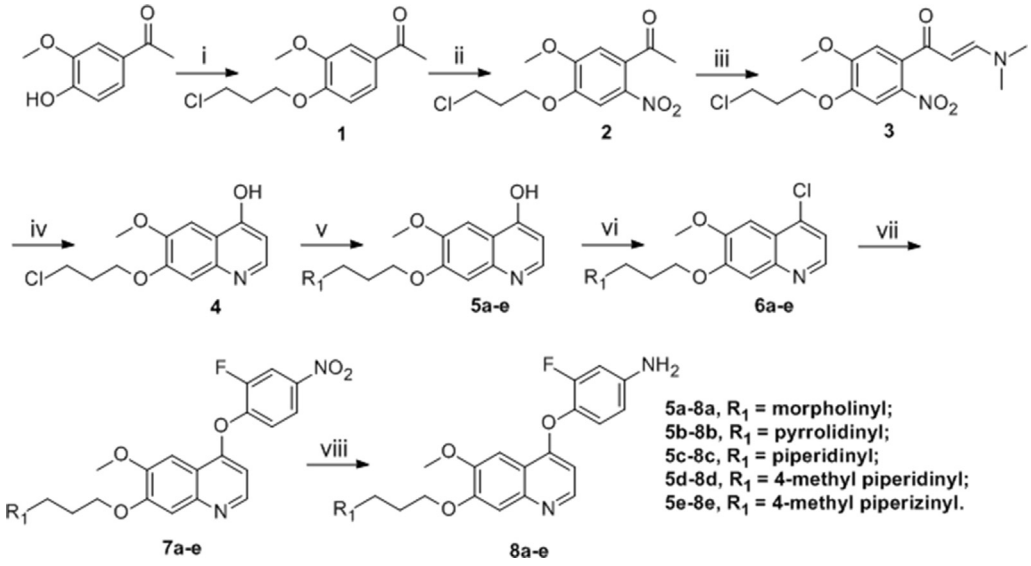


Fig. 2. Structure of compound **1**, **2** and the target compounds.



Scheme 1. Reagents and conditions: (i) $Br(CH_2)_3Cl$, acetone, 0 °C, 30 min, rt., 12 h; (ii) 98%HNO_3, CH_2Cl_2, 0 °C, 4 h; (iii) DMF-DMA, toluene, 110 °C, 10 h; (iv) Fe powder, HOAc, rt., 30 min, 80 °C, 2 h; (v) secondary amines, CH_3CN, 85 °C, 10 h; (vi) $POCl_3$, 85 °C, 6 h; (vii) 2-fluoro-4-nitrophenol, PhCl, 140 °C, 30 h; (viii) Fe powder, NH_4Cl (cat.), $EtOH/H_2O$, reflux, 5 h.

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

The synthesis of target compounds **13a**–**20e** is summarized in Scheme 2. The condensation of commercially available ethyl acetylacetate with different substituted diazotized anilines in the presence of sodium acetate in ethanol/water mixture afforded intermediates **9** as yellow solids. The cyclization of **9** with (ethoxycarbonylmethylene)triphenylphosphorane in refluxing toluene under basic conditions afforded compounds **10** [27], which were converted to acids **11** using 10% sodium hydroxide solution at 50 °C for 4 h. Acids **11** were refluxed in toluene and $SOCl_2$ for 5 h to afford acyl chlorides **12**, which were then condensed with intermediates **8a**–**e** in the presence of sodium carbonate in dichloromethane at room temperature overnight to afford the target compounds **13a**–**20e** [28].

3. Results and discussion

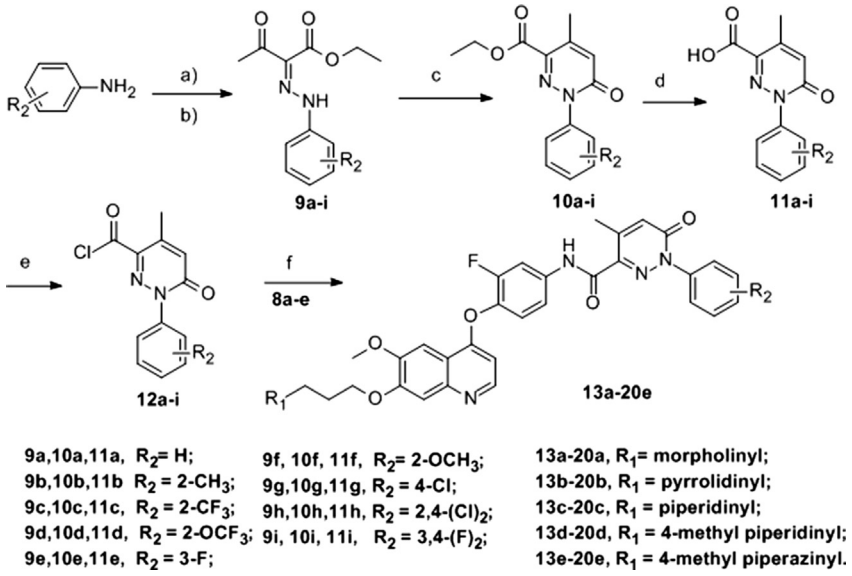
3.1. In vitro cytotoxicity and structure–activity relationships

The cytotoxicity of the target compounds were evaluated against the cancer cells lines HT-29 (human colon cancer), H460 (human lung cancer), A549 (human lung adenocarcinoma), MKN-45 (human gastric cancer), and U87MG (human glioblastoma) by using MTT assay with foretinib as the positive control. 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 moderate-to-excellent cytotoxic activity against different cancer cells with potencies in the single-digit μM range, indicating that the introduction of 6-oxo-1,6-dihydropyridazinone-3-carboxamide moiety as the linker maintained potent cytotoxicity. In contrast, the introduction of different R_1 groups only slightly affected cytotoxicity, indicating that the R_1 group was insignificant. For example, compounds **16a** (R_1 = morpholinyl, R_2 = 2-trifluoromethoxyl), **15b** (R_1 = pyrrolidinyl, R_2 = 2-trifluoromethyl), **16c** (R_1 = piperidinyl, R_2 = 2-trifluoromethoxyl), **16d** (R_1 = 4-methyl piperidinyl, R_2 = 2-trifluoromethoxyl), and **16e** (R_1 = 4-methyl piperazinyl, R_2 = 2-trifluoromethoxyl) exhibited comparable antitumor activity with IC_{50} in the range from 0.09 to 0.13 μM against A549 cells. Moreover, most of the target compounds showed higher selectivity against HT-29 and H460 cells than against the other three cell lines. Notably, The IC_{50} values of the most promising compound **15a** were 0.10 μM, 0.13 μM, 0.05 μM, 0.03 μM, and 1.06 μM against HT-29, H460, A549, MKN-45, and U87MG cell lines, respectively.

Preliminary structure–activity relationships (SARs) indicated that different biological properties were observed when various R_2 groups were introduced into the phenyl ring (moiety B). Introduction of mono-EWGs and double-EWGs exhibited a positive effect on the cytotoxic activity. However, the electron-donating groups (EDGs) exhibited a negative effect. Compound **13c**, with no substitute on the phenyl ring, displayed strong cytotoxicity with an IC_{50} of 0.16 μM against HT-29 cells. The addition of mono-EWGs, particularly trifluoromethyl and trifluoromethoxyl groups clearly improved activity, such as compound **15a** (R_2 = 2-trifluoromethyl, IC_{50} = 0.10 μM) and **16b** (R_2 = 2-trifluoromethoxyl, IC_{50} = 0.18 μM), which could be further confirmed by introduction of these groups in compounds **15c**, **15d**, and **16e**. In contrast, the introduction of EDGs (**14a**, R_2 = 2-methyl, IC_{50} = 1.01 μM; **18c**, R_2 = 4-methoxy, IC_{50} = 3.20 μM) reduced the activity by 5.3-fold and 16.7-fold against HT-29 cells compared to (**13c,** R_2 = H, IC_{50} = 0.16 μM), and the same trend was observed for compounds **14b**, **18a**, and **18e**. However, the incorporation of double-EWGs (**20a**, R_2 = 3,4-difluoro, IC_{50} = 0.16 μM [HT-29]; **20d**, R_2 = 2,4-dichloro, IC_{50} = 0.17 μM [HT-29]) also improved the inhibitory activity of the compounds. For example, the activities of compounds **20b** (R_1 = pyrrolidinyl, R_2 = 3,4-difluoro) and **20e** (R_1 = 4-methyl piperazinyl, R_2 = 3,4-difluoro) increased by 1.1-fold and 1.5-fold against H460 cells.

Further analysis revealed that the position of R_2 group was closely related to antitumor activity as well. The compounds with a substituent at the 3-position of the phenyl ring (**17a**, IC_{50} = 0.29 μM [H460]) exhibited a higher potency than those with a substituent at the 4-position of the phenyl ring (**19a**, IC_{50} = 0.38 μM [H460]). The pharmacological data indicate that an appropriate amount of electron density on the pyridazinone ring was probably essential to enhance the antitumor activity. The pyridazinone ring, which is a



Scheme 2. Reagents and conditions: (a) $NaNO_2$, HCl, H_2O, 0 °C, 30 min; (b) Ethyl acetylacetate, C_2H_5COONa, EtOH/H_2O, 0–25 °C, 2 h; (c) $Ph_3P{=}CHCOOC_2H_5$, PhMe, reflux, 12 h; (d) 10% NaOH, EtOH/THF, 50 °C, 4 h; (e) PhMe, $SOCl_2$, reflux, 5 h; (f) Na_2CO_3, CH_2Cl_2, 25 °C, 3 h.

part of the 5-atom linker, requires strong EWGs (such as a trifluoromethyl group) to reduce its electron density. The target compounds of the water solubility were measured (refer to the Chinese pharmacopoeia 2010 edition of the second collection method). All the target compounds showed freely to sparingly solubility, for example, compounds **15a** (R_1 = morpholinyl, R_2 = 2-trifluoromethyl, 6.7 mg/μL), **16b** (R_1 = pyrrolidinyl, R_2 = 2-trifluoromethoxyl, 9.2 mg/μL), **17c** (R_1 = piperidinyl, R_2 = 3-difluoro, 18.4 mg/μL), **20d** (R_1 = 4-methyl piperidinyl, R_2 = 2,4-dichloro, 27.8 mg/μL), and **16e** (R_1 = 4-methyl piperazinyl, R_2 = 4-methoxyl, 53.2 mg/μL).

The pharmacological data showed that the hydrophobic pocket can accommodate the EWGs of moiety B. The SARs based on the IC_{50} values (Table 1) showed that three main factors, the water solubility of different cyclic tertiary amines, electronic effects, and size/number of the substituent on the phenyl ring, were responsible for the antitumor activity.

3.2. In vitro enzymatic assays

As shown in Table 2, all the six tested compounds exhibited excellent c-Met enzymatic potency with IC_{50} values in the single-digit nanomolar range, indicating that the inhibition of c-Met may be a mechanism for the antitumor effect. Compound **15a** showed the most potent activity with an IC_{50} value of 2.15 nM, which was comparable to that of the positive control, foretinib (IC_{50} = 1.16 nM), indicating that this compound deserves further study with regard to its application in the treatment of cancer.

3.3. Enzymatic selectivity assays

Compound **15a** (c-Met half-maximal inhibitory concentration [IC_{50}] = 2.15 nM) showed remarkable cytotoxicity against HT-29, H460, and A549 cell lines with IC_{50} values of 0.10 μM, 0.13 μM, and 0.05 μM, respectively. In order to examine the selectivity of compound **15a** on c-Met over other kinases, it was screened against other 5 tyrosine kinases (Table 3). Compared to its high potency against c-Met (IC_{50} = 2.15 nM), **15a** also exhibited high inhibitory effects against c-Kit (IC_{50} = 4.32 nM) and Flt-3 (IC_{50} = 9.28 nM). Moreover, compound **15a** exhibited inhibitory effects against platelet-derived growth factor receptor-β (PDGFR-β) and KDR even though the potency was 42.9- to 197.8-fold lower than that of c-Met. Moreover, this compound exhibited a slight or no tyrosine kinase inhibitory activity against epidermal growth factor receptor (EGFR) kinase (IC_{50} > 10 μM). These data indicated that compound **15a** is a promising multitarget inhibitor of tyrosine kinases.

4. Conclusions

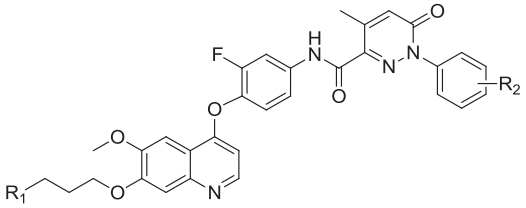
In summary, we designed and synthesized a series of novel 4-phenoxyquinoline derivatives containing pyridazinone moiety and the target compounds were evaluated for their cytotoxic activity against five human cancer cell lines. The pharmacological data indicate that most of them exhibited moderate-to-excellent cytotoxicity and high selectivity against one or more cell lines. Our preliminary investigation showed that most of the compounds possess good-to-excellent activity with higher selectivity against HT-29 and H460 cells than A549, MKN-45, and U87MG cells. In particular, compound **15a** (IC_{50} = 2.15 nM) exhibited remarkable cytotoxicity against HT-29, H460, and A549 cell lines with IC_{50} values of 0.10 μM, 0.13 μM, and 0.05 μM, respectively 1.5- to 2.3-fold more potent than foretinib. The preliminary studies on enzymatic selectivity also revealed that compound **15a** is a multitarget inhibitor of tyrosine kinases. The SARs analyses indicate that the compounds with mono/double-EWGs on the phenyl ring were more active than those without substituents or EDGs. Further SARs studies and mechanism of action of these compounds are in progress, and the results will be reported in the future.

5. Experimental

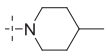
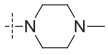
5.1. Chemistry

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.). ^1H NMR and ^{13}C NMR spectra were recorded on Bruker ARX-400, 400 MHz or Bruker ARX-600, 600 MHz spectrometers (Bruker Bioscience, Billerica, MA, USA) with TMS as an internal standard.

Table 1
Structures and cytotoxic activities of compounds **13a**–**20e** against H460, HT-29, A549, MKN-45 and U87MG cell lines *in vitro*.



13a-20e

Compd.	R_1	R_2	IC_{50} (μmol/L) ± SD[a]				
			HT-29	H460	A549	MKN-45	U87MG
13a		H	0.35 ± 0.03	0.45 ± 0.05	0.72 ± 0.01	0.11 ± 0.008	1.60 ± 0.07
14a		2-CH_3	1.01 ± 0.09	1.38 ± 0.01	0.53 ± 0.01	0.27 ± 0.03	2.00 ± 0.31
15a		2-CF_3	**0.10 ± 0.002**	**0.13 ± 0.002**	**0.05 ± 0.005**	**0.03 ± 0.001**	**1.06 ± 0.05**
16a		2-OCF_3	**0.17 ± 0.004**	**0.20 ± 0.03**	0.12 ± 0.002	0.09 ± 0.01	1.30 ± 0.02
17a		3-F	0.27 ± 0.01	0.29 ± 0.01	0.55 ± 0.07	0.11 ± 0.02	1.98 ± 0.01
18a		4-OCH_3	1.23 ± 0.01	1.77 ± 0.02	1.50 ± 0.03	0.26 ± 0.05	ND
19a		4-Cl	0.26 ± 0.01	0.38 ± 0.05	0.33 ± 0.05	0.07 ± 0.03	1.97 ± 0.21
20a		3,4-$(F)_2$	**0.16 ± 0.01**	0.39 ± 0.06	0.32 ± 0.08	0.09 ± 0.02	ND
13b		H	0.22 ± 0.03	0.46 ± 0.03	0.37 ± 0.03	0.12 ± 0.07	1.10 ± 0.07
14b		2-CH_3	1.40 ± 0.04	1.59 ± 0.05	1.30 ± 0.02	0.76 ± 0.02	2.96 ± 0.05
15b		2-CF_3	**0.14 ± 0.003**	0.21 ± 0.003	0.13 ± 0.002	0.10 ± 0.001	**1.01 ± 0.07**
16b		2-OCF_3	**0.18 ± 0.02**	0.21 ± 0.03	0.14 ± 0.01	0.06 ± 0.001	1.28 ± 0.03
17b		3-F	0.25 ± 0.01	0.28 ± 0.02	0.17 ± 0.01	0.12 ± 0.05	1.70 ± 0.22
18b		4-OCH_3	3.30 ± 0.03	3.61 ± 0.17	2.77 ± 0.12	1.29 ± 0.02	2.96 ± 0.17
19b		4-Cl	0.26 ± 0.02	0.36 ± 0.01	0.23 ± 0.07	0.15 ± 0.11	1.43 ± 0.01
20b		3,4-$(F)_2$	**0.15 ± 0.02**	**0.17 ± 0.05**	0.22 ± 0.08	0.08 ± 0.003	1.40 ± 0.15
13c		H	**0.16 ± 0.04**	0.28 ± 0.03	0.15 ± 0.15	0.16 ± 0.05	1.37 ± 0.03
14c		2-CH_3	2.81 ± 0.04	3.22 ± 0.02	1.92 ± 0.03	1.31 ± 0.08	2.50 ± 0.02
15c		2-CF_3	**0.17 ± 0.002**	0.21 ± 0.02	0.14 ± 0.003	0.09 ± 0.002	1.15 ± 0.02
16c		2-OCF_3	0.19 ± 0.01	0.23 ± 0.01	0.12 ± 0.01	0.04 ± 0.01	1.30 ± 0.08
17c		3-F	0.29 ± 0.04	0.36 ± 0.03	0.25 ± 0.17	0.13 ± 0.01	1.50 ± 0.03
18c		4-OCH_3	3.20 ± 0.05	3.73 ± 0.01	1.50 ± 0.01	0.33 ± 0.03	1.80 ± 0.02
19c		4-Cl	0.36 ± 0.01	0.46 ± 0.04	0.32 ± 0.08	0.23 ± 0.01	1.40 ± 0.07
20c		2,4-$(Cl)_2$	0.29 ± 0.03	0.39 ± 0.01	0.22 ± 0.03	0.08 ± 0.01	1.80 ± 0.01
13d		H	0.30 ± 0.01	0.27 ± 0.08	0.32 ± 0.02	0.12 ± 0.01	1.16 ± 0.20
14d		2-CH_3	2.81 ± 0.02	2.26 ± 0.05	1.46 ± 0.07	1.29 ± 0.08	2.24 ± 0.03
15d		2-CF_3	**0.18 ± 0.04**	**0.20 ± 0.002**	0.16 ± 0.01	0.06 ± 0.03	1.12 ± 0.02
16d		2-OCF_3	0.25 ± 0.01	0.29 ± 0.01	**0.09 ± 0.01**	0.07 ± 0.01	**0.80 ± 0.04**
17d		3-F	0.30 ± 0.05	0.25 ± 0.01	0.25 ± 0.01	0.14 ± 0.01	1.80 ± 0.01
18d		4-OCH_3	5.45 ± 0.01	4.65 ± 0.08	1.10 ± 0.22	0.40 ± 0.08	2.84 ± 0.22
19d		4-Cl	**0.18 ± 0.01**	0.37 ± 0.03	0.21 ± 0.02	0.15 ± 0.02	1.35 ± 0.08
20d		2,4-$(Cl)_2$	**0.17 ± 0.03**	0.25 ± 0.01	0.20 ± 0.03	0.12 ± 0.01	ND
13e		H	0.27 ± 0.04	0.36 ± 0.07	0.35 ± 0.12	0.13 ± 0.03	2.12 ± 0.10
14e		2-CH_3	3.79 ± 0.01	3.42 ± 0.01	2.83 ± 0.17	1.63 ± 0.03	3.72 ± 0.02
15e		2-CF_3	**0.17 ± 0.01**	0.24 ± 0.03	0.17 ± 0.08	0.04 ± 0.001	1.17 ± 0.03
16e		2-OCF_3	**0.18 ± 0.01**	0.26 ± 0.03	0.13 ± 0.05	0.10 ± 0.02	1.44 ± 0.01
17e		3-F	0.25 ± 0.05	0.26 ± 0.02	0.15 ± 0.03	0.12 ± 0.01	1.59 ± 0.22
18e		4-OCH_3	3.52 ± 0.01	3.66 ± 0.07	2.20 ± 0.02	1.23 ± 0.03	ND
19e		4-Cl	0.32 ± 0.02	0.44 ± 0.02	0.27 ± 0.07	0.04 ± 0.001	1.56 ± 0.01
20e		3,4-$(F)_2$	**0.17 ± 0.03**	**0.19 ± 0.20**	0.13 ± 0.01	0.12 ± 0.02	ND
Foretinib[b]			0.19 ± 0.01	0.21 ± 0.03	0.11 ± 0.01	0.032 ± 0.005	1.08 ± 0.12

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

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

[b] Used as a positive control.

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. Elemental analysis was determined on a Carlo-Erba 1106 Elemental analysis instrument (Carlo Erba, Milan, Italy). (In the mode of measurement C, H, and N, the sample into the combustion tube in pure oxygen atmosphere static combustion and products by a specific reagent after formation of CO_2, H_2O, N_2 and nitrogen oxides, uniform mixing under the atmospheric pressure. The thermal conductivity detector is used for determining the content of C, H and N from mixed gases.).

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

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

5.2.1. 3-Fluoro-4-(6-methoxy-7-(3-morpholinopropoxy)quinolin-4-yloxy)aniline (**8a**)

White solid; Yield: 81.8%; M.p.: 217–218 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.47 (d, J = 5.2 Hz, 1H), 7.58 (s, 1H), 7.44 (s, 1H), 7.04 (t, J = 8.7 Hz, 1H), 6.57 (dd, J = 11.9, 2.6 Hz, 1H), 6.50 (m, 1H), 6.41 (d, J = 5.3 Hz, 1H), 4.27 (t, J = 6.6 Hz, 2H), 4.04 (s, 3H), 3.82 (s, 2H), 3.74 (m, 4H), 2.60 (t, J = 7.1 Hz, 2H), 2.51 (d, J = 4.2 Hz, 4H), 2.13 (m, 2H); MS (ESI) m/z (%): 428.2 $[M+H]^+$, 450.1 $[M+Na]^+$.

5.2.2. 3-Fluoro-4-(6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy) quinolin-4-yloxy)aniline (**8b**)

Light yellow solid; Yield: 72.3%; M.p.: 208–209 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.49 (d, J = 5.2 Hz, 1H), 7.55 (s, 1H), 7.44 (s, 1H), 7.08 (t, J = 9.0 Hz, 1H), 6.57 (d, J = 14.1 Hz, 1H), 6.46 (m, J = 12.8, 7.1 Hz, 2H), 4.28 (t, J = 5.7 Hz, 2H), 3.96 (s, 3H), 3.59 (s, 2H), 3.35 (m, 4H), 3.04 (s, 2H), 2.28 (m, 2H), 1.96 (d, J = 28.0 Hz, 4H); MS (ESI) m/z (%): 412.5 $[M+H]^+$.

5.2.3. 3-Fluoro-4-(6-methoxy-7-(3-(piperdine-1-yl)propoxy) quinolin-4-yloxy)aniline (**8c**)

Gray solid; Yield: 85.5%; M.p.: 196–97 °C; IR (KBr) cm^{-1}: 3482.2, 3387.0, 2946.5, 2835.1, 2788.1, 1621.1, 1587.8, 1512.8, 1483.4, 1252.9, 1215.4, 853.5; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.46 (d, J = 5.3 Hz, 1H), 7.58 (s, 1H), 7.41 (s, 1H), 7.03 (t, J = 8.7 Hz, 1H), 6.56 (dd, J = 11.8, 2.6 Hz, 1H), 6.50 (m, 1H), 6.39 (dd, J = 5.3, 1.1 Hz, 1H), 4.24 (t, J = 6.8 Hz, 2H), 4.04 (s, 3H), 3.81 (s, 2H), 2.54 (m, 2H), 2.43 (s, 4H), 2.14 (m, 2H), 1.60 (m, 4H), 1.55 (m, 2H); MS (ESI) m/z (%): 426.3 $[M+H]^+$.

5.2.4. 3-Fluoro-4-(6-methoxy-7-(3-(4-methylpiperdine-1-yl) propoxy)quinolin-4-yl-oxy)aniline (**8d**)

White solid; Yield: 77.4%; M.p.: 193–194 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.46 (d, J = 5.3 Hz, 1H), 7.58 (s, 1H), 7.41 (s, 1H), 7.03 (t, J = 8.7 Hz, 1H), 6.56 (dd, J = 11.8, 2.6 Hz, 1H), 6.50 (dd, J = 9.0, 2.9 Hz, 1H), 6.39 (dd, J = 5.3, 0.8 Hz, 1H), 4.25 (t, J = 6.7 Hz, 2H), 4.03 (s, 3H), 3.82 (s, 2H), 2.94 (d, J = 11.5 Hz, 2H), 2.57 (m, 2H), 2.15 (m, 2H), 1.98 (t, J = 10.9 Hz, 2H), 1.63 (d, J = 10.4 Hz, 2H), 1.28 (m, 3H), 0.93 (d, J = 6.0 Hz, 3H); MS (ESI) m/z (%): 440.3 $[M+H]^+$.

5.2.5. 3-Fluoro-4-(6-methoxy-7-(3-(4-methylpiperazine-1-yl) propoxy)quinolin-4-yl-oxy)aniline (**8e**)

White solid; yield: 77%; M.p.: 201–202 °C ^{1}H NMR (300 MHz, CDCl3) δ 8.48 (d, J = 5.3 Hz, 1H), 7.61 (s, 1H), 7.41 (s, 1H), 7.06 (t, J = 8.7 Hz, 1H), 6.58 (dd, J = 11.8, 2.6 Hz, 1H), 6.54 (dd, J = 9.0, 2.9 Hz, 1H), 6.41 (dd, J = 5.3, 0.8 Hz, 1H), 4.28 (t, J = 6.7 Hz, 2H), 4.06 (s, 3H),3.84 (s, 2H), 2.64–2.51 (m, 8H), 2.18 (s, 3H), 2.11 (t, J = 10.9 Hz, 2H), 1.88 (m, 2H); MS (ESI) m/z (%): 441.4 $[M+H]^+$, 463.3 $[M+Na]^+$.

5.3. General procedure for preparation intermediates of 3-oxo-2-(2-arylhydrazono)butanoic acid ethyl ester (**9a**–**i**)

To a mixture of substituted phenyl amine (0.06 mol) and 15% HCl (60 mL), $NaNO_2$ (5 g, 0.072 mol) in H_2O (200 mL) was added dropwise at 0 °C. After the completion of addition, the reaction mixture was stirred at this temperature for 30 min, and then added into a mixture of ethyl acetylacetate (8.2 g, 0.063 mol), anhydrous sodium acetate (14.76 g, 0.18 mol), and EtOH (200 mL) at 0 °C. Then, the mixture was filtered, and the residue was dried to afford light yellow solids (**9a**–**i**) in 90–95% yields.

5.3.1. 3-Oxo-2-(2-phenylhydrazono)butanoic acid ethyl ester (**9a**)

Light yellow solid; Yield: 92%; M.p.: 94–96 °C; MS (ESI) m/z (%): 235.3 $[M+H]^+$.

5.3.2. 3-Oxo-2-(2-(2-methylphenyl)hydrazono)butanoic acid ethyl ester (**9b**)

Yellow solid; Yield: 91.5%; M.p.: 95–96 °C; MS (ESI) m/z (%): 249.3 $[M+H]^+$, 261.2 $[M+Na]^+$.

5.3.3. 3-Oxo-2-(2-(2-(trifluoromethyl)phenyl)hydrazono)butanoic acid ethyl ester (**9c**)

Yellow solid; Yield: 92.2%; M.p.: 94.8–95.6 °C; MS (ESI) m/z (%): 303.3 $[M+H]^+$, 325.2 $[M+Na]^+$.

5.3.4. 3-Oxo-2-(2-(2-(trifluoromethoxy)phenyl)hydrazono) butanoic acid ethyl ester (**9d**)

Yellow solid; Yield: 92.3%; M.p.: 96–97 °C; MS (ESI) m/z (%):319.3 $[M+H]^+$.

5.3.5. 3-Oxo-2-(2-(3-fluorophenyl)hydrazono)butanoic acid ethyl ester (**9e**)

Light yellow solid; Yield: 91.8%; M.p.: 93–94 °C; MS (ESI) m/z (%): 253.2 $[M+H]^+$, 275.3 $[M+Na]^+$.

5.3.6. 3-Oxo-2-(2-(4-methoxyphenyl)hydrazono)butanoic acid ethyl ester (**9f**)

Yellow solid; Yield: 92.4%; M.p.: 94–95 °C; MS (ESI) m/z (%): 265.3 $[M+H]^+$, 287.3 $[M+Na]^+$.

Table 2
c-Met kinase activity of selected compounds **15a**, **20a**, **15b**, **15c**, **20d**, **16e**, and foretinib *in vitro*.

Compd.	IC_{50} on c-Met (nM)
15a	2.15
20a	9.16
15b	5.02
15c	5.63
20d	9.95
16e	8.27
Foretinib	1.16

Table 3
Inhibition of tyrosine kinases by compound **15a**.

Kinase	Enzyme IC_{50} (nM)
c-Kit	4.32
Flt-3	9.28
PDGFR-β	92.30
KDR	425.42
EGFR	>10,000

*5.3.7. 3-Oxo-2-(2-(4-chlorophenyl)hydrazono)butanoic acid ethyl ester (**9g**)*

Light yellow solid; Yield: 92.1%; M.p.: 97–98 °C; MS (ESI) *m/z* (%): 269.7 $[M+H]^+$.

*5.3.8. 3-Oxo-2-(2-(2,4-dichlorophenyl)hydrazono)butanoic acid ethyl ester (**9h**)*

Light yellow solid; Yield: 93.2%; M.p.: 96–97 °C; MS (ESI) *m/z* (%): 304.2 $[M+H]^+$, 326.2 $[M+Na]^+$.

*5.3.9. 3-Oxo-2-(2-(3,4-difluorophenyl)hydrazono)butanoic acid ethyl ester (**9i**)*

Light yellow solid; Yield: 90%; M.p.: 93–94 °C; MS (ESI) *m/z* (%): 271.2 $[M+H]^+$.

*5.4. General procedure for preparation of 4-methyl-6-oxo-1-(substituted phenyl)-1,6-dihydropyridazine -3-carboxylate (**10a**–**i**)*

To a solution of appropriate intermediate (**9a**–**i**) (2 g, 7.4 mmol) and (carbethoxymethylene) triphenylphosphorane (3.12 g, 9 mmol) were dissolved into 20 mL of dried toluene and refluxed for 12 h under heating. The solvent was removed under reduced pressure and the residue was triturated with petroleum ether. The solid product obtained was collected by filtration and recrystallized from EtOH to afford white solids (**10a**–**i**) in 50–55% yields.

*5.4.1. Ethyl 4-methyl-6-oxo-1-phenyl-1,6-dihydropyridazine-3-carboxylate (**10a**)*

White solid; Yield: 50.3%; M.p.: 102–103 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, J = 7.8 Hz, 2H), 7.46 (t, J = 7.5 Hz, 2H), 7.38 (t, J = 7.0 Hz, 1H), 6.83 (s, 1H), 4.37 (q, J = 7.0 Hz, 2H), 2.44 (s, 3H), 1.37 (t, J = 7.0 Hz, 3H); MS (ESI) *m/z* (%): 539.0 $[2M+Na]^+$.

*5.4.2. Ethyl 4-methyl-6-oxo-1-(2-methylphenyl)-1,6-dihydropyridazine-3-carboxylate (**10b**)*

White solid; Yield: 51.2%; M.p.: 100–101 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (t, J = 7.5 Hz, 3H), 7.29 (d, J = 8.3 Hz, 1H), 6.89 (s, 1H), 4.40 (q, J = 7.1 Hz, 2H), 2.50 (s, 3H), 2.19 (s, 3H), 1.39 (t, J = 7.1 Hz, 3H); MS (ESI) *m/z* (%): 273.2 $[M+H]^+$.

*5.4.3. Ethyl 4-methyl-6-oxo-1-(2-(trifluoromethyl)phenyl)-1,6-dihydropyridazine-3-carboxylate (**10c**)*

White solid; Yield: 52.3%; M.p.: 101–102 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (t, J = 7.3 Hz, 2H), 7.32–7.23 (m, 2H), 6.88 (s, 1H), 4.41 (q, J = 7.1 Hz, 2H), 2.49 (s, 3H), 1.39 (t, J = 7.1 Hz, 3H); MS (ESI) *m/z* (%): 349.0 $[M+Na]^+$.

*5.4.4. Ethyl 4-methyl-6-oxo-1-(2-(trifluoromethoxy)phenyl)-1,6-dihydropyridazine-3-carboxylate (**10d**)*

White solid; Yield: 51.4%; M.p.: 102–103 °C; MS (ESI) *m/z* (%): 707.5 $[2M+Na]^+$.

*5.4.5. Ethyl 1-(3-fluorophenyl)-4-methyl-6-oxo-1,6-dihydropyridazine-3-carboxylate (**10e**)*

White solid; Yield: 52.5%; M.p.: 102.5–103 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (t, J = 7.2 Hz, 2H), 7.34–7.24 (m, 2H), 6.89 (s, 1H), 4.41 (q, J = 7.1 Hz, 2H), 2.49 (s, 3H), 1.39 (t, J = 7.1 Hz, 3H); MS (ESI) *m/z* (%): 277.3 $[M+H]^+$, 575.5 $[2M+Na]^+$.

*5.4.6. Ethyl 1-(4-methoxyphenyl)-4-methyl-6-oxo-1,6-dihydropyridazine-3-carboxylate (**10f**)*

White solid; Yield: 52.1%; M.p.: 101–102 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, J = 8.8 Hz, 2H), 6.99 (d, J = 8.8 Hz, 2H), 6.85 (s, 1H), 4.41 (q, J = 7.1 Hz, 2H), 3.85 (s, 3H), 2.47 (s, 3H), 1.40 (t, J = 7.1 Hz, 3H); MS (ESI) *m/z* (%): 311.3 $[M+Na]^+$, 599.5 $[2M+Na]^+$.

*5.4.7. Ethyl 1-(4-chlorophenyl)-4-methyl-6-oxo-1,6-dihydropyridazine-3-carboxylate (**10g**)*

White solid; Yield: 51.8%; M.p.: 100–103 °C; MS (ESI) *m/z* (%): 293.7 $[M+H]^+$, 315.8 $[M+Na]^+$.

*5.4.8. Ethyl 1-(2,4-dichlorophenyl)-4-methyl-6-oxo-1,6-dihydropyridazine-3-carboxylate (**10h**)*

White solid; Yield: 50.9%; M.p.: 103–104 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (s, 1H), 7.40 (q, J = 8.5 Hz, 2H), 6.88 (s, 1H), 4.41 (q, J = 7.0 Hz, 2H), 2.50 (s, 3H), 1.39 (t, J = 7.0 Hz, 3H); MS (ESI) *m/z* (%): 675.2 $[2M+Na]^+$.

*5.4.9. Ethyl 1-(3,4-difluorophenyl)-4-methyl-6-oxo-1,6-dihydropyridazine-3-carboxylate (**10i**)*

White solid; Yield: 52.6%; M.p.: 102–103 °C; MS (ESI) *m/z* (%): 311.7 $[M+Na]^+$, 611.2 $[2M+Na]^+$.

*5.5. General procedure for preparation of acids (**11a**–**i**)*

To a solution of an appropriate intermediate (**10a**–**i**) (4 mmol) dissolved in THF (20 mL), was added drop-wise 10% NaOH (5 mL) at room temperature. After the completion of addition, the mixture was heated to 50 °C for 4 h. Then, most of the solvent was evaporated, and the residue was poured into H_2O (50 mL) and acidified (6 N HCl) to afford substituted acids (**11a**–**i**) as white precipitate in 90.5–95.2% yields.

*5.5.1. 4-Methyl-6-oxo-1-phenyl-1,6-dihydropyridazine-3-carboxylic acid (**11a**)*

White solid; Yield: 93.2%; M.p.: 230–231 °C; ^{1}H NMR (400 MHz, DMSO) δ 13.57 (s, 1H), 7.53 (dt, J = 14.4, 7.2 Hz, 4H), 7.47 (d, J = 6.7 Hz, 1H), 6.99 (s, 1H), 2.40 (s, 3H); MS (ESI) *m/z* (%): 229.2 $[M-H]^-$.

*5.5.2. 4-Methyl-6-oxo-1-(2-methylphenyl)-1,6-dihydropyridazine-3-carboxylic acid (**11b**)*

White solid; Yield: 93.0%; M.p.: 213–214 °C; ^{1}H NMR (400 MHz, DMSO) δ 13.57 (s, 1H), 7.44–7.36 (m, 2H), 7.33 (dd, J = 12.6, 7.7 Hz, 2H), 7.01 (s, 1H), 2.42 (s, 3H), 2.05 (s, 3H); MS (ESI) *m/z* (%): 243.3 $[M-H]^-$.

*5.5.3. 4-Methyl-6-oxo-1-(2-(trifluoromethyl)phenyl)-1,6-dihydropyridazine-3-carboxylic acid (**11c**)*

White solid; Yield: 91.7%; M.p.: 212–213 °C; ^{1}H NMR (400 MHz, DMSO) δ 13.68 (s, 1H), 7.95 (d, J = 7.8 Hz, 1H), 7.89 (t, J = 7.5 Hz, 1H), 7.78 (t, J = 7.7 Hz, 1H), 7.68 (d, J = 7.8 Hz, 1H), 7.03 (d, J = 1.1 Hz, 1H), 2.42 (d, J = 0.8 Hz, 3H); MS (ESI) *m/z* (%): 297.2 $[M-H]^-$.

*5.5.4. 4-Methyl-6-oxo-1-(2-(trifluoromethoxy)phenyl)-1,6-dihydropyridazine-3-carboxylic acid (**11d**)*

White solid; Yield: 92.7%; M.p.: 215–216 °C; MS (ESI) *m*/*z* (%): 313.2 $[M-H]^-$.

*5.5.5. 1-(3-Fluorophenyl)-4-methyl-6-oxo-1,6-dihydropyridazine-3-carboxylic acid (**11e**)*

White solid; Yield: 91.9%; M.p.: 211–212 °C; ^{1}H NMR (400 MHz, DMSO) δ 13.64 (s, 1H), 7.92 (d, J = 7.8 Hz, 1H), 7.87 (t, J = 7.5 Hz, 1H), 7.74 (t, J = 7.7 Hz, 1H), 7.63 (d, J = 7.8 Hz, 1H), 7.03 (d, J = 1.1 Hz, 1H), 2.42 (d, J = 0.8 Hz, 3H); MS (ESI) *m*/*z* (%): 247.3 $[M-H]^-$.

*5.5.6. 1-(4-Methoxyphenyl)-4-methyl-6-oxo-1,6-dihydropyridazine-3-carboxylic acid (**11f**)*

White solid; Yield: 92.5%; M.p.: 210–212 °C; MS (ESI) *m*/*z* (%): 259.3 $[M-H]^-$.

*5.5.7. 1-(4-Chlorophenyl)-4-methyl-6-oxo-1,6-dihydropyridazine-3-carboxylic acid (**11g**)*

White solid; Yield: 91.8%; M.p.: 214–215 °C; ^{1}H NMR (400 MHz, DMSO) δ 13.66 (s, 1H), 7.93 (d, J = 7.8 Hz, 1H), 7.88 (t, J = 7.5 Hz, 1H), 7.76 (t, J = 7.7 Hz, 1H), 7.65 (d, J = 7.8 Hz, 1H), 7.03 (d, J = 1.1 Hz, 1H), 2.42 (d, J = 0.8 Hz, 3H); MS (ESI) *m*/*z* (%): 264.3 $[M-H]^-$.

*5.5.8. 1-(2,4-Dichlorophenyl)-4-methyl-6-oxo-1,6-dihydropyridazine-3-carboxylic acid (**11h**)*

White solid; Yield: 93.1%; M.p.: 210–212 °C; ^{1}H NMR (400 MHz, DMSO) δ 13.73 (s, 1H), 7.91 (d, J = 1.6 Hz, 1H), 7.69–7.61 (m, 2H), 7.05 (s, 1H), 2.41 (s, 3H); MS (ESI) *m*/*z* (%): 298.1 $[M-H]^-$.

*5.5.9. 1-(3,4-Difluorophenyl)-4-methyl-6-oxo-1,6-dihydropyridazine-3-carboxylic acid (**11i**)*

White solid; Yield: 92.9%; M.p.: 211–213 °C; ^{1}H NMR (400 MHz, DMSO) δ 13.70 (s, 1H), 7.90 (d, J = 1.6 Hz, 1H), 7.67–7.60 (m, 2H), 7.05 (s, 1H), 2.41 (s, 3H); MS (ESI) *m*/*z* (%): 265.1 $[M-H]^-$.

*5.6. General procedure for preparation of the target compounds (**13a**–**20e**)*

A mixture of the corresponding acid (**11a**–**i**) (0.872 mmol), toluene (10 mL), and $SOCl_2$ (5 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 dropwise added to a mixture of the corresponding aniline (**8a**–**e**) (0.486 mmol), Na_2CO_3 (0.972 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 using a mixture of CH_2Cl_2/MeOH (25:1) to afford **13a**–**20e** as white solids in 75.1–85.6% yields.

*5.6.1. N-(3-fluoro-4-((6-methoxy-7-(3-morpholinopropoxy) quinolin-4-yl)oxy)phenyl)-4-methyl-6-oxo-1-phenyl-1,6-dihydropyridazine-3-carboxamide (**13a**)*

Yield: 81.6%; M.p.: 121–122 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.10 (s, 1H), 8.42 (d, J = 5.3 Hz, 1H), 7.80 (d, J = 11.9 Hz, 1H), 7.56 (d, J = 7.6 Hz, 2H), 7.53–7.46 (m, J = 13.7, 6.4 Hz, 3H), 7.43 (t, J = 7.2 Hz, 1H), 7.38 (s, 1H), 7.31 (d, J = 8.9 Hz, 1H), 7.20 (t, J = 8.6 Hz, 1H), 6.87 (s, 1H), 6.35 (d, J = 5.2 Hz, 1H), 4.22 (t, J = 6.6 Hz, 2H), 3.99 (s, 3H), 3.68 (t, J = 4.4 Hz, 4H), 2.62 (s, 3H), 2.53 (t, J = 7.1 Hz, 2H), 2.44 (t, 4H), 2.14–2.03 (m, 2H); MS (ESI) *m*/*z* (%): 640.5 $[M+H]^+$; Anal. calcd. for $C_{35}H_{34}FN_5O_6$ (%): C, 65.72; H, 5.36; N, 10.95. Found (%): C, 65.73; H, 5.37; N, 10.96.

*5.6.2. N-(3-fluoro-4-((6-methoxy-7-(3-morpholinopropoxy) quinolin-4-yl)oxy)phenyl)-4-methyl-6-oxo-1-(2-methylphenyl)-1,6-dihydropyridazine-3-carboxamide (**14a**)*

Yield: 81.2%; M.p.: 122–124 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.16 (s, 1H), 8.47 (d, J = 5.2 Hz, 1H), 7.83 (d, J = 11.9 Hz, 1H), 7.56 (s, 1H), 7.46 (d, J = 8.3 Hz, 2H), 7.42 (s, 1H), 7.33 (t, J = 10.4 Hz, 3H), 7.24 (t, J = 8.6 Hz, 1H), 6.89 (s, 1H), 6.39 (d, J = 5.2 Hz, 1H), 4.26 (t, J = 6.6 Hz, 2H), 4.04 (s, 3H), 3.72 (t, 4H), 2.66 (s, 3H), 2.57 (t, J = 7.1 Hz, 2H), 2.48 (t, 4H), 2.43 (s, 3H), 2.17–2.09 (m, 2H); MS (ESI) *m*/*z* (%): 654.2 $[M+H]^+$; Anal. calcd. for $C_{36}H_{36}FN_5O_6$ (%): C, 66.14; H, 5.55; N, 10.71; Found (%): C, 66.15; H, 5.57; N, 10.76.

*5.6.3. N-(3-fluoro-4-((6-methoxy-7-(3-morpholinopropoxy) quinolin-4-yl)oxy)phenyl)-4-methyl-6-oxo-1-(2-(trifluoromethyl) phenyl)-1,6-dihydropyridazine-3-carboxamide (**15a**)*

Yield: 80.6%; M.p.: 123–123.8 °C; IR (KBr) cm^{-1}: 3392.3, 1954.9, 2853.7, 2813.2, 1689.5, 1620.9, 1598.5, 1508.9, 1479.8, 1456.0, 1431.2, 1349.2, 1317.1, 1250.2, 1211.4, 1145.5, 1115.9, 1061.1, 1036.0, 854.2, 721.2; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.89 (s, 1H), 8.43 (d, J = 5.3 Hz, 1H), 7.87 (d, J = 7.5 Hz, 1H), 7.80–7.69 (m, 2H), 7.65 (t, J = 7.7 Hz, 1H), 7.51 (d, J = 7.4 Hz, 2H), 7.39 (s, 1H), 7.29–7.24 (m, 1H), 7.19 (t, J = 8.6 Hz, 1H), 6.90 (s, 1H), 6.34 (d, J = 5.1 Hz, 1H), 4.23 (t, J = 6.7 Hz, 2H), 4.00 (s, 3H), 3.74–3.64 (m, 4H), 2.67 (s, 3H), 2.54 (t, J = 7.1 Hz, 2H), 2.46 (t, J = 3.5 Hz, 4H), 2.15–2.04 (m, J = 6.8 Hz, 2H). ^{13}C NMR (600 MHz, $CDCl_3$) δ 160.57, 160.47, 159.78, 155.57, 153.91, 152.68, 150.23, 148.74, 146.79, 145.53, 138.26, 138.06, 137.81, 136.26, 133.42, 131.02, 130.46, 129.88, 128.26, 124.20, 116.53, 115.74, 109.84, 109.68, 108.77, 102.44, 99.81, 67.47, 66.98 (2C), 56.48, 55.68, 53.85 (2C), 25.90, 20.96; MS (ESI) *m*/*z* (%): 608.5 $[M+H]^+$; Anal. calcd. for $C_{36}H_{33}F_4N_5O_6$ (%): C, 61.10; H, 4.70; N, 9.90; Found (%): C, 61.13; H, 4.37; N, 9.96.

*5.6.4. N-(3-fluoro-4-((6-methoxy-7-(3-morpholinopropoxy) quinolin-4-yl)oxy)phenyl)-4-methyl-6-oxo-1-(2-(trifluoromethoxy) phenyl)-1,6-dihydropyridazine-3-carboxamide (**16a**)*

Yield: 81.4%; M.p.: 122–124 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.02 (s, 1H), 8.48 (d, J = 5.2 Hz, 1H), 7.85 (dd, J = 11.8, 1.8 Hz, 1H), 7.68 (d, J = 8.8 Hz, 2H), 7.57 (s, 1H), 7.43 (s, 1H), 7.42–7.31 (m, 3H), 7.25 (d, J = 8.6 Hz, 1H), 6.94 (s, 1H), 6.39 (d, J = 5.1 Hz, 1H), 4.27 (t, J = 6.6 Hz, 2H), 4.04 (s, 3H), 3.73 (t, 4H), 2.69 (s, 3H), 2.58 (t, J = 7.1 Hz, 2H), 2.49 (t, 4H), 2.23–2.06 (m, 2H). ^{13}C NMR (600 MHz, $CDCl_3$) δ 160.67, 160.58, 159.75, 155.67, 153.93, 152.58, 150.03, 148.56, 146.75, 145.43, 138.16, 138.10, 137.82, 136.75, 133.38, 131.12, 130.48, 129.79, 128.24, 126.25, 116.51, 115.68, 109.79, 109.71, 108.73, 102.42, 99.79, 67.50, 66.94 (2C), 56.48, 55.68, 53.79 (2C), 25.85, 20.92; MS (ESI) *m*/*z* (%): 724.0 $[M+H]^+$; Anal. calcd. for $C_{36}H_{33}F_4N_5O_7$ (%): C, 59.75; H, 4.60; N, 9.68; Found (%): C, 59.73; H, 4.61; N, 9.66.

*5.6.5. N-(3-fluoro-4-((6-methoxy-7-(3-morpholinopropoxy) quinolin-4-yl)oxy)phenyl)-1-(3-fluorphenyl)-4-methyl-6-oxo-1,6-dihydropyridazine-3-carboxamide (**17a**)*

Yield: 81.8%; M.p.: 121–122.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.04 (s, 1H), 8.48 (d, J = 5.2 Hz, 1H), 7.85 (dd, J = 11.9, 2.3 Hz, 1H), 7.57 (s, 1H), 7.50 (t, J = 3.9 Hz, 1H), 7.48–7.42 (m, 2H), 7.42–7.32 (m, 2H), 7.25 (d, J = 8.7 Hz, 1H), 7.20 (t, J = 8.1 Hz, 1H), 6.93 (d, J = 1.3 Hz, 1H), 6.40 (d, J = 5.3 Hz, 1H), 4.27 (t, J = 6.3 Hz, 2H), 4.05 (s, 3H), 3.73 (t, J = 4.3 Hz, 4H), 2.68 (s, 1H), 2.58 (t, J = 7.1 Hz, 1H), 2.50 (t, 4H), 2.19–2.08 (m, J = 6.7 Hz, 2H); MS (ESI) *m*/*z* (%): 658.6 $[M+H]^+$; Anal. calcd. for $C_{35}H_{33}F_2N_5O_6$ (%): C, 63.92; H, 5.06; N, 10.65; Found (%): C, 63.93; H, 5.07; N, 10.66.

*5.6.6. N-(3-fluoro-4-((6-methoxy-7-(3-morpholinopropoxy) quinolin-4-yl)oxy)phenyl)-1-(4-methoxyphenyl)-4-methyl-6-oxo-1,6-dihydropyridazine-3-carboxamide (**18a**)*

Yield: 80.2%; M.p.: 120–121 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.07 (s, 1H), 8.49 (d, J = 5.2 Hz, 1H), 7.84 (dd, J = 11.9, 2.3 Hz, 1H), 7.58 (s,

1H), 7.53 (d, J = 9.0 Hz, 2H), 7.45 (s, 1H), 7.35 (d, J = 8.9 Hz, 1H), 7.25 (d, J = 8.7 Hz, 1H), 7.05 (d, J = 9.0 Hz, 2H), 6.92 (d, J = 1.0 Hz, 1H), 6.41 (d, J = 5.1 Hz, 1H), 4.29 (t, J = 6.6 Hz, 2H), 4.05 (s, 3H), 3.89 (s, 3H), 3.78–3.69 (m, 4H), 2.68 (s, 3H), 2.59 (t, J = 7.1 Hz, 2H), 2.50 (s, 4H), 2.19–2.10 (m, 2H); MS (ESI) m/z (%): 670.6 $[M+H]^+$; Anal. calcd. for $C_{36}H_{36}FN_5O_7$ (%): C, 64.56; H, 5.42; N, 10.46; Found (%): C, 64.57; H, 5.47; N, 10.46.

*5.6.7. 1-(4-Chlorophenyl)-N-(3-fluoro-4-((6-methoxy-7-(3-morpholinopropoxy)quinolin-4-yl)oxy)phenyl)-4-methyl-6-oxo-1,6-dihydropyridazine-3-carboxamide (**19a**)*

Yield: 80%; M.p.: 122–123 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.04 (s, 1H), 8.48 (d, J = 5.2 Hz, 1H), 7.85 (dd, J = 11.9, 2.3 Hz, 1H), 7.57 (s, 1H), 7.50 (t, J = 3.9 Hz, 1H), 7.48–7.42 (m, 2H), 7.42–7.32 (m, 2H), 7.25 (d, J = 8.7 Hz, 1H), 7.20 (t, J = 8.1 Hz, 1H), 6.93 (d, J = 1.3 Hz, 1H), 6.40 (d, J = 5.3 Hz, 1H), 4.27 (t, J = 6.3 Hz, 2H), 4.05 (s, 3H), 3.73 (t, J = 4.3 Hz, 4H), 2.68 (s, 1H), 2.58 (t, J = 7.1 Hz, 1H), 2.50 (t, 4H), 2.19–2.08 (m, J = 6.7 Hz, 2H). ^{13}C NMR (600 MHz, $CDCl_3$) δ 160.55, 160.45, 159.75, 155.52, 153.90, 152.54, 150.20, 148.72, 146.75, 145.51, 138.24, 138.03, 137.79, 136.46, 133.40, 131.02, 130.42, 129.82, 128.24, 116.49, 115.72, 109.81, 109.65, 108.72, 102.41, 99.79, 67.42, 66.86 (2C), 56.42, 55.63, 53.79 (2C), 25.94, 20.89; MS (ESI) m/z (%): 674.3 $[M+H]^+$; Anal. calcd. for $C_{35}H_{33}ClFN_5O_6$ (%): C, 62.36; H, 4.93; Cl, 5.26; N, 10.39; Found (%): C, 62.37; H, 4.95; N, 10.36.

*5.6.8. 1-(3,4-Difluorophenyl)-N-(3-fluoro-4-((6-methoxy-7-(3-morpholinopropoxy)quinolin-4-yl)oxy)phenyl)-4-methyl-6-oxo-1,6-dihydropyridazine-3-carboxamide (**20a**)*

Yield: 81.8%; M.p.: 124–125 °C; IR (KBr) cm^{-1}: 3393.4, 3066.6, 2923.9, 2851.3, 2815.6, 1687.0, 1620.6, 1596.7, 1579.3, 1511.5, 1480.8, 1431.1, 1348.8, 1272.9, 1252.5, 1169.7, 1140.4, 1117.2, 1013.7, 854.6, 718.5; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.99 (s, 1H), 8.48 (d, J = 5.2 Hz, 1H), 7.83 (dd, J = 11.9, 2.3 Hz, 1H), 7.63 (d, J = 2.0 Hz, 1H), 7.57 (s, 1H), 7.47–7.40 (m, 3H), 7.35 (d, J = 8.7 Hz, 1H), 7.24 (d, J = 8.6 Hz, 1H), 6.96 (d, J = 1.0 Hz, 1H), 6.40 (d, J = 5.2 Hz, 1H), 4.28 (t, J = 6.6 Hz, 2H), 4.05 (s, 3H), 3.74 (t, 4H), 2.71 (s, 3H), 2.59 (t, J = 7.1 Hz, 2H), 2.50 (s, 4H), 2.20–2.09 (m, J = 6.8 Hz, 2H); MS (ESI) m/z (%): 676.1 $[M+H]^+$; Anal. calcd. for $C_{35}H_{32}F_3N_5O_6$ (%): C, 62.22; H, 4.77; N, 10.37; Found (%): C, 62.23; H, 4.78; N, 10.36.

*5.6.9. N-(3-fluoro-4-((6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl)-4-methyl-6-oxo-1-phenyl-1,6-dihydropyridazine-3-carboxamide (**13b**)*

Yield: 82.2%; M.p.: 131–132 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.05 (s, 1H), 8.49 (d, J = 5.2 Hz, 1H), 7.85 (dd, J = 11.9, 2.2 Hz, 1H), 7.62 (d, J = 7.5 Hz, 2H), 7.56 (dd, J = 8.4, 6.6 Hz, 3H), 7.50 (t, J = 7.1 Hz, 1H), 7.43 (s, 1H), 7.38–7.30 (m, 1H), 7.24 (d, J = 8.7 Hz, 1H), 6.94 (s, 1H), 6.40 (d, J = 5.2 Hz, 1H), 4.28 (t, J = 6.7 Hz, 2H), 4.05 (s, 3H), 2.74 (t, 2H), 2.69 (s, 3H), 2.59 (t, 4H), 2.26–2.12 (m, J = 14.1, 6.9 Hz, 2H), 1.82 (t, 4H); MS (ESI) m/z (%): 640.5 $[M+H]^+$; Anal. calcd. for $C_{35}H_{34}FN_5O_5$ (%): C, 67.40; H, 5.49; N, 11.23; Found (%): C, 67.43; H, 5.47; N, 11.26.

*5.6.10. N-(3-fluoro-4-((6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl)-4-methyl-6-oxo-1-(2-methylphenyl)-1,6-dihydropyridazine-3-carboxamide (**14b**)*

Yield: 82.4%; M.p.: 132–133 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.97 (s, 1H), 8.49 (d, J = 5.2 Hz, 1H), 7.83 (dd, J = 11.9, 2.4 Hz, 1H), 7.57 (s, 1H), 7.49–7.38 (m, 4H), 7.33 (d, J = 7.7 Hz, 2H), 7.24 (t, J = 8.6 Hz, 1H), 6.97 (d, J = 0.9 Hz, 1H), 6.39 (d, J = 5.2 Hz, 1H), 4.28 (t, J = 6.6 Hz, 2H), 4.05 (s, 3H), 2.82–2.72 (m, J = 6.4 Hz, 2H), 2.72 (s, 3H), 2.68–2.52 (m, J = 6.7 Hz, 4H), 2.23 (s, 3H), 2.21–2.16 (m, J = 6.5 Hz, 2H), 1.89–1.77 (m, J = 6.3 Hz, 4H); MS (ESI) m/z (%): 638.2 $[M+H]^+$; Anal. calcd. for $C_{36}H_{36}FN_5O_5$ (%): C, 67.80; H, 5.69; N, 10.98; Found (%): C, 67.83; H, 5.67; N, 10.96.

*5.6.11. N-(3-fluoro-4-((6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl)-4-methyl-6-oxo-1-(2-(trifluoromethyl)phenyl)-1,6-dihydropyridazine-3-carboxamide (**15b**)*

Yield: 83.2%; M.p.: 130.2–131.2 °C; IR (KBr) cm^{-1}: 3392.1, 2959.9, 2794.9, 1688.6, 1620.6, 1606.7, 1508.6, 1479.9, 1455.4, 1431.2, 1349.7, 1317.1, 1250.4, 1211.6, 1171.1, 1147.0, 1112.6, 1060.9, 1036.0, 970.9, 854.3; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.87 (s, 1H), 8.43 (d, J = 5.2 Hz, 1H), 7.88 (d, J = 7.8 Hz, 1H), 7.80–7.68 (m, 2H), 7.65 (t, J = 7.6 Hz, 1H), 7.53 (d, J = 4.9 Hz, 2H), 7.39 (s, 1H), 7.26 (d, 1H), 7.19 (t, J = 8.5 Hz, 1H), 6.91 (s, 1H), 6.34 (d, J = 5.2 Hz, 1H), 4.23 (t, J = 6.6 Hz, 2H), 4.00 (s, 3H), 2.70 (t, J = 7.4 Hz, 2H), 2.67 (s, 3H), 2.63–2.51 (m, 4H), 2.22–2.08 (m, 2H), 1.85–1.71 (m, 4H). ^{13}C NMR (600 MHz, $CDCl_3$) δ 160.57, 160.47, 159.78, 155.57, 153.91, 152.68, 150.23, 148.74, 146.79, 145.53, 138.77, 138.53, 136.67, 136.44, 132.55, 130.85, 130.58, 129.83, 128.31, 123.99, 116.57, 115.52, 109.86, 109.71, 108.71, 102.23, 99.58, 67.48, 56.27, 54.30 (2C), 53.08, 28.32, 23.60 (2C), 20.78; MS (ESI) m/z (%): 692.5 $[M+H]^+$; Anal. calcd. for $C_{36}H_{33}F_4N_5O_5$ (%): C, 62.51; H, 4.81; N, 10.13; Found (%): C, 62.53; H, 4.82; N, 10.16.

*5.6.12. N-(3-fluoro-4-((6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl)-4-methyl-6-oxo-1-(2-(trifluoromethoxy)phenyl)-1,6-dihydropyridazine-3-carboxamide (**16b**)*

Yield: 82.6%; M.p.: 133–134 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.92 (s, 1H), 8.45 (d, J = 5.3 Hz, 1H), 7.81 (dd, J = 11.9, 2.4 Hz, 1H), 7.76 (t, J = 1.9 Hz, 1H), 7.61–7.51 (m, 3H), 7.40 (t, J = 8.1 Hz, 2H), 7.31 (dd, J = 8.6, 1.7 Hz, 1H), 7.21 (d, 1H), 6.91 (d, J = 1.2 Hz, 1H), 6.37 (d, J = 5.2 Hz, 1H), 4.24 (t, J = 6.6 Hz, 2H), 4.01 (s, 3H), 2.72 (t, 2H), 2.66 (s, 3H), 2.63–2.55 (m, 4H), 2.22–2.11 (m, J = 13.9, 6.7 Hz, 2H), 1.85–1.74 (m, 4H). ^{13}C NMR (600 MHz, $CDCl_3$) δ 160.59, 160.50, 159.74, 155.53, 153.89, 152.62, 150.20, 148.71, 146.74, 145.52, 138.75, 138.51, 136.62, 136.41, 132.52, 130.83, 130.55, 129.80, 128.30, 123.96, 116.54, 115.50, 109.84, 109.69, 108.70, 102.21, 99.52, 67.43, 56.25, 54.28 (2C), 53.05, 28.30, 23.62 (2C), 20.73; MS (ESI) m/z (%): 708.1 $[M+H]^+$; Anal. calcd. for $C_{36}H_{33}F_4N_5O_6$ (%): C, 61.10; H, 4.70; N, 9.90; Found (%): C, 61.13; H, 4.37; N, 9.96.

*5.6.13. N-(3-fluoro-4-((6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl)-1-(3-fluorophenyl)-4-methyl-6-oxo-1,6-dihydropyridazine-3-carboxamide (**17b**)*

Yield: 81.5%; M.p.: 131–133 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.97 (s, 1H), 8.49 (d, J = 5.2 Hz, 1H), 7.85 (dd, J = 11.9, 2.3 Hz, 1H), 7.62 (dd, J = 9.0, 4.7 Hz, 2H), 7.57 (s, 1H), 7.43 (s, 1H), 7.34 (dd, J = 8.8, 1.4 Hz, 1H), 7.27–7.25 (m, 1H), 7.24 (d, J = 8.6 Hz, 2H), 6.95 (d, J = 0.9 Hz, 1H), 6.40 (d, J = 5.1 Hz, 1H), 4.29 (t, J = 6.7 Hz, 2H), 4.05 (s, 3H), 2.78 (t, J = 6.4 Hz, 2H), 2.70 (s, 3H), 2.29–2.15 (m, J = 6.0 Hz, 2H), 1.93–1.79 (m, J = 6.6 Hz, 4H), 1.38–1.17 (m, J = 6.5 Hz, 4H); MS (ESI) m/z (%): 642.2 $[M+H]^+$; Anal. calcd. for $C_{35}H_{33}F_2N_5O_5$ (%): C, 65.51; H, 5.18; N, 10.91; Found (%): C, 65.53; H, 5.17; N, 10.92.

*5.6.14. N-(3-fluoro-4-((6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl)-1-(4-methoxyphenyl)-4-methyl-6-oxo-1,6-dihydropyridazine-3-carboxamide (**18b**)*

Yield: 81.8%; M.p.: 134–135 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.04 (s, 1H), 8.49 (d, J = 5.3 Hz, 1H), 7.85 (dd, J = 11.9, 2.3 Hz, 1H), 7.59–7.51 (m, 3H), 7.44 (s, 1H), 7.35 (d, J = 8.8 Hz, 1H), 7.25 (d, J = 8.6 Hz, 1H), 7.06 (d, J = 9.0 Hz, 2H), 6.93 (d, J = 1.0 Hz, 1H), 6.41 (d, J = 5.2 Hz, 1H), 4.29 (t, J = 6.6 Hz, 2H), 4.05 (s, 3H), 3.90 (s, 3H), 2.74 (t, J = 7.3 Hz, 2H), 2.69 (s, 3H), 2.62 (t, J = 6.7 Hz, 4H), 2.26–2.15 (m, 2H), 1.84 (t, J = 6.5 Hz, 4H); MS (ESI) m/z (%): 654.1 $[M+H]^+$; Anal. calcd. for $C_{36}H_{36}FN_5O_6$ (%): C, 66.14; H, 5.55; N, 10.71; Found (%): C, 66.13; H, 5.57; N, 10.72.

*5.6.15. 1-(4-chlorophenyl)-N-(3-fluoro-4-((6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl)-4-methyl-6-oxo-1,6-dihydropyridazine-3-carboxamide (**19b**)*

Yield: 83.1%; M.p.: 132–134 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.99 (s, 1H), 8.48 (d, J = 5.2 Hz, 1H), 7.86 (dd, J = 11.9, 2.3 Hz, 1H), 7.61 (dd, J = 9.0, 4.7 Hz, 2H), 7.58 (s, 1H), 7.44 (s, 1H), 7.32 (dd, J = 8.8, 1.4 Hz, 1H), 7.28–7.25 (m, 1H), 7.24 (d, J = 8.6 Hz, 2H), 6.96 (d, J = 0.9 Hz, 1H), 6.40 (d, J = 5.1 Hz, 1H), 4.28 (t, J = 6.7 Hz, 2H), 4.05 (s, 3H), 2.77 (t, J = 6.4 Hz, 2H), 2.70 (s, 3H), 2.29–2.18 (m, J = 6.0 Hz, 2H), 1.93–1.80 (m, J = 6.6 Hz, 4H), 1.38–1.19 (m, J = 6.5 Hz, 4H); MS (ESI) m/z (%): 658.2 $[M+H]^+$; Anal. calcd. for $C_{35}H_{33}ClFN_5O_5$ (%): C, 63.88; H, 5.05; N, 10.64; Found (%): C, 63.89; H, 5.07; N, 10.66.

*5.6.16. 1-(3,4-difluorophenyl)-N-(3-fluoro-4-((6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl)-4-methyl-6-oxo-1,6-dihydropyridazine-3-carboxamide (**20b**)*

Yield: 82.8%; M.p.: 135–136 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.03 (s, 1H), 8.47 (d, J = 5.2 Hz, 1H), 7.83 (dd, J = 11.9, 2.0 Hz, 1H), 7.62 (d, J = 1.6 Hz, 1H), 7.57 (d, J = 9.5 Hz, 1H), 7.49–7.37 (m, 3H), 7.35 (d, J = 8.6 Hz, 1H), 7.23 (d, J = 8.7 Hz, 1H), 6.95 (d, J = 0.6 Hz, 1H), 6.39 (d, J = 5.1 Hz, 1H), 4.27 (t, J = 6.5 Hz, 2H), 4.04 (s, 3H), 2.77 (t, 2H), 2.70 (s, 3H), 2.66 (t, 4H), 2.30–2.14 (m, J = 13.7, 6.7 Hz, 2H), 1.85 (t, 4H). ^{13}C NMR (600 MHz, $CDCl_3$) δ 160.48, 160.07, 158.99, 155.37, 153.72, 152.39, 149.98, 148.68, 146.92, 145.35, 138.77, 136.67, 136.44, 132.55, 130.85, 130.58, 129.83, 128.31, 123.99, 116.57, 115.52, 109.86, 109.71, 108.71, 102.23, 99.58, 67.48, 56.27, 54.30 (2C), 53.08, 28.32, 23.60 (2C), 20.78; MS (ESI) m/z (%): 660.4 $[M+H]^+$; Anal. calcd. for $C_{35}H_{32}F_3N_5O_5$ (%): C, 63.73; H, 4.89; N, 10.62; Found (%): C, 63.74; H, 4.90; N, 10.66.

*5.6.17. N-(3-fluoro-4-((6-methoxy-7-(3-(piperidin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl)-4-methyl-6-oxo-1-phenyl-1,6-dihydropyridazine-3-carboxamide (**13c**)*

Yield: 81.3%; M.p.: 145–146 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.04 (s, 1H), 8.49 (d, J = 5.2 Hz, 1H), 7.85 (dd, J = 11.9, 2.1 Hz, 1H), 7.63 (d, J = 7.7 Hz, 2H), 7.60–7.53 (m, 3H), 7.50 (t, J = 7.1 Hz, 1H), 7.43 (s, 1H), 7.38–7.31 (m, 1H), 7.25 (d, J = 8.6 Hz, 1H), 6.95 (s, 1H), 6.40 (d, J = 5.2 Hz, 1H), 4.26 (t, J = 6.6 Hz, 2H), 4.05 (s, 3H), 2.70 (s, 3H), 2.66–2.55 (m, 2H), 2.54–2.38 (m, 4H), 2.24–2.11 (m, 2H), 1.63 (t, J = 4.7 Hz, 4H), 1.52–1.40 (m, 2H); MS (ESI) m/z (%): 638.2 $[M+H]^+$; Anal. calcd. for $C_{36}H_{36}FN_5O_5$ (%): C, 67.80; H, 5.69; N, 10.98; Found (%): C, 67.83; H, 5.67; N, 10.99.

*5.6.18. N-(3-fluoro-4-((6-methoxy-7-(3-(piperidin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl)-4-methyl-6-oxo-1-(2-methylphenyl)-1,6-dihydropyridazine-3-carboxamide (**14c**)*

Yield: 79.6%; M.p.: 142–143 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.92 (s, 1H), 8.42 (d, J = 5.2 Hz, 1H), 7.81 (dd, J = 11.8, 2.4 Hz, 1H), 7.53 (s, 1H), 7.44 (d, J = 7.9 Hz, 1H), 7.39 (d, J = 2.8 Hz, 1H), 7.36–7.32 (m, 2H), 7.30 (d, J = 4.8 Hz, 1H), 7.23–7.15 (m, 2H), 6.94 (d, J = 1.2 Hz, 1H), 6.32 (d, J = 5.2 Hz, 1H), 4.22 (t, J = 6.7 Hz, 2H), 4.05 (s, 3H), 2.68 (s, 3H), 2.58 (t, 2H), 2.52–2.38 (m, J = 2.0 Hz, 4H), 2.18 (s, 3H), 2.16–2.08 (m, J = 14.2, 7.1 Hz, 2H), 1.67–1.55 (m, J = 10.6, 5.3 Hz, 4H), 1.49–1.35 (m, 2H); MS (ESI) m/z (%): 652.2 $[M+H]^+$; Anal. calcd. for $C_{37}H_{38}FN_5O_5$ (%): C, 68.19; H, 5.88; N, 10.75; Found (%): C, 68.20; H, 5.87; N, 10.76.

*5.6.19. N-(3-fluoro-4-((6-methoxy-7-(3-(piperidin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl)-4-methyl-6-oxo-1-(2-(trifluoromethyl)phenyl)-1,6-dihydropyridazine-3-carboxamide (**15c**)*

Yield: 79.9%; M.p.: 140–141 °C; IR (KBr) cm^{-1}: 2934.6, 2770.4, 1689.4, 1598.5, 1528.6, 1508.7, 1479.9, 1455.0, 1430.9, 1376.1, 1349.1, 1316.9, 1250.1, 1211.5, 1148.4, 1133.2, 1060.7, 1035.9, 852.7; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.88 (s, 1H), 8.43 (d, J = 5.3 Hz, 1H), 7.88 (d, J = 7.6 Hz, 1H), 7.80–7.70 (m, 2H), 7.65 (t, J = 7.7 Hz, 1H), 7.53 (d, J = 5.2 Hz, 2H), 7.39 (s, 1H), 7.28–7.24 (m, 1H), 7.19 (t, J = 8.5 Hz, 1H), 6.91 (d, J = 1.1 Hz, 1H), 6.34 (d, J = 5.2 Hz, 1H), 4.21 (t, J = 6.7 Hz, 2H), 4.00 (s, 3H), 2.68 (s, 3H), 2.54–2.46 (m, 2H), 2.39 (t, 4H), 2.14–2.05 (m, J = 13.9, 6.8 Hz, 2H), 1.63–1.49 (m, 4H), 1.46–1.35 (m, 2H). ^{13}C NMR (600 MHz, $CDCl_3$) δ 160.57, 160.47, 159.78, 155.57, 153.91, 152.68, 150.23, 148.74, 146.79, 145.53, 138.26, 138.06, 137.81, 137.73, 133.42, 131.02, 130.46, 129.88, 128.26, 124.20, 116.53, 115.74, 109.84, 109.68, 108.77, 102.44, 99.81, 67.48, 56.13, 55.71, 54.48 (2C), 26.13, 25.70 (2C), 24.25, 20.68; MS (ESI) m/z (%): 706.1 $[M+H]^+$; Anal. calcd. for $C_{37}H_{35}F_4N_5O_5$ (%): C, 62.97; H, 5.00; N, 9.92; Found (%): C, 62.98; H, 5.01; N, 9.93.

*5.6.20. N-(3-fluoro-4-((6-methoxy-7-(3-(piperidin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl)-4-methyl-6-oxo-1-(2-(trifluoromethoxy)phenyl)-1,6-dihydropyridazine-3-carboxamide (**16c**)*

Yield: 81.6%; M.p.: 146–147 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.91 (s, 1H), 8.45 (d, J = 5.2 Hz, 1H), 7.89 (d, J = 7.8 Hz, 1H), 7.80–7.72 (m, 2H), 7.67 (t, J = 7.8 Hz, 1H), 7.54 (d, J = 5.3 Hz, 2H), 7.38 (s, 1H), 7.28–7.23 (m, 1H), 7.18 (t, J = 8.5 Hz, 1H), 6.90 (d, J = 1.2 Hz, 1H), 6.35 (d, J = 5.2 Hz, 1H), 4.21 (t, J = 6.8 Hz, 2H), 4.05 (s, 3H), 2.69 (s, 3H), 2.54–2.47 (m, 2H), 2.39 (t, 4H), 2.14–2.08 (m, J = 13.9, 6.8 Hz, 2H), 1.63–1.51 (m, 4H), 1.46–1.36 (m, 2H); MS (ESI) m/z (%): 722.1 $[M+H]^+$; Anal. calcd. for $C_{37}H_{35}F_4N_5O_6$ (%): C, 61.58; H, 4.89; N, 9.70; Found (%): C, 61.59; H, 4.87; N, 9.71.

*5.6.21. N-(3-fluoro-4-((6-methoxy-7-(3-(piperidin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl)-1-(3-fluorophenyl)-4-methyl-6-oxo-1,6-dihydropyridazine-3-carboxamide (**17c**)*

Yield: 80.6%; M.p.: 152–153 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.90 (s, 1H), 8.42 (d, J = 5.3 Hz, 1H), 7.86 (d, J = 7.6 Hz, 1H), 7.80–7.75 (m, 2H), 7.64 (t, J = 7.7 Hz, 1H), 7.52 (d, J = 5.2 Hz, 2H), 7.41 (s, 1H), 7.28–7.23 (m, 1H), 7.18 (t, J = 8.5 Hz, 1H), 6.92 (d, J = 1.1 Hz, 1H), 6.34 (d, J = 5.2 Hz, 1H), 4.21 (t, J = 6.7 Hz, 2H), 4.05 (s, 3H), 2.68 (s, 3H), 2.54–2.47 (m, 2H), 2.38 (t, 4H), 2.14–2.04 (m, J = 13.9, 6.8 Hz, 2H), 1.63–1.50 (m, 4H), 1.46–1.38 (m, 2H); MS (ESI) m/z (%): 656.5 $[M+H]^+$; Anal. calcd. for $C_{36}H_{35}F_2N_5O_5$ (%): C, 65.94; H, 5.38; N, 10.68; Found (%): C, 65.93; H, 5.37; N, 10.69.

*5.6.22. N-(3-fluoro-4-((6-methoxy-7-(3-(piperidin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl)-1-(4-methoxyphenyl)-4-methyl-6-oxo-1,6-dihydropyridazine-3-carboxamide (**18c**)*

Yield: 81.9%; M.p.: 151–152 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.06 (s, 1H), 8.49 (d, J = 5.3 Hz, 1H), 7.84 (dd, J = 11.9, 2.4 Hz, 1H), 7.58–7.50 (m, 3H), 7.44 (s, 1H), 7.35 (d, J = 8.7 Hz, 1H), 7.25 (d, J = 8.6 Hz, 1H), 7.05 (d, J = 9.0 Hz, 2H), 6.93 (d, J = 1.1 Hz, 1H), 6.41 (d, J = 5.2 Hz, 1H), 4.26 (t, J = 6.7 Hz, 2H), 4.05 (s, 3H), 3.90 (s, 3H), 2.69 (s, 3H), 2.59 (t, J = 7.3 Hz, 2H), 2.52–2.40 (m, 4H), 2.17 (dt, J = 13.8, 6.8 Hz, 2H), 1.68–1.58 (m, 4H), 1.47 (t, J = 4.4 Hz, 2H); MS (ESI) m/z (%): 668.1 $[M+H]^+$; Anal. calcd. for $C_{37}H_{38}FN_5O_6$ (%): C, 66.55; H, 5.74; N, 10.49; Found (%): C, 66.53; H, 5.77; N, 10.50.

*5.6.23. 1-(4-Chlorophenyl)-N-(3-fluoro-4-((6-methoxy-7-(3-(piperidin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl)-4-methyl-6-oxo-1,6-dihydropyridazine-3-carboxamide (**19c**)*

Yield: 78.6%; M.p.: 156–157 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.02 (s, 1H), 8.48 (d, J = 5.1 Hz, 1H), 7.86 (dd, J = 11.8, 2.1 Hz, 1H), 7.64 (d, J = 7.6 Hz, 2H), 7.60–7.54 (m, 2H), 7.50 (t, J = 7.1 Hz, 1H), 7.42 (s, 1H), 7.38–7.32 (m, 1H), 7.26 (d, J = 8.6 Hz, 1H), 6.96 (s, 1H), 6.42 (d, J = 5.1 Hz, 1H), 4.26 (t, J = 6.6 Hz, 2H), 4.05 (s, 3H), 2.71 (s, 3H), 2.66–2.58 (m, 2H), 2.54–2.39 (m, 4H), 2.24–2.12 (m, 2H), 1.64 (t, J = 4.7 Hz, 4H), 1.52–1.43 (m, 2H); MS (ESI) m/z (%): 672.4 $[M+H]^+$; Anal. calcd. for $C_{36}H_{35}ClFN_5O_5$ (%): C, 64.33; H, 5.25; N, 10.42; Found (%): C, 64.34; H, 5.27; N, 10.46.

*5.6.24. 1-(2,4-Dichlorophenyl)-N-(3-fluoro-4-((6-methoxy-7-(3-(piperidin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl)-4-methyl-6-oxo-1,6-dihydropyridazine-3-carboxamide (**20c**)*

Yield: 79.6%; M.p.: 146–147 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.98 (s, 1H), 8.48 (d, J = 5.2 Hz, 1H), 7.84 (dd, 1H), 7.63 (s, 1H), 7.56 (s, 1H), 7.49–7.39 (m, 3H), 7.34 (d, J = 8.9 Hz, 1H), 7.25 (t, J = 8.7 Hz, 1H), 6.96 (s, 1H), 6.39 (d, J = 5.2 Hz, 1H), 4.26 (t, J = 6.5 Hz, 2H), 4.04 (s, 3H), 2.71 (s, 3H), 2.62 (t, 2H), 2.56–2.30 (m, 4H), 2.27–2.09 (m, 2H), 1.75–1.55 (m, 4H), 1.53–1.41 (m, 2H). ^{13}C NMR (600 MHz, $CDCl_3$) δ 160.27, 159.93, 158.85, 155.26, 153.61, 152.28, 149.86, 148.57, 146.82, 145.23, 138.53, 136.53, 136.35, 132.44, 130.77, 130.51, 129.70, 128.20, 123.87, 116.38, 115.38, 109.72, 109.56, 108.61, 102.10, 99.43, 67.48, 56.13, 55.71, 54.48 (2C), 26.13, 25.70 (2C), 24.25, 20.68; MS (ESI) m/z (%): 706.4 $[M+H]^+$; Anal. calcd. for $C_{36}H_{34}Cl_2FN_5O_5$ (%): C, 61.19; H, 4.85; N, 9.91; Found (%): C, 61.20; H, 4.87; N, 9.96.

*5.6.25. N-(3-fluoro-4-((6-methoxy-7-(4-methylpiperidin-1-yl)) propoxy)quinolin-4-yl)oxy)phenyl)-4-methyl-6-oxo-1-phenyl-1,6-dihydropyridazine-3-carboxamide (**13d**)*

Yield: 80.5%; M.p.: 135–136 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.03 (s, 1H), 8.44 (d, J = 5.2 Hz, 1H), 7.81 (d, J = 11.8 Hz, 1H), 7.58 (d, J = 7.4 Hz, 2H), 7.54–7.49 (m, J = 10.2 Hz, 3H), 7.48–7.43 (m, 1H), 7.39 (s, 1H), 7.31 (d, J = 8.9 Hz, 1H), 7.20 (d, J = 8.7 Hz, 1H), 6.90 (s, 1H), 6.36 (d, J = 5.1 Hz, 1H), 4.21 (t, J = 6.6 Hz, 2H), 4.00 (s, 3H), 2.89 (d, J = 11.0 Hz, 2H), 2.65 (s, 3H), 2.51 (t, J = 7.2 Hz, 2H), 2.19–2.02 (m, 2H), 1.92 (t, J = 11.3 Hz, 2H), 1.60 (d, J = 12.2 Hz, 2H), 1.38–1.29 (m, 1H), 1.23 (t, J = 12.1 Hz, 2H), 0.89 (d, J = 6.2 Hz, 3H); MS (ESI) m/z (%): 652.6 $[M+H]^+$; Anal. calcd. for $C_{37}H_{38}FN_5O_5$ (%): C, 68.19; H, 5.88; N, 10.75; Found (%): C, 68.20; H, 5.87; N, 10.76.

*5.6.26. N-(3-fluoro-4-((6-methoxy-7-(3-(4-methylpiperidin-1-yl) propoxy)quinolin-4-yl)oxy)phenyl)-4–methyl-6-oxo-1-(2-methylphenyl)-1,6-dihydropyridazine-3-carboxamide (**14d**)*

Yield: 82.1%; M.p.: 137–138 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.92 (s, 1H), 8.49 (d, J = 5.2 Hz, 1H), 7.85 (dd, J = 11.8, 2.4 Hz, 1H), 7.55 (s, 1H), 7.47 (d, J = 7.8 Hz, 1H), 7.41 (s, 1H), 7.38 (d, J = 5.3 Hz, 1H), 7.32 (t, J = 5.6 Hz, 2H), 7.25 (t, J = 8.7 Hz, 2H), 6.98 (d, J = 1.1 Hz, 1H), 6.39 (d, J = 5.2 Hz, 1H), 4.25 (t, J = 6.7 Hz, 2H), 4.05 (s, 3H), 3.01 (t, 2H), 2.74 (s, 3H), 2.63 (t, J = 4.2 Hz, 2H), 2.25 (s, 3H), 2.17 (t, J = 6.0 Hz, 2H), 2.03 (t, 2H), 1.67 (t, J = 12.5 Hz, 2H), 1.37–1.22 (m, 3H), 0.98 (d, J = 6.2 Hz, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 160.58, 160.08, 158.96, 155.81, 153.33, 152.42, 150.03, 148.77, 147.03, 145.24, 138.78, 137.83, 137.22, 136.04, 132.16, 131.05, 130.70, 129.65, 128.11, 123.94, 116.60, 115.56, 109.74, 108.89, 102.28, 99.63, 67.61, 56.26, 55.43, 54.00 (2C), 34.11 (2C), 30.78, 26.37, 21.94, 20.79, 18.09; MS (ESI) m/z (%): 666.4 $[M+H]^+$; Anal. calcd. for $C_{38}H_{40}FN_5O_5$ (%): C, 68.55; H, 6.06; N, 10.52; Found (%): C, 68.56; H, 6.07; N, 10.53.

*5.6.27. N-(3-fluoro-4-((6-methoxy-7-(3-(4-methylpiperidin-1-yl) propoxy)quinolin-4-yl)oxy)phenyl)-4-methyl-6-oxo-1-(2-(trifluoromethyl)phenyl)-1,6-dihydropyridazine-3-carboxamide (**15d**)*

Yield: 80.9%; M.p.: 132–133 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.87 (s, 1H), 8.44 (d, J = 5.3 Hz, 1H), 7.88 (d, J = 7.6 Hz, 1H), 7.81–7.70 (m, 2H), 7.66 (t, J = 7.6 Hz, 1H), 7.53 (d, J = 7.4 Hz, 2H), 7.39 (s, 1H), 7.29–7.24 (m, 1H), 7.19 (t, J = 8.5 Hz, 1H), 6.91 (s, 1H), 6.34 (d, J = 5.2 Hz, 1H), 4.21 (t, J = 6.7 Hz, 2H), 4.00 (s, 3H), 2.92 (d, J = 9.9 Hz, 2H), 2.68 (s, 3H), 2.55 (t, 2H), 2.17–2.07 (m, J = 13.9, 6.8 Hz, 2H), 1.95 (t, J = 10.7 Hz, 2H), 1.61 (d, J = 12.8 Hz, 2H), 1.41–1.31 (m, 1H), 1.29–1.19 (m, 2H), 0.90 (d, J = 6.2 Hz, 3H); MS (ESI) m/z (%): 720.5 $[M+H]^+$; Anal. calcd. for $C_{38}H_{37}F_4N_5O_5$ (%): C, 63.41; H, 5.18; N, 9.73; Found (%): C, 63.42; H, 5.17; N, 9.74.

*5.6.28. N-(3-fluoro-4-((6-methoxy-7-(3-(4-methylpiperidin-1-yl) propoxy)quinolin-4-yl)oxy)phenyl)-4-methyl-6-oxo-1-(2-(trifluoromethoxy)phenyl)-1,6-dihydropyridazine-3-carboxamide (**16d**)*

Yield: 82.0%; M.p.: 138–139 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.98 (s, 1H), 8.44 (d, J = 5.2 Hz, 1H), 7.81 (dd, J = 11.9, 2.2 Hz, 1H), 7.64 (d, J = 8.9 Hz, 2H), 7.52 (s, 1H), 7.35 (dd, J = 16.1, 7.4 Hz, 3H), 7.30 (s, 1H), 7.21 (d, J = 8.6 Hz, 1H), 6.90 (s, 1H), 6.35 (d, J = 5.2 Hz, 1H), 4.21 (t, J = 6.7 Hz, 2H), 4.00 (s, 3H), 2.91 (d, J = 9.5 Hz, 2H), 2.65 (s, 3H), 2.60–2.46 (m, 2H), 2.19–2.03 (m, J = 13.6, 6.8 Hz, 2H), 1.94 (t, J = 9.7 Hz, 2H), 1.60 (d, J = 12.4 Hz, 2H), 1.40–1.30 (m, 1H), 1.23 (t, J = 7.6 Hz, 2H), 0.90 (d, J = 6.2 Hz, 3H); MS (ESI) m/z (%): 736.6 $[M+H]^+$; Anal. calcd. for $C_{38}H_{37}F_4N_5O_6$ (%): C, 62.04; H, 5.07; N, 9.52; Found (%): C, 62.03; H, 5.07; N, 9.56.

*5.6.29. N-(3-fluoro-4-((6-methoxy-7-(3-(4-methylpiperidin-1-yl) propoxy)quinolin-4-yl)oxy)phenyl)-1-(3-fluorophenyl)-4-methyl-6-oxo-1,6-dihydropyridazine-3-carboxamide (**17d**)*

Yield: 82.2%; M.p.: 142–144 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.96 (s, 1H), 8.48 (d, J = 5.2 Hz, 1H), 7.93 (s, 1H), 7.86 (t, J = 8.4 Hz, 2H), 7.76 (d, J = 7.7 Hz, 1H), 7.70 (t, J = 7.9 Hz, 1H), 7.57 (s, 1H), 7.42 (s, 1H), 7.37–7.30 (m, 1H), 7.27–7.21 (m, 1H), 6.97 (d, J = 0.9 Hz, 1H), 6.40 (d, J = 5.1 Hz, 1H), 4.26 (t, J = 6.6 Hz, 2H), 4.04 (s, 3H), 2.99 (t, J = 6.1 Hz, 2H), 2.70 (s, 3H), 2.61 (t, J = 6.2 Hz, 2H), 2.18 (t, J = 6.0 Hz, 2H), 2.01 (t, J = 6.2 Hz, 2H), 1.65 (t, J = 6.1 Hz, 2H), 1.48–1.33 (m, 2H), 1.29–1.23 (m, 1H), 0.94 (d, J = 6.0 Hz, 3H); MS (ESI) m/z (%): 670.2 $[M+H]^+$; Anal. calcd. for $C_{37}H_{37}F_2N_5O_5$ (%): C, 66.36; H, 5.57; N, 10.46; Found (%): C, 66.37; H, 5.58; N, 10.47.

*5.6.30. N-(3-fluoro-4-((6-methoxy-7-(3-(4-methylpiperidin-1-yl) propoxy)quinolin-4-yl)oxy)phenyl)-1-(4-methoxyphenyl)-4-methyl-6-oxo-1,6-dihydropyridazine-3-carboxamide (**18d**)*

Yield: 82.3%; M.p.: 146–148 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.06 (s, 1H), 8.49 (d, J = 5.2 Hz, 1H), 7.84 (dd, J = 11.9, 2.2 Hz, 1H), 7.57 (s, 1H), 7.54 (d, J = 8.9 Hz, 2H), 7.44 (s, 1H), 7.35 (d, J = 8.8 Hz, 1H), 7.24 (d, J = 8.6 Hz, 1H), 7.05 (d, J = 8.9 Hz, 2H), 6.93 (s, 1H), 6.41 (d, J = 5.2 Hz, 1H), 4.26 (t, J = 6.6 Hz, 2H), 4.05 (s, 3H), 3.89 (s, 3H), 2.95 (d, J = 11.1 Hz, 2H), 2.69 (s, 3H), 2.58 (t, J = 7.2 Hz, 2H), 2.16 (dt, J = 13.7, 6.7 Hz, 2H), 1.99 (t, J = 11.2 Hz, 2H), 1.65 (d, J = 12.2 Hz, 2H), 1.45–1.34 (m, 1H), 1.27 (dd, J = 14.7, 8.1 Hz, 2H), 0.94 (d, J = 6.3 Hz, 3H); MS (ESI) m/z (%): 682.5 $[M+H]^+$; Anal. calcd. for $C_{38}H_{40}FN_5O_6$ (%): C, 66.95; H, 5.91; N, 10.27; Found (%): C, 66.96; H, 5.92; N, 10.28.

*5.6.31. 1-(4-Chlorophenyl)-N-(3-fluoro-4-((6-methoxy-7-(3-(4-methylpiperidin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl)-4-methyl-6-oxo-1,6-dihydropyridazine-3-carboxamide (**19d**)*

Yield: 80.1%; M.p.: 152–153 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.92 (s, 1H), 8.47 (d, J = 5.1 Hz, 1H), 7.92 (s, 1H), 7.87 (t, J = 8.4 Hz, 2H), 7.78 (d, J = 7.7 Hz, 1H), 7.70 (t, J = 7.9 Hz, 1H), 7.58 (s, 1H), 7.43 (s, 1H), 7.37–7.31 (m, 1H), 7.27–7.22 (m, 1H), 6.96 (d, J = 0.9 Hz, 1H), 6.40 (d, J = 5.1 Hz, 1H), 4.25 (t, J = 6.6 Hz, 2H), 4.05 (s, 3H), 2.98 (t, J = 6.2 Hz, 2H), 2.70 (s, 3H), 2.60 (t, J = 6.2 Hz, 2H), 2.18 (t, J = 6.0 Hz, 2H), 2.01 (t, J = 6.2 Hz, 2H), 1.66 (t, J = 6.2 Hz, 2H), 1.48–1.32 (m, 2H), 1.29–1.24 (m, 1H), 0.96 (d, J = 6.1 Hz, 3H); MS (ESI) m/z (%): 686.3 $[M+H]^+$; Anal. calcd. for $C_{37}H_{37}ClFN_5O_5$ (%): C, 64.76; H, 5.44; N, 10.21; Found (%): C, 64.77; H, 5.45; N, 10.22.

*5.6.32. 1-(2,4-Dichlorophenyl)-N-(3-fluoro-4-((6-methoxy-7-(3-(4-methylpiperidin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl)-4-methyl-6-oxo-1,6-dihydropyridazine-3-carboxamide (**20d**)*

Yield: 78.6%; M.p.: 145–146 °C; IR (KBr) cm^{-1}: 2948.1, 2769.9, 1689.6, 1620.5, 1597.8, 1581.7, 1508.3, 1479.3, 1430.4, 1377.1, 1348.8, 1305.2, 1250.1, 1211.2, 1170.4, 1149.8, 1101.0, 854.7; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.93 (s, 1H), 8.48 (d, J = 5.3 Hz, 1H), 7.84 (dd, J = 11.9, 2.3 Hz, 1H), 7.55 (d, J = 3.1 Hz, 2H), 7.53 (s, 1H), 7.49–7.40 (m,

2H), 7.36 (dd, J = 8.7, 1.2 Hz, 1H), 7.25 (t, J = 8.6 Hz, 1H), 6.99 (d, J = 1.1 Hz, 1H), 6.38 (d, J = 5.2 Hz, 1H), 4.25 (t, J = 6.7 Hz, 2H), 4.04 (s, 3H), 3.05–2.90 (m, 2H), 2.73 (s, 3H), 2.59 (t, J = 15.5 Hz, 2H), 2.24–2.10 (m, 2H), 2.00 (t, 2H), 1.65 (d, J = 12.4 Hz, 2H), 1.44–1.30 (m, 2H), 1.26–1.21 (m, 1H), 0.94 (d, J = 6.2 Hz, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 160.61, 159.92, 159.40, 155.67, 152.30, 149.89, 148.6, 146.91, 144.71, 139.57, 137.65, 137.03, 135.83, 131.61, 131.03, 130.72, 130.60, 127.43, 123.79, 116.42, 115.40, 109.81, 109.58, 108.75, 102.13, 99.47, 67.42, 56.13, 54.18 (2C), 52.96, 28.27, 23.49 (2C), 20.85, 20.61, 17.10; MS (ESI) m/z (%): 720.3 $[M+H]^+$; Anal. calcd. for $C_{37}H_{36}Cl_2FN_5O_5$ (%): C, 61.67; H, 5.04; N, 9.72; Found (%): C, 61.68; H, 5.37; N, 9.73.

*5.6.33. N-(3-fluoro-4-((6-methoxy-7-(3-(4-methylpiperazin-1-yl) propoxy)quinolin-4-yl)oxy)phenyl)-4-methyl-6-oxo-1-phenyl-1,6-dihydropyridazine-3-carboxamide (**13e**)*

Yield: 79.7%; M.p.: 162–163 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.92 (s, 1H), 8.45 (d, J = 5.2 Hz, 1H), 7.87 (d, J = 7.9 Hz, 1H), 7.76 (t, J = 9.7 Hz, 2H), 7.67 (t, J = 7.6 Hz, 2H), 7.54 (d, J = 6.5 Hz, 2H), 7.38 (s, 1H), 7.26 (d, J = 10.4 Hz, 1H), 7.18 (t, J = 8.6 Hz, 1H), 6.91 (s, 1H), 6.34 (d, J = 5.2 Hz, 1H), 4.23 (t, J = 6.7 Hz, 2H), 4.00 (s, 3H), 2.68 (s, 3H), 2.51–2.33 (br, 10H), 2.26 (s, 3H), 2.14–2.05 (m, 2H); MS (ESI) m/z (%): 653.1 $[M+H]^+$; Anal. calcd. for $C_{36}H_{37}FN_6O_5$ (%): C, 66.24; H, 5.71; N, 12.88; Found (%): C, 66.25; H, 5.72; N, 12.89.

*5.6.34. N-(3-fluoro-4-((6-methoxy-7-(3-(4-methylpiperazin-1-yl) propoxy)quinolin-4-yl)oxy)phenyl)-4-methyl-6-oxo-1-(2-methylphenyl)-1,6-dihydropyridazine-3-carboxamide (**14e**)*

Yield: 80.2%; M.p.: 157–158 °C; IR (KBr) cm^{-1}: 3346.3, 2935.4, 2794.2, 1730.5, 1681.0, 1620.5, 1596.5, 1508.7, 1479.5, 1431.6, 1375.9, 1348.8, 1328.8, 1249.8, 1211.4, 1168.3, 1146.7, 1100.9, 1014.2, 992.8, 854.4; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.98 (s, 1H), 8.48 (d, J = 5.3 Hz, 1H), 7.83 (dd, J = 11.9, 2.4 Hz, 1H), 7.56 (s, 1H), 7.49–7.37 (m, 4H), 7.33 (dd, J = 6.6, 3.7 Hz, 2H), 7.24 (t, J = 8.6 Hz, 1H), 6.96 (d, J = 1.1 Hz, 1H), 6.39 (d, J = 5.1 Hz, 1H), 4.27 (t, J = 6.7 Hz, 2H), 4.04 (s, 3H), 2.72 (d, J = 0.9 Hz, 3H), 2.68–2.33 (br, 10H), 2.31 (s, 3H), 2.23 (s, 3H), 2.19–2.09 (m, 2H); MS (ESI) m/z (%): 667.4 $[M+H]^+$; Anal. calcd. for $C_{37}H_{39}FN_6O_5$ (%): C, 66.65; H, 5.90; N, 12.60; Found (%): C, 66.66; H, 5.91; N, 12.61.

*5.6.35. N-(3-fluoro-4-((6-methoxy-7-(3-(4-methylpiperazin-1-yl) propoxy)quinolin-4-yl)oxy)phenyl)-4-methyl-6-oxo-1-(2-(trifluoromethyl)phenyl)-1,6-dihydropyridazine-3-carboxamide (**15e**)*

Yield: 80.3%; M.p.: 146–147 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.86 (s, 1H), 8.44 (d, J = 5.3 Hz, 1H), 7.88 (d, J = 7.8 Hz, 1H), 7.75 (t, J = 9.6 Hz, 2H), 7.66 (t, J = 7.6 Hz, 1H), 7.53 (d, J = 6.5 Hz, 2H), 7.39 (s, 1H), 7.25 (d, J = 10.3 Hz, 1H), 7.19 (t, J = 8.5 Hz, 1H), 6.91 (s, 1H), 6.34 (d, J = 5.2 Hz, 1H), 4.23 (t, J = 6.7 Hz, 2H), 4.00 (s, 3H), 2.68 (s, 3H), 2.51–2.31 (br, 10H), 2.27 (s, 3H), 2.14–2.04 (m, 2H). ^{13}C NMR (600 MHz, $CDCl_3$) δ 160.80, 160.55, 160.05, 155.87, 154.22, 152.87, 150.44, 149.27, 147.45, 145.82, 138.53, 138.29, 138.10, 136.42, 133.68, 131.31, 130.73, 130.13, 128.54, 124.49, 116.75, 115.98, 110.09, 109.94, 109.27, 102.70, 100.05, 67.86, 56.74, 55.51 (2C), 55.41, 53.36 (2C), 46.33, 26.85, 21.24; MS (ESI) m/z (%): 721.1 $[M+H]^+$; Anal. calcd. for $C_{37}H_{36}F_4N_6O_5$ (%): C, 61.66; H, 5.03; N, 11.66; Found (%): C, 61.67; H, 5.04; N, 11.67.

*5.6.36. N-(3-fluoro-4-((6-methoxy-7-(3-(4-methylpiperazin-1-yl) propoxy)quinolin-4-yl)oxy)phenyl)-4-methyl-6-oxo-1-(2-(trifluoromethoxy)phenyl)-1,6-dihydropyridazine-3-carboxamide (**16e**)*

Yield: 83.6%; M.p.: 151–152 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.93 (s, 1H), 8.45 (d, J = 5.2 Hz, 1H), 7.89 (d, J = 7.9 Hz, 1H), 7.76 (t, J = 9.6 Hz, 2H), 7.67 (t, J = 7.6 Hz, 1H), 7.52 (d, J = 6.6 Hz, 2H), 7.38 (s, 1H), 7.24 (d, J = 10.2 Hz, 1H), 7.18 (t, J = 8.6 Hz, 1H), 6.92 (s, 1H), 6.35 (d, J = 5.2 Hz, 1H), 4.22 (t, J = 6.7 Hz, 2H), 4.05 (s, 3H), 2.69 (s, 3H), 2.51–2.32 (br, 10H), 2.27 (s, 3H), 2.14–2.06 (m, 2H); MS (ESI) m/z (%): 736.7 $[M+H]^+$; Anal. calcd. for $C_{37}H_{36}F_4N_6O_6$ (%): C, 60.32; H, 4.93; N, 11.41; Found (%): C, 60.33; H, 4.94; N, 11.42.

*5.6.37. N-(3-fluoro-4-((6-methoxy-7-(3-(4-methylpiperazin-1-yl) propoxy)quinolin-4-yl)oxy)phenyl)-1-(3-fluorophenyl)-4-methyl-6-oxo-1,6-dihydropyridazine-3-carboxamide (**17e**)*

Yield: 80.2%; M.p.: 132–133 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.92 (s, 1H), 8.46 (d, J = 5.2 Hz, 1H), 7.82 (dd, J = 13.9 Hz, 1H), 7.59–7.54 (m, 3H), 7.52 (d, J = 8.7 Hz, 2H), 7.41 (s, 1H), 7.37–7.29 (m, J = 8.8 Hz, 1H), 7.23 (s, 1H), 6.94 (s, 1H), 6.39 (d, J = 5.2 Hz, 1H), 4.25 (t, J = 6.8 Hz, 2H), 4.05 (s, 3H), 2.58 (t, J = 7.3 Hz, 2H), 2.48–2.32 (br, 8H), 2.28 (s, 3H), 2.21–2.07 (m, J = 5.8 Hz, 2H); MS (ESI) m/z (%): 671.1 $[M+H]^+$; Anal. calcd. for $C_{36}H_{36}F_2N_6O_5$ (%): C, 64.47; H, 5.41; N, 12.53; Found (%): C, 64.48; H, 5.42; N, 12.54.

*5.6.38. N-(3-fluoro-4-((6-methoxy-7-(3-(4-methylpiperazin-1-yl) propoxy)quinolin-4-yl)oxy)phenyl)-1-(4-methoxyphenyl)-4-methyl-6-oxo-1,6-dihydropyridazine-3-carboxamide (**18e**)*

Yield: 77.6%; M.p.: 151–152 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.05 (s, 1H), 8.49 (d, J = 5.3 Hz, 1H), 7.84 (dd, J = 11.9, 2.4 Hz, 1H), 7.58 (s, 1H), 7.54 (d, J = 9.0 Hz, 2H), 7.44 (s, 1H), 7.35 (d, J = 10.2 Hz, 1H), 7.25 (d, J = 8.6 Hz, 1H), 7.06 (d, J = 9.0 Hz, 2H), 6.93 (d, J = 1.1 Hz, 1H), 6.41 (d, J = 5.1 Hz, 1H), 4.27 (t, J = 6.7 Hz, 2H), 4.05 (s, 3H), 3.90 (s, 3H), 2.69 (s, 3H), 2.64–2.34 (br, 10H), 2.31 (s, 3H), 2.19–2.10 (m, 2H); MS (ESI) m/z (%): 683.5 $[M+H]^+$; Anal. calcd. for $C_{37}H_{39}FN_6O_6$ (%): C, 65.09; H, 5.76; N, 12.31; Found (%): C, 65.10; H, 5.77; N, 12.32.

*5.6.39. 1-(4-Chlorophenyl)-N-(3-fluoro-4-((6-methoxy-7-(3-(4-methylpiperazin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl)-4-methyl-6-oxo-1,6-dihydropyridazine-3-carboxamide (**19e**)*

Yield: 77.1%; M.p.: 134–135 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.95 (s, 1H), 8.47 (d, J = 5.2 Hz, 1H), 7.83 (dd, J = 14.0 Hz, 1H), 7.59–7.55 (m, 3H), 7.51 (d, J = 8.8 Hz, 2H), 7.42 (s, 1H), 7.37–7.28 (m, J = 8.6 Hz, 1H), 7.23 (s, 1H), 6.93 (s, 1H), 6.38 (d, J = 5.2 Hz, 1H), 4.25 (t, J = 6.7 Hz, 2H), 4.03 (s, 3H), 2.58 (t, J = 7.2 Hz, 2H), 2.48 (br, 8H), 2.29 (s, 3H), 2.21–2.06 (m, J = 5.9 Hz, 2H); MS (ESI) m/z (%): 687.2 $[M+H]^+$; Anal. calcd. for $C_{36}H_{36}ClFN_6O_5$ (%): C, 62.92; H, 5.28; N, 12.23; Found (%): C, 62.93; H, 5.29; N, 12.24.

*5.6.40. 1-(3,4-Difluorophenyl)-N-(3-fluoro-4-((6-methoxy-7-(3-(4-methylpiperazin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl)-4-methyl-6-oxo-1,6-dihydropyridazine-3-carboxamide (**20e**)*

Yield: 75.6%; M.p.: 138–139 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.97 (s, 1H), 8.48 (d, J = 5.3 Hz, 1H), 7.83 (dd, J = 11.9, 2.3 Hz, 1H), 7.56 (s, 1H), 7.50 (d, J = 3.0 Hz, 1H), 7.48 (t, 1H), 7.43 (s, 1H), 7.39 (d, J = 7.7 Hz, 1H), 7.34 (dd, J = 9.9, 2.2 Hz, 1H), 7.24 (d, J = 8.6 Hz, 1H), 6.94 (d, J = 1.0 Hz, 1H), 6.39 (d, J = 5.2 Hz, 1H), 4.26 (t, J = 6.7 Hz, 2H), 4.04 (s, 3H), 2.69 (s, 3H), 2.64–2.34 (br, J = 15.5, 14.5, 8.3 Hz, 10H), 2.30 (s, 3H), 2.18–2.09 (m, 2H). ^{13}C NMR (600 MHz, $CDCl_3$) δ 160.48, 160.07, 158.99, 155.37, 153.72, 152.39, 149.98, 148.68, 146.92, 145.35, 138.77, 136.67, 136.44, 132.55, 130.85, 130.58, 129.83, 128.31, 123.99, 116.57, 115.52, 109.86, 109.71, 108.71, 102.23, 99.58, 67.86, 56.74, 55.51 (2C), 55.41, 53.36 (2C), 46.33, 26.85, 21.24; MS (ESI) m/z (%): 689.5 $[M+H]^+$; Anal. calcd. for $C_{36}H_{35}F_3N_6O_5$ (%): C, 62.78; H, 5.12; N, 12.20; Found (%): C, 62.79; H, 5.13; N, 12.21.

5.7. Pharmacology

5.7.1. MTT assay in vitro

The anti-proliferative activities of compounds **13a**–**20e** were evaluated against HT-29, H460, A549, MKN-45, and U87MG 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.

5.7.2. c-Met kinase assay

The c-Met kinase activity was evaluated using homogeneous time-resolved fluorescence (HTRF) assays as previously reported protocol [29,30]. 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 related to this article can be found at http://dx.doi.org/10.1016/j.ejmech.2014.06.068.

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