Bioorganic & Medicinal Chemistry 21 (2013) 5246–5260

Contents lists available at SciVerse ScienceDirect

Bioorganic & Medicinal Chemistry

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

# Discovery and optimization of novel 4-phenoxy-6,7-disubstituted quinolines possessing semicarbazones as *c*-Met kinase inhibitors

Baohui Qi, Bin Mi, Xin Zhai, Ziyi Xu, Xiaolong Zhang, Zeru Tian, Ping Gong *

*Key Laboratory of Structure-Based Drugs Design & Discovery of Ministry of Education, School of Pharmaceutical Engineering, Shenyang Pharmaceutical University, Shenyang, Liaoning Province 110016, PR China*

ARTICLE INFO

*Article history:*
Received 23 May 2013
Revised 10 June 2013
Accepted 11 June 2013
Available online 19 June 2013

*Keywords:*
*c*-Met
Kinase inhibitor
Anti-tumor
Quinoline
Semicarbazone

ABSTRACT

A novel series of $N^1$-(3-fluoro-4-(6,7-disubstituted-quinolin-4-yloxy)phenyl)-$N^4$-arylidenesemicarbazide derivatives were synthesized and evaluated for their *c*-Met kinase inhibition and cytotoxicity against A549, HT-29, MKN-45 and MDA-MB-231 cancer cell lines in vitro. Several potent compounds were further evaluated against three other cancer cell lines (U87MG, NCI-H460 and SMMC7721). Most of compounds tested exhibited moderate to excellent activity. The studies of SARs identified the most promising compound **28** (*c*-Met $IC_{50}$ = 1.4 nM) as a *c*-Met kinase inhibitor. In this study, a promising compound **28** was identified, which displayed 2.1-, 3.3-, 48.4- and 3.6-fold increase against A549, HT-29, U87MG and NCI-H460 cell lines, respectively, compared with that of Foretinib.



## 1. Introduction

The *c*-mesenchymal-epithelia transition factor (*c*-Met) discovered in 1980s is a prototype member of the receptor tyrosine kinases (RTKs) subfamily.[1,2] Compared to normal *c*-Met/HGF signaling, aberrant *c*-Met kinase activity stimulates signaling pathways responsible for proliferation, invasion, migration, angiogenesis, survival, metastasis, and drug resistance.[3,4] Accordingly, deregulation of the *c*-Met/HGF signaling axis has been identified as a key contributing factor in a wide variety of human malignancies, including glioma, renal, lung, gastric, prostate and colorectal cancers.[5,6] Given the strong connection of abnormal *c*-Met/HGF signaling to human carcinomas, recently, developing its inhibitors have been actively pursued by researchers, especially small-molecule inhibitors targeting the catalytic domains of kinase.

Cabozantinib (Cometriq™, **1**), a quinoline-based multitargeted tyrosine kinase inhibitor,[7] was approved by U.S. FDA in November, 2012 for the treatment of patients with progressive metastatic medullary thyroid cancer (MTC). In addition, a variety of small-molecule inhibitors have emerged in recent years, which included Kirin Brewery's acylthiourea (**2**), BMS-777607 (**3**), AM7 (**4**), Foretinib (GSK1363089, **5**) and Crizotinib (PF-02341066, **6**) (Fig. 1).[8–12]

Of the *c*-Met kinase inhibitors undergoing clinical trials or launched, compounds bearing quinoline pharmacophores exhibited excellent inhibitory activity, such as compounds **1**, **2**, **4** and **5** shown in (Fig. 1). [13] The SARs of quinoline-based inhibitors suggested that quinoline pharmacophores were responsible for forming hydrogen bonds with the backbone of *c*-Met kinase, and an aryl fragment (B) probably extended into the hydrophobic pocket. Additional hydrogen bonds, which were also crucial for inhibitory activity, are formed by linkers connected phenyl rings A and B.[13–16] By using of Discovery Studio 3.0, the spatial distances of the linkers in compounds **3** (PDB: 3F82), **4** (PDB: 2RFN) and **5** (PDB: 3LQ8) were determined according to co-crystal structures bound to *c*-Met kinase as 6.434, 6.549 and 6.327 Å, respectively. The distances probably fitted aryl fragment (B) into the hydrophobic pocket which resulted in excellent inhibition. Since a large number of quinoline-based inhibitors were examined, it was found that whether the structures of linkers were constrained (**3** and **4**) or not (**1**, **2** and **5**), six chemical bonds (shown in Fig. 1) were retained in linkers which could afford proper spatial distances between phenyl ring A and B.

Several investigations have recognized that *N*-acylhydrazone and its mimics, which contained several hydrogen donors and acceptors, were of diverse biologic activity and strong coordination ability. Especially, they were widely used as building blocks in the design of anticancer agents, exemplified by procaspase-3 activator **7**, *c*-Met kinase inhibitor **8** and topo II inhibitor **9** (Fig. 2).[17–19] Accordingly, we designed a series of $N^1$-(3-fluoro-4-(6,7-disubstituted-quinolin-4-yloxy) phenyl)-$N^4$-arylidenesemicarbazide derivatives by molecular hybrid of the 4-phenoxy-6,7-disubstituted quinoline cores and *N*-acylhydrazone scaffolds in which six chemical bonds were reserved in the linkers and the spatial distance,

* Corresponding author. Tel./fax: +86 24 2398 6429.
*E-mail address:* gongpinggp@126.com (P. Gong).

0968-0896/$ - see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.bmc.2013.06.026

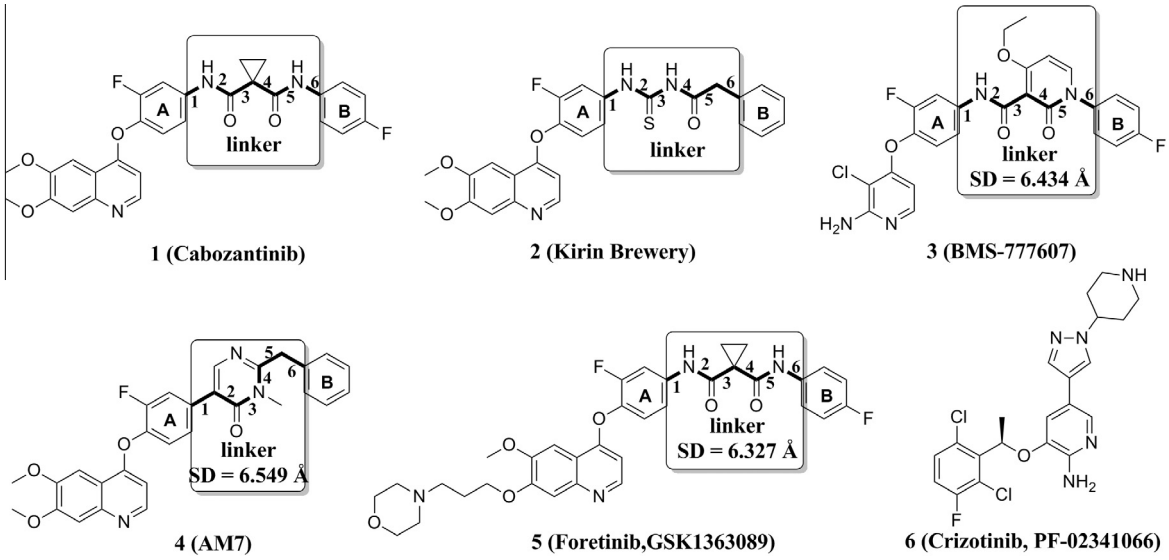



**Fig. 1.** The representative small-molecule *c*-Met kinase inhibitors.

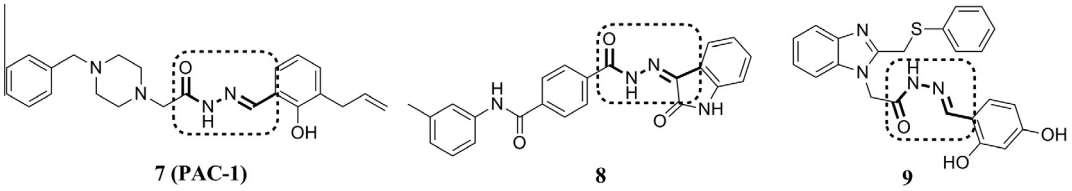



**Fig. 2.** Anticancer agents bearing *N*-acylhydrazone fragments.

approximate 6.422 Å (determined by Discovery Studio 3.0), was similar to that of **3**, **4** and **5**. In addition, at the 7-position of quinolines, a three-carbon tether which contained different cyclic tertiary amines were introduced as polar and water-solubilizing fragments. The SARs of the novel quinoline-based derivatives were investigated by modifying cyclic tertiary amines ($R_1$), the aryl rings ($R_2$), as well as linkers and the most promising compound **28** was found (Fig. 3).

All target compounds were evaluated for their antiproliferative activity in vitro against three *c*-Met-addicted cancer cells which included A549 (human nonsmall-cell lung cancer cell), HT-29 (human colorectal cancer cell) and MKN-45 (human gastric cancer cell) and a *c*-Met less sensitive MDA-MB-231 (human breast cancer cell) for ruling out off-target effects. Several potent compounds were further evaluated against three other cancer cell lines (U87MG, NCI-H460 and SMMC7721). The enzymatic assays were performed in order to determine *c*-Met kinase inhibition and detail the SARs and most of them showed promising inhibition. With Foretinib and PAC-1 as references, the inhibitory activity expressed as $IC_{50}$ are summarized in Tables 1–3.

## 2. Chemistry

Compounds **20a–e**, **21a–c**, **22a–c**, **23a–c** and **24–42** were synthesized according to the routes outlined in Scheme 1. Commercially available 4-hydroxy-3-methoxyacetophenone was alkylated with 1-bromo-3- chloropropane in the presence of $K_2CO_3$ to provide **10**.[20] Nearly regioselective nitration with fuming nitric acid,[21] subsequent aminomethylenation by means of modified Vilsmeier–Haack reagent *N*,*N*-dimethylformamide dimethylacetal (DMF-DMA) afforded **12**.[22] The intramolecular cyclization in the presence of iron powder and acetic acid afforded the quinolinol core **13**, which underwent a nucleophilic substitution with different amines (morpholine, piperidine, 4-methylpiperidine and pyrrolidine) to

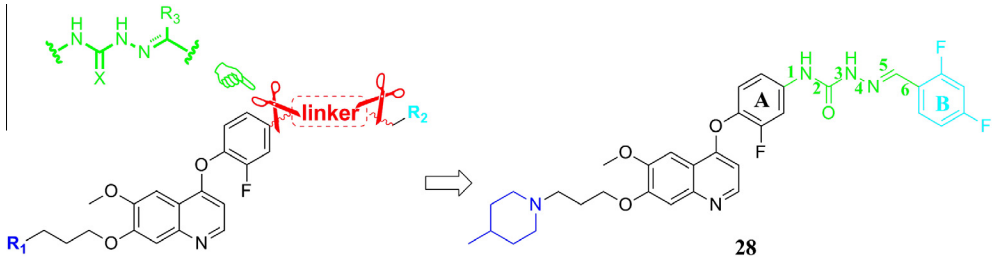
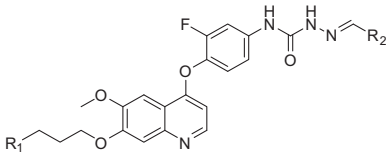



**Fig. 3.** The design of compound **28**.

**Table 1**
Cytotoxicity of compounds **20a–e**, **21a–c**, **22a–c** and **23a–c** against A549, HT-29, MKN-45 and MDA-MB-231 and *c*-Met kinase inhibition in vitro



| Entry | $R_1$ | $R_2$ | $IC_{50}$ (μM) | | | | *c*-Met $IC_{50}$ (μM) |
|---|---|---|---|---|---|---|---|
| | | | A549 | HT-29 | MKN-45 | MDA-MB-231 | |
| **20a** |  | Ph | 0.35 ± 0.029 | 0.20 ± 0.026 | 0.67 ± 0.056 | 2.1 ± 0.32 | 0.056 |
| **20b** |  | 4-F-Ph | 0.20 ± 0.017 | 0.096 ± 0.013 | 0.56 ± 0.027 | 1.6 ± 0.15 | 0.043 |
| **20c** |  | 4-Cl-Ph | 0.33 ± 0.059 | 0.16 ± 0.024 | 0.64 ± 0.029 | 1.2 ± 0.11 | ND[a] |
| **20d** |  | 4-$OCF_3$-Ph | 0.88 ± 0.12 | 1.4 ± 0.12 | 1.2 ± 0.036 | 1.8 ± 0.31 | 0.11 |
| **20e** |  | 4-$CF_3$-Ph | 0.79 ± 0.10 | 1.1 ± 0.14 | 0.78 ± 0.061 | 1.1 ± 0.15 | 0.095 |
| **21a** |  | 4-F-Ph | 0.089 ± 0.019 | 0.13 ± 0.021 | 0.49 ± 0.075 | 0.82 ± 0.070 | 0.019 |
| **21b** |  | Ph | 0.16 ± 0.015 | 0.18 ± 0.012 | 0.58 ± 0.080 | 1.0 ± 0.18 | 0.029 |
| **21c** |  | 4-Cl-Ph | 0.22 ± 0.035 | 0.098 ± 0.026 | 0.47 ± 0.13 | 0.94 ± 0.13 | 0.022 |
| **22a** |  | Ph | 0.30 ± 0.026 | 0.24 ± 0.036 | 0.51 ± 0.15 | 0.93 ± 0.11 | 0.021 |
| **22b** |  | 4-F-Ph | 0.11 ± 0.040 | 0.083 ± 0.019 | 0.61 ± 0.037 | 0.93 ± 0.055 | 0.018 |
| **22c** |  | 4-Cl-Ph | 0.17 ± 0.015 | 0.14 ± 0.026 | 0.62 ± 0.083 | 1.2 ± 0.25 | 0.026 |
| **23a** |  | Ph | 0.42 ± 0.085 | 0.44 ± 0.042 | 0.77 ± 0.14 | 0.95 ± 0.16 | 0.032 |
| **23b** |  | 4-F-Ph | 0.27 ± 0.045 | 0.22 ± 0.062 | 0.59 ± 0.15 | 1.3 ± 0.26 | 0.034 |
| **23c** |  | 4-Cl-Ph | 0.41 ± 0.055 | 0.18 ± 0.038 | 0.61 ± 0.13 | 1.3 ± 0.20 | ND |
| **Foretinib** | | — | 0.17[b] | 0.26 ± 0.026[c] | 0.023 ± 0.0015[d] | ND | 0.0011[e] |
| **PAC-1** | | — | ND | 0.83 ± 0.079 | 0.82 ± 0.063 | 4.6 ± 0.50 | ND |

[a] ND = not determined.
[b] Reported $IC_{50}$ = 0.029 μM.[31]
[c] Reported $IC_{50}$ = 0.165 μM.[31]
[d] Reported $IC_{50}$ = 0.008 μM.[32]
[e] Reported $IC_{50}$ = 0.004 μM.[31]

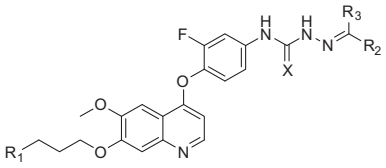
give access to the desired intermediates **14a–d**. The resultant hydroxyl moieties **14a–d** were converted to the corresponding **15a–d** on exposure to phosphorus oxychloride. $S_N2$ reactions of chloride in the intermediates **15a–d** with 2-fluoro-4-nitrophenol furnished **16a–d** which were reduced by iron powder and concentrated hydrochloric acid in ethanol/water (9:1 v/v) to provide anilines **17a–d** in excellent yields. By further treatment with phenyl chloroformate, **17a–d** were converted into amides **18a–d**. Subsequently, the key intermediate semicarbazides **19a–d** were available via hydrazinolysis of **18a–d** with 80% hydrazine monohydrate in refluxing 1,4-dioxane. Finally, target compounds were available via the condensation of **19a–d** with appropriate aldehydes or ketones in isopropanol at 80 °C with catalytic amounts of acetic acid.[23]

Scheme 2 depicts the sequence of reactions that led to the preparation of compounds **45a–c**. Treatment of amine **17b** with thiophosgen in saturated sodium bicarbonate aqueous solution and $CHCl_3$ furnished isothiocyanate **43**,[24] which was then treated with 80% hydrazine monohydrate in $CHCl_3$ at room temperature to give thiosemicarbazide **44**. The synthesis of compounds **45a–c** was progressed as previously described reactions shown in Scheme 1.

As shown in Scheme 3, compound **46** was obtained by reduction of **28** using sodium triacetoxyborohyride (STAB) in THF and acetic acid at room temperature.[17]

The structures of target compounds were confirmed by IR, $^1$H NMR, $^{13}$C NMR, 2D NOESY NMR and MS spectra. All target compounds, with the exception of compound **46**, might exist in the *E* or *Z* isomeric form due to the imino bond. In addition, it was reported that the hydrazone fragment could isomerize to the azo form in solution (Scheme 4), however, the hydrazone form is more stable.[25] It was interesting that the conditions and reagents adopted in this report selectively led to the hydrazone forms, which were confirmed by $^1$H NMR. In order to further confirm the configuration of target compounds, compound **28** was selected

**Table 2**
Cytotoxicity of compounds **24-42**, **45a-c** and **46** against A549, HT-29, MKN-45 and MDA-MB-231 and *c*-Met kinase inhibition in vitro



| Entry | $R_1$ | X | $R_2$ | $R_3$ | $IC_{50}$ (μM) | | | | *c*-Met $IC_{50}$ (μM) |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | A549 | HT-29 | MKN-45 | MDA-MB-231 | |
| **24** |  | O | 3,4-F-Ph | H | 0.27 ± 0.026 | 0.38 ± 0.041 | 0.71 ± 0.092 | 1.3 ± 0.18 | 0.026 |
| **25** |  | O | 2-F-Ph | H | 0.13 ± 0.010 | 0.22 ± 0.012 | 0.57 ± 0.041 | 0.92 ± 0.055 | 0.013 |
| **26** |  | O | 2,4-F-Ph | H | 0.078 ± 0.011 | 0.19 ± 0.022 | 0.56 ± 0.078 | 0.85 ± 0.069 | 0.0044 |
| **27** |  | O | 2-F-Ph | H | 0.22 ± 0.017 | 0.18 ± 0.019 | 0.49 ± 0.060 | 0.88 ± 0.095 | 0.0039 |
| **28** |  | O | 2,4-F-Ph | H | 0.080 ± 0.012 | 0.080 ± 0.014 | 0.51 ± 0.093 | 1.1 ± 0.14 | 0.0014 |
| **29** |  | O | 2-$CF_3$-Ph | H | 0.13 ± 0.027 | 0.16 ± 0.010 | 0.59 ± 0.059 | 0.73 ± 0.11 | 0.043 |
| **30** |  | O | 2-CN-Ph | H | 0.19 ± 0.025 | 0.26 ± 0.029 | 0.52 ± 0.17 | 0.61 ± 0.055 | 0.024 |
| **31** |  | O | 3-$NO_2$-Ph | H | 0.75 ± 0.12 | 0.32 ± 0.055 | 0.76 ± 0.027 | 1.0 ± 0.096 | 0.022 |
| **32** |  | O | 4-$NO_2$-Ph | H | 0.82 ± 0.096 | 0.37 ± 0.040 | 0.89 ± 0.097 | 1.4 ± 0.26 | 0.035 |
| **33** |  | O | 2-$NO_2$-Ph | H | 0.19 ± 0.020 | 0.15 ± 0.0091 | 0.48 ± 0.026 | 0.55 ± 0.072 | 0.012 |
| **34** |  | O | 3-$OCH_3$-Ph | H | 0.34 ± 0.045 | 0.33 ± 0.062 | 0.73 ± 0.10 | 1.2 ± 0.25 | 0.049 |
| **35** |  | O | 2,5-$OCH_3$-Ph | H | 0.86 ± 0.11 | 0.59 ± 0.11 | 0.86 ± 0.10 | 1.5 ± 0.16 | ND[a] |
| **36** |  | O | 2,4,6-$CH_3$-Ph | H | 1.9 ± 0.30 | 0.70 ± 0.13 | 0.65 ± 0.055 | 1.1 ± 0.24 | 0.19 |
| **37** |  | O | 3-Pyridyl | H | 0.46 ± 0.055 | 0.32 ± 0.053 | 0.79 ± 0.17 | 0.88 ± 0.19 | 0.061 |
| **38** |  | O | 2-Furanyl | H | 0.44 ± 0.047 | 0.36 ± 0.033 | 0.71 ± 0.068 | 0.91 ± 0.14 | 0.091 |
| **39** |  | O | 2-Pyrrolyl | H | 0.54 ± 0.060 | 0.44 ± 0.017 | 0.93 ± 0.14 | 1.0 ± 0.15 | 0.089 |
| **40** |  | O | Ph | Me | 0.16 ± 0.015 | 0.20 ± 0.022 | 0.64 ± 0.082 | 0.96 ± 0.21 | 0.038 |
| **41** |  | O | Ph | Et | 0.29 ± 0.033 | 0.33 ± 0.053 | 0.93 ± 0.094 | 1.1 ± 0.18 | 0.046 |
| **42** |  | O | 2-Propyl | H | 1.9 ± 0.25 | 1.1 ± 0.13 | 2.0 ± 0.47 | 2.7 ± 0.35 | 0.94 |
| **45a** |  | S | 2,4-F-Ph | H | 0.19 ± 0.025 | 0.33 ± 0.011 | 0.68 ± 0.036 | 0.95 ± 0.10 | 0.0053 |
| **45b** |  | S | 2-$NO_2$-Ph | H | 0.25 ± 0.026 | 0.14 ± 0.019 | 0.45 ± 0.046 | 0.83 ± 0.11 | 0.0044 |
| **45c** |  | S | 2-Furanyl | H | 0.47 ± 0.052 | 0.40 ± 0.036 | 0.88 ± 0.035 | 1.1 ± 0.21 | 0.12 |
| **46** |  | O | 2,4-F-Ph | — | 0.35 ± 0.046 | 0.66 ± 0.056 | 0.86 ± 0.060 | 1.3 ± 0.22 | 0.12 |
| **Foretinib** | | — | — | — | 0.17[b] | 0.26 ± 0.026[c] | 0.023 ± 0.0015[d] | ND | 0.0011[e] |
| **PAC-1** | | — | — | — | ND | 0.83 ± 0.079 | 0.82 ± 0.063 | 4.6 ± 0.50 | ND |

[a] ND = not determined.
[b] Reported $IC_{50}$ = 0.029 μM.[31]
[c] Reported $IC_{50}$ = 0.165 μM.[31]
[d] Reported $IC_{50}$ = 0.008 μM.[32]
[e] Reported $IC_{50}$ = 0.004 μM.[31]

**Table 3**
Cytotoxicity of compounds **21a, 21c, 26** and **28** against U87MG, NCI-H460 and SMMC-7721 in vitro

| Entry | $IC_{50}$ (μM) | | |
|---|---|---|---|
| | U87MG | NCI-H460 | SMMC-7721 |
| **21a** | 0.019 ± 0.0023 | 0.069 ± 0.0081 | 0.33 ± 0.028 |
| **21c** | 0.024 ± 0.0041 | 0.063 ± 0.0055 | 0.41 ± 0.039 |
| **26** | 0.018 ± 0.0016 | 0.077 ± 0.0082 | 0.30 ± 0.041 |
| **28** | 0.0097 ± 0.001 | 0.057 ± 0.008 | 0.29 ± 0.035 |
| **Foretinib** | 0.47 ± 0.058 | 0.21 ± 0.018 | 0.32 ± 0.049 |

and underwent 2D NOESY NMR, and the NOESY effect (Fig. 4) was observed between the $H_1$ (–C***H***=N–, $\delta$ = 8.18 ppm) and $H_2$ (=N–N***H***–, $\delta$ = 11.00 ppm), which existed only in the *E* isomer and should not be observed in the *Z* isomer due to the larger intramolecular $H_1$–$H_2$ distance (see Supplementary information).

## 3. Biology

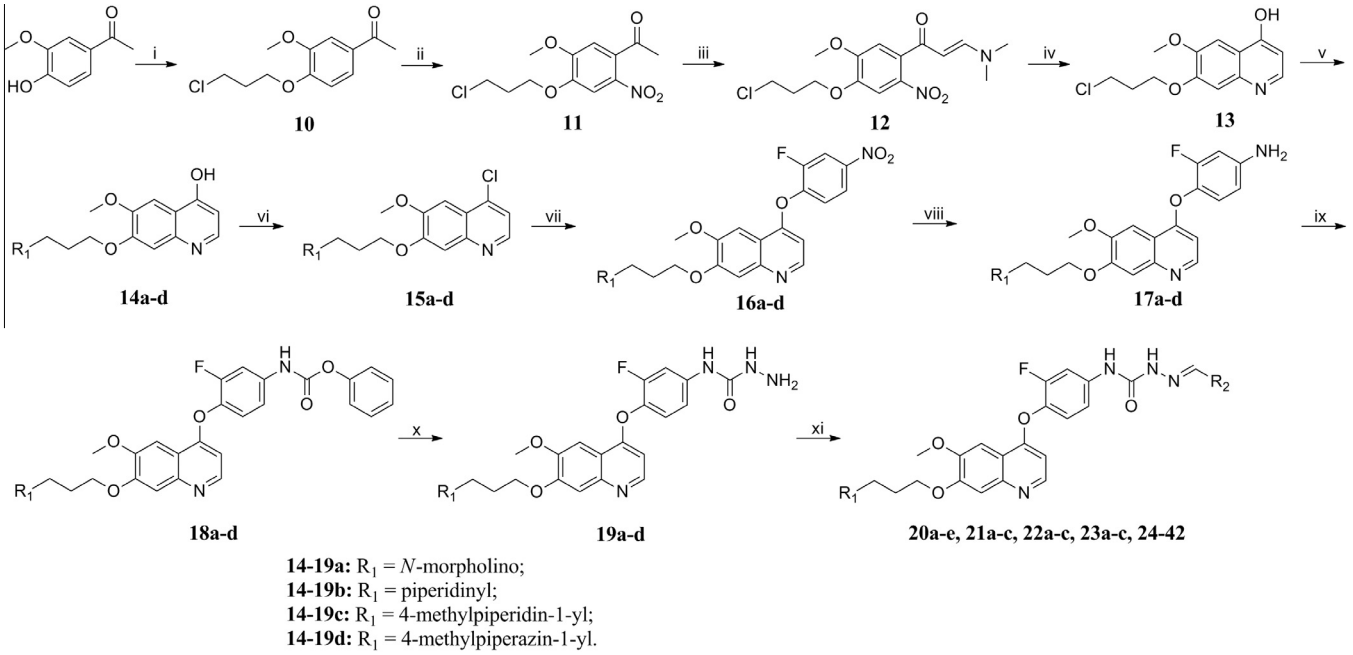
### 3.1. Cytotoxicity against tumor cells assay

All target compounds were evaluated for their cytotoxicity in vitro against *c*-Met-addicted cancer cell lines including A549, HT-29, MKN-45 and a *c*-Met less sensitive MDA-MB-231 by the 3-(4,5-dimethylthiazol-2-yl)-2,5- diphenyltetrazolium bromide (MTT) assay, taking Foretinib and PAC-1 as references.[26–28] Several potent compounds were further evaluated against three other cancer cell lines (U87MG, NCI-H460 and SMMC7721). Each compound was tested in three independent experiments, and the data, which are presented as the mean ± SD, are summarized in Tables 1–3.

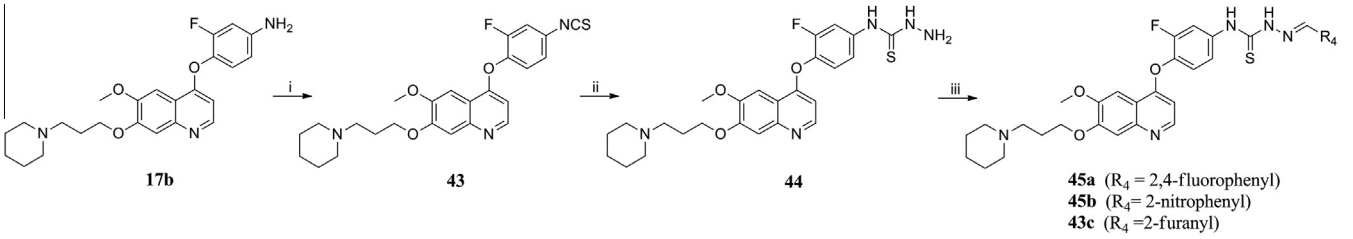
The cancer cells were cultured in minimum essential medium (MEM) supplemented with 10% fetal bovine serum (FBS). Approximately $4 \times 10^3$ cells, suspended in MEM medium, were plated onto each well of a 96-well plate and incubated in 5% $CO_2$ at 37 °C for 24 h. The test compounds were added to the culture medium at the indicated final concentrations and the cell cultures were continued for 72 h. Fresh MTT was added to each well at a final concentration of 5 μg/mL and incubated with cells at 37 °C for 4 h. The formazan crystals were dissolved in 100 μL DMSO per each well, and the absorbency at 492 nm (for the absorbance of MTT formazan) and 630 nm (for the reference wavelength) was measured with the ELISA reader. All of the compounds were tested three times in each of the cell lines. The results expressed as $IC_{50}$ (inhibitory concentration of 50%) were the mean ± SD and were calculated by using the Bacus Laboratories Incorporated Slide Scanner (Bliss) software.

### 3.2. HTRF kinase assay

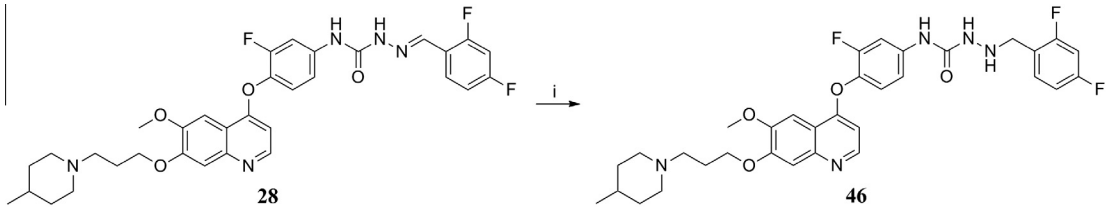
The *c*-Met kinase assays were performed by homogenous time-resolved fluorescence (HTRF) assay in order to determine the *c*-Met



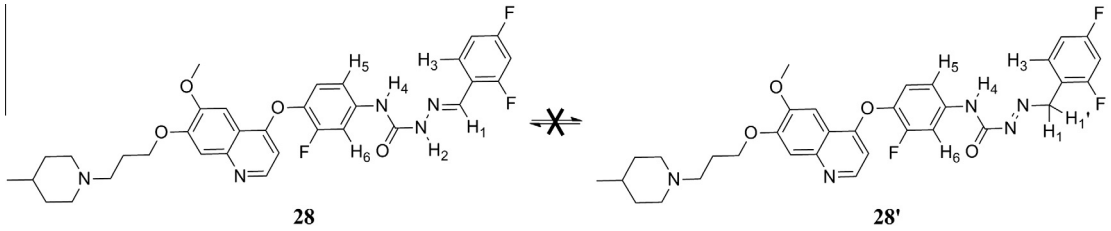

**Scheme 1.** Reagents and conditions: (i) $Cl(CH_2)_3Br$, $K_2CO_3$, DMF, rt; (ii) fuming nitric acid, $CH_2Cl_2$, −10 °C; (iii) DMF-DMA, toluene, reflux; (iv) Fe (powder), acetic acid, 80 °C; (v) amines, MeCN, reflux; (vi) $POCl_3$, MeCN, reflux; (vii) 2-fluoro-4-nitrophenol, chlorobenzene, reflux; (viii) Fe (powder), conc. HCl, ethanol/water (9:1 v/v), reflux; (ix) phenyl chloroformate, anhydrous $K_2CO_3$, dry acetone, 0 °C to rt; (x) 80% hydrazine monohydrate, 1,4-dioxane, reflux; (xi) aldehydes or ketones, acetic acid, *i*-PrOH, reflux.




**Scheme 2.** Reagents and conditions: (i) $CSCl_2$, sat. aq. $NaHCO_3$, $CHCl_3$, 0 °C to rt; (ii) 80% hydrazine monohydrate, $CHCl_3$, rt; (iii) *i*-PrOH, aldehyde, acetic acid, reflux.




**Scheme 3.** Reagents and conditions: (i) 5:1/THF/$CH_3COOH$, $(CH_3COO)_3BHNa$ (STAB), 0 °C to rt.




**Scheme 4.** The tautomerism of hydrazone **28** to azo **28′**.

kinase inhibition and detail the SARs.[29,30] Served as the positive control, the $IC_{50}$ value of Foretinib was determined simultaneously. The $IC_{50}$ values that are shown in Tables 1 and 2 are the average of two independent experiments. In addition, the most promising compound **28** was further evaluated against six other tyrosine kinases using the same screening method. Briefly, 20 μg/mL poly (Glu, Tyr) 4:1 (Sigma) was precoated 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, 1.0 M DTT, 1.0 M $MgCl_2$, 1.0 M $MnCl_2$, and 0.1% $NaN_3$) was added to each well. Various concentrations of compounds diluted in 10 μL of 1% DMSO (v/v) were used as the negative control. The kinase reaction was initiated by the addition of purified tyrosine kinase proteins diluted in 39 μL of kinase reaction buffer solution. The incubation time for the reactions was 30 min at 25 °C and stopped by the addition of 5 μL of Streptavidin-XL665 and 5 μL Tk Antibody Cryptate working solution to all of wells. The plates were read using Envision (PerkinElmer) at 320 and 615 nm. The inhibition rate (%) was calculated using the following equation: $\%\text{inhibition} = 100 - [(\text{Activity of enzyme with tested compounds} - \text{Min})/(\text{Max} - \text{Min})] - 100$ (Max: the observed enzyme activity measured in the presence of enzyme, substrates, and co-factors; 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.

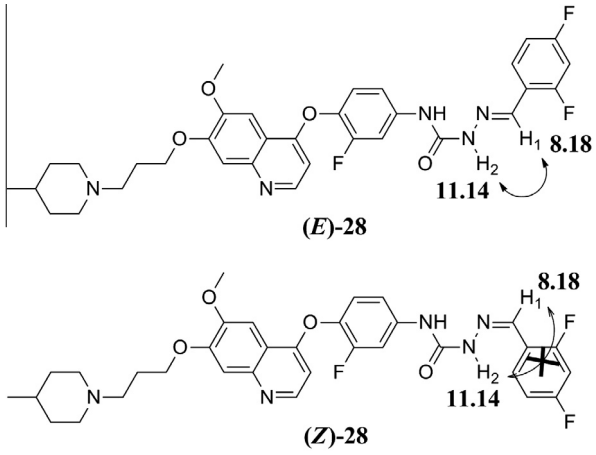



**Fig. 4.** The 2D NOESY effects of representative compound **28**.

## 4. Results and discussion

### 4.1. Enzymatic assay, cytotoxicity and lead generation

As illustrated in Tables 1 and 2, most of compounds exhibited moderate to excellent cytotoxity, with $IC_{50}$ values ranging from 0.078 to 1.9 μM against *c*-Met-addicted A549, HT-29 and MKN-45. As a general trend, the target compounds were more potent against A549 and HT-29 than against MKN-45, which suggests that designed compounds possess selectivity for A549 and HT-29 cancer cells. The most promising compound **28** (*c*-Met $IC_{50}$ = 1.4 nM) displayed excellent activity against A549 and HT-29 cell lines with the same $IC_{50}$ value of 0.080 μM, which were 2.1- and 3.2-fold more active than that of Foretinib (0.17 and 0.26 μM), respectively. Additionally, as shown in Table 3, compound **28** also showed very excellent activity against U87MG and NCI-H460 cell lines with $IC_{50}$ values of 0.0097 μM and 0.057 μM, which were 48.4- and 3.6-fold more active than that of Foretinib.

In order to explore SARs preliminarily, a small set of compounds with different amino groups at $R_1$ and aryl rings at $R_2$ were synthesized and evaluated for their activity. The data shown in Table 1 indicated that the introduction of fluoro or chloro group at the 4-position of phenyl ring B made a good contribution to potency, with following rank order: H < Cl < F. Compounds with bulky groups at 4-position, such as **20d** with 4-trifluoromethoxy group and **20e** with 4-trifluoromethyl group, lost significant potency against A549, HT-29 and *c*-Met kinase. It suggests that the 4-position of phenyl ring B is sensitive to the substituent's steric size. Further analysis revealed that amino groups at $R_2$ had a moderate influence on activity. The activity of piperidinyl and 4-methylpiperidinyl derivatives **21a–c** and **22a–c** was proved to be superior to **20a–c** and **23a–c** bearing morpholino and pyrrolidinyl groups, respectively. Accordingly, piperidinyl and 4-methylpiperidinyl derivatives were further studied in the following work.

Comprehensive piperidinyl analogs with diverse $R_2$ groups, which includes aryl rings, heterocyclic groups and isopropyl group, were examined for potency. The SARs based on $IC_{50}$ values (Table 2) shows that variations of $R_2$ groups have a marked impact on activity against cancer cells and *c*-Met kinase. Compared 3,4-difluoro analog **24** with 4-fluoro analog **21a**, a 1.3-fold drop in *c*-Met inhibition and approximate 3-fold decrease against HT-29 and A549 were observed when incorporating of well tolerated fluoro group into the 3-position of phenyl ring B. It suggests that fluoro group at ortho- and/or para-position of phenyl ring B is a

preference for enhanced activity. As such, 4-methylpiperidinyl derivatives **27** and **28** with well tolerated 2- and/or 4-fluoro groups at the phenyl ring B were prepared and examined for activity. To our delight, compound **28**, which exhibited moderate cytotoxicity against MKN-45 ($IC_{50}$ = 0.51 μM) cancer cell as well as excellent *c*-Met kinase inhibition ($IC_{50}$ = 1.4 nM) and cytotoxicity against A549 ($IC_{50}$ = 0.080 μM) and HT-29 ($IC_{50}$ = 0.080 μM), was obtained as the most promising inhibitor so far.

It can be noted from Table 2 that 2-nitro analog **33** shows a 2.4-fold enhanced inhibition of *c*-Met kinase compared to the unsubstituted **21b**. Moving the nitro group from 2-position to 3- or 4-position led to decrease in cytotoxicity against three cancer cells and *c*-Met kinase, especially to 4-position. Moreover, for compounds **29** and **30**, the replacement of 2-nitro group in **33** with other electron-withdrawing groups (EWGs), such as $-CF_3$ or –CN, brought about a loss in activity. Further investigation commenced on the studies of effectiveness of incorporating electron-donating groups (EDGs) into phenyl ring B. Unfortunately, methoxy derivatives **34** and **35** and methyl derivative **36** displayed decreased potency in cancer cells and *c*-Met kinase. The loss of activity might due to steric hindrance which results in a steric clash with the hydrophobic pocket.

Compared with compound **21b** ($R_2$ = Ph), incorporation of five- or six-membered heterocyclic groups in $R_2$ group, such as the 3-pyridyl, 2-furanyl or 2-pyrrolyl group in compounds **37**, **38** and **39**, led to 1.2- to 3.3-fold loss of activity against MKN-45, HT-29 and A459. In addition, the replacement of the phenyl ring B with an isopropyl group resulted in a 32-fold decrease in *c*-Met kinase inhibition (**42** vs **21b**). It emphasizes that the presence of an aryl ring in $R_2$ is of significance to inhibition potency.

Attention was turned to focus on linkers in the subsequent efforts. Initially, the replacement of semicarbazone with thiosemicarbazone was carried out to investigate the effects of the oxygen atom. Although thiosemicarbazone derivatives **45a**–**c** displayed a slightly boost in kinase-biochemical assays, their activity against A549 and HT-29 cancer cells decreased somewhat. Further optimization came from modification to the methine and compared with **21b** ($R_3$ = H), compounds **40** ($R_3$ = Me) and **41** ($R_3$ = Et) showed a slight loss in inhibition, and the larger the substituents were, the less potency the compounds probably became (**41** vs **40**). Additionally, it was found that compound **46**, the reductive derivative of **28**, suffered from an over 85-fold drop in *c*-Met kinase inhibition. This significant loss might be ascribed to the conformational change caused by the saturation of the double bond in imine. Accordingly, we can conclude that the semicarbazone scaffolds with an unsubstituted $sp^2$ hybridized carbon ($R_3$ = H) adjacent to a substituted phenyl ring ($R_2$) is indispensible in maintaining inhibitory activity.

### 4.2. Effects on *c*-Met phosphorylation

From the enzymatic and cellular results mentioned above, compound **28** stood out as the most potent inhibitor among the compounds synthesized. To determine whether *c*-Met kinase inhibition of compounds in cell-free system could be recapitulated in vitro, compound **28** was selected to suffer from Western blotting of A549. As the results shown in Figure 5, compound **28** can inhibit *c*-Met kinaase autophosphorylation when the concentration was 1.0 μM.

### 4.3. Kinase selectivity profile of compound 28

In order to examine whether the most potent compound **28** was a selective inhibitor, it was screened against six other tyrosine kinases inhibited by most of reported quinoline-based multi-targeted kinase inhibitors. As shown in Table 4, compound **28** exhibited excellent selectivity versus KDR ($IC_{50}$ = 690 nM, 493-fold), PDGFRα ($IC_{50}$ = 390 nM, 278-fold), c-kit ($IC_{50}$ = 230 nM, 164-fold), Flt-3 ($IC_{50}$ = 380 nM, 271-fold), and no inhibition activity against EGFR ($IC_{50}$ > 100 μM). In addition, it also can inhibit Ron kinase ($IC_{50}$ = 18.7 nM).

Furthermore, although the most potent compound **28** exhibited similar *c*-Met kinase inhibition ($IC_{50}$ = 1.4 nM) to the positive control Foretinib ($IC_{50}$ = 1.1 nM), the results of *c*-Met kinase assay in Tables 1 and 2 showed that most of compounds were less active than Foretinib. It suggested that the compounds might act through some other mechanism rather than only by inhibiting *c*-Met and Ron. Further studies on the mechanism of these compounds are in progress.

## 5. Binding mode analysis

To further elucidate the binding mode of compounds, docking analysis was performed by means of the eHITS softwares (SimBioSys) and a proposed binding mode was obtained. The co-crystal structure of Foretinib with *c*-Met kinase was selected as the docking model (PDB ID: 3LQ8). Autodock was run 200 times to give proper docked conformations and analysis of the predicted energy. The binding model was exemplified by the interaction of compound **22b** with *c*-Met kinase. As shown in Fig. 6 (B), the nitrogen atom of the quinoline and semicarbazone moiety formed five hydrogen bonds with protein residues Met1160, Asp1222 and Lys1110. The terminal 4-fluorophenyl ring (aryl B) fitted into the hydrophobic pocket that was formed by Met1131, Phe1134, Val1139, Leu1195 and Asp1222, etc.

## 6. Conclusions

In summary, a series of $N^1$-(3-fluoro-4-(6,7-disubstituted-quinolin-4-yloxy)phenyl)-$N^4$- arylidenesemicarbazide derivatives were synthesized and evaluated for their *c*-Met kinase inhibition and cytotoxicity against A549, HT-29, MKN-45 and MDA-MB-231 cancer cell lines in vitro. Most compounds exhibited moderate to excellent activity, with $IC_{50}$ values ranging from 0.078–1.9 μM against *c*-Met-addicted A549, HT-29 and MKN-45 cancer cells. Moreover, they were more potent against A549 and HT-29 than against MKN-45. The studies of SARs indicated that the presence of a semicarbazone scaffold with an unsubstituted $sp^2$ hybridized carbon ($R_3$ = H) adjacent to a 2,4-difluoro-substituted phenyl ring ($R_2$) is of significant importance to the inhibitory potency. Moreover, the introduction of a three-carbon tether containing 4-methylpiperidine ($R_1$) into the 7-position of quinolines is advantageous to the potency. To our delight, the most promising compound **28** showed an excellent inhibition of *c*-Met kinase ($IC_{50}$ = 1.4 nM) over six other kinases screened in this report, as well as 2.1-, 3.3-, 48.4- and 3.6-fold increase against A549, HT-29, U87MG and NCI-H460 cell lines than that of Foretinib, respectively.

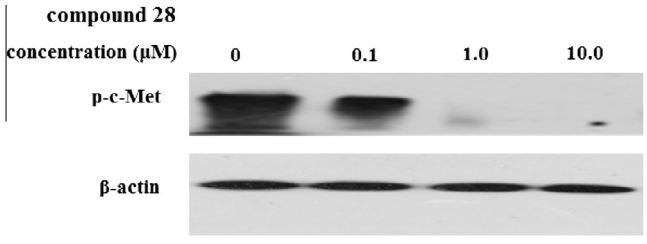



**Fig. 5.** Effects of compound **28** on *c*-Met kinase phosphorylation in A549 cancer cell.

**Table 4**
Kinase selectivity profile of compound **28**

| | Kinases | | | | | | |
|---|---|---|---|---|---|---|---|
| | *c*-Met | Ron | KDR | PDGFRα | c-kit | Flt-3 | EGFR |
| Enzyme $IC_{50}$ [a] (nM) | 1.4 | 18.7 | 690 | 390 | 230 | 380 | >100 000 |

[a] Average of $n = 2$.

## 7. Experimental protocols

### 7.1. Chemistry

Unless otherwise noted, all materials were obtained from commercial suppliers and used without further purification. All melting points were obtained on a Büchi Melting Point B-540 apparatus (Büchi Labortechnik, Flawil, Switzerland) and were uncorrected. The IR spectra were recorded by means of the KBr pellet technique on a Bruker FTS 135 spectrometer. $^1$H NMR (1D and 2D) and $^{13}$C NMR spectra were generated on a Bruker ARX-300 or ARX-600 spectrometers (Bruker Bioscience, Billerica, MA, USA). Column chromatography was carried out on silica gel (200–300 mesh). Mass spectra (MS) were taken in ESI mode on Agilent 1100 LC-MS (Agilent, Palo Alto, CA, USA). Elemental analysis was determined on a Carlo-Erba 1106 Elemental analysis instrument (Carlo Erba, Milan, Italy).

#### 7.1.1. 4-(3-Chloropropoxy)-3-methoxyacetophenone (10)

To a solution of 4-hydroxy-3-methoxy-acetophenone (6.00 g, 36.1 mmol) in DMF (25 mL) was added $K_2CO_3$ and 1-bromo-3-chloropropane (6.98 g, 50.6 mmol). The reaction mixture was then stirred at rt for 10 h. The mixture was then poured into cold water (100 mL) with vigorously agitating, and the resulting precipitate was filtered off, washed with water, and dried under vacuum to afford the title compound **10** (8.27 g) as a white solid, yield: 93.8%. Mp: 61–63 °C (Lit.[33] Mp: 57.5–58.5 °C). MS (ESI) *m*/*z*: 242.2, 244.1 ($M^+$).

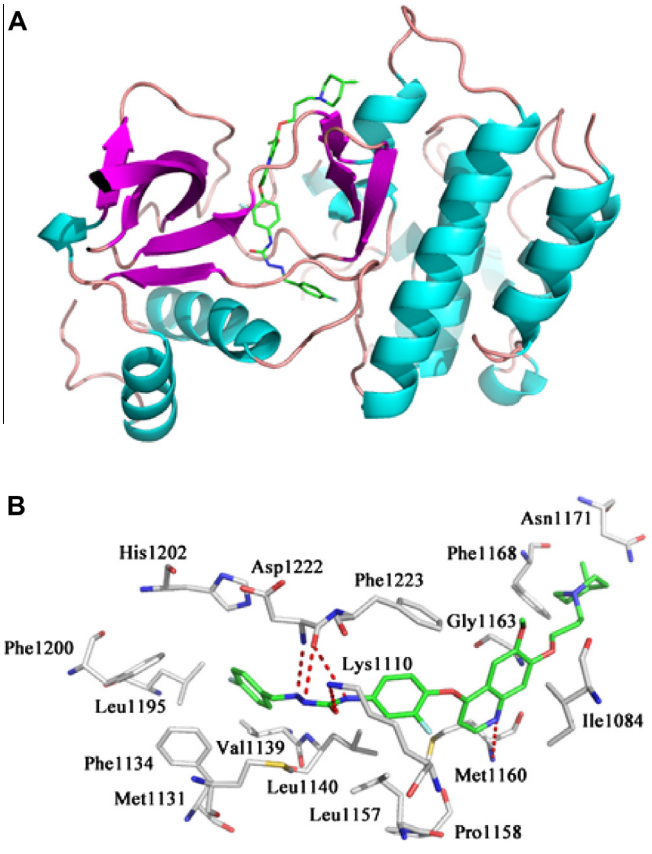



**Fig. 6.** The proposed binding mode of compound **22b** and *c*-Met kinase. (A) The proteins were displayed by ribbon and the compound **22b** was displayed by green sticks. (B) The proposed binding mode of compound **22b** and *c*-Met. The amino acid residues were displayed by sticks and the compound **22b** was displayed by green sticks. H-bonding interactions between the **22b** and *c*-Met are shown in red dotted lines.

#### 7.1.2. 4-(3-Chloropropoxy)-5-methoxy-2-nitroacetophenone (11)

A stirred solution of **10** (2.00 g, 8.22 mmol) in $CH_2Cl_2$ (10 mL) was cooled to −10 °C, and fuming nitric acid (95%, 1.30 g, 20.6 mmol) was added at a rate such that the temperature did not exceed −10 °C. The reaction mixture was allowed to stir at −10 °C for 2 h, then transferred with stirring to cold water (20 mL). After 15 min, the organic layer was separated and the aqueous layer washed with additional $CH_2Cl_2$ (10 mL). The organic portions were combined and washed with 10% w/w aqueous sodium bicarbonate solution (2 × 10 mL), then water (10 mL), then concentrated under reduced pressure to afford crude **11**, which was recrystallized from 90% ethanol to afford **11** (1.91 g) as a light yellow solid, yield: 80.1%. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.64 (s, 1H), 6.76 (s, 1H), 4.26 (t, $J$ = 6.0 Hz, 2H), 3.96 (s, 3H), 3.77 (t, $J$ = 6.6 Hz, 2H), 2.50 (s, 3H), 2.29–2.37 (m, 2H). Mp: 60-61 °C. MS (ESI) *m*/*z*: 287.0, 289.0 ($M^+$).

#### 7.1.3. 1-(4-(3-Chloropropoxy)-5-methoxy-2-nitrophenyl)-3-(dimethylamino)prop-2-en-1-one (12)

DMF-DMA (4.15 g, 34.8 mmol) was added to a solution of **11** (2.00 g, 6.95 mmol) in toluene (10 mL). The reaction was heated to 110 °C until TLC showed the completion of the reaction. After cooling to −10 °C, the resultant solid was collected by filtration, washed with toluene (5 mL) and then dried under vacuum to yield **12** (1.84 g) as a yellow solid, yield: 75.8%. Mp: 117–119 °C. MS (ESI) *m*/*z*: 342.2, 344.1 ($M^+$).

#### 7.1.4. 6-Methyloxy-7-(4-(3-chloropropoxy))-4-quiolin-ol (13)

Fe (powder, 1.23 g, 22.0 mmol) was added to a solution of **12** (1.50 g, 4.40 mmol) in acetic acid (12 mL) at 40 °C, then the mixture was stirred at 80 °C with vigorous agitation for 2 h. The hot solution was filtered through celite and washed with hot acetic acid. The combined filtrate was cooled to 20 °C, and the resultant solid was collected by filtration which was recrystallized from acetic acid (6 mL) and washed with water to afford **13** (0.820 g) as a light yellow solid , yield: 65.0%. Mp: 232–234 °C. MS (ESI) *m*/*z*: 267.0, 269.0 ($M^+$).

#### 7.1.5. General procedure for preparation of 4-hydroxyquinolines (14a–d)

To a stirring solution of **13** (10.0 g, 37.4 mmol) in acetonitrile (100 mL) at 25 °C was added appropriate secondary amines (0.374 mol), and the resulting reaction mixture was heated to 80 °C for 8 h, then cooled to room temperature. Approximately 60 mL acetonitrile was removed under reduced pressure. The residue was cooled to −10 °C, and the resultant precipitate was filtered, washed with ethyl acetate (35 mL) to give the corresponding 4-hydroxyquinolines **14a–d**.

**7.1.5.1. 6-Methyloxy-7-(4-(3-morpholino-propoxy))-4-quiolinol (14a).** Yellow solid, yield: 93.9%. Mp: 187–189 °C. MS (ESI) *m*/*z*: 319.3 ($M^+$).

**7.1.5.2. 6-Methyloxy-7-(4-(3-(piperidin-1-yl)propoxy))-4-quiolin-ol (14b).** White solid, yield: 88.7%. Mp: 176–77 °C. MS (ESI) *m*/*z*: 317.3 ($M^+$).

**7.1.5.3. 6-Methoxy-7-(3-(4-methylpiperidin-1-yl)propoxy)quinolin-4-ol (14c).** Sallow solid, yield: 87.9%. Mp: 182–184 °C. MS (ESI) *m*/*z*: 331.4 ($M^+$).

**7.1.5.4. 6-Methoxy-7-(3-(pyrrolidin-1-yl)propoxy)quinolin-4-ol (14d).** Yellow solid, yield: 84.5%. Mp: 167–169 °C. MS (ESI) *m*/*z*: 303.4 ($M^+$).

### 7.1.6. General procedure for preparation of 4-chloroquinolines (15a–d)

A solution of an appropriate dry 4-hydroxyquinoline (20.0 mmol) and $POCl_3$ (40 mL) in dry acetonitrile (40 mL) was refluxed on an oil-bath for approximate 6 h. After cooling to ambient temperature, the contents were concentrated under reduced pressure and the pale residue was poured into ice-water (100 mL) with vigorous agitation. The solution was treated with concentrated ammonium hydroxide to achieve pH to 8 while maintaining the temperature below 20 °C, and the mixture was extracted with $CH_2Cl_2$ (3 × 20 mL). The combined organic layer was washed with brine, then water, and dried over anhydrous $Na_2SO_4$, concentrated under reduced pressure to give corresponding 4-chloroquinolines **15a–d**.

**7.1.6.1. 4-Chloro-6-methyloxy-7-(4-(3-morpholino-propoxy))quinoline (15a).** White solid, yield: 82.4%. Mp: 173–176 °C. MS (ESI) *m*/*z*: 336.2, 338.2 ($M^+$).

**7.1.6.2. 4-Chloro-6-methoxy-7-(3-(piperidin-1-yl)propoxy)quinoline 15b.** White solid, yield: 85.9%. Mp: 187–188 °C. MS (ESI) *m*/*z*: 335.5 ($M^+$).

**7.1.6.3. 4-Chloro-6-methoxy-7-(3-(4-methylpiperidin-1-yl)propoxy)quinoline 15c.** White solid, yield: 81.4%. Mp: 179–181 °C. MS (ESI) *m*/*z*: 349.3 ($M^+$).

**7.1.6.4. 4-Chloro-6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy)quinoline 15d.** White solid, yield: 83.1%. Mp: 172–174 °C. MS (ESI) *m*/*z*: 321.4 ($M^+$).

### 7.1.7. General procedure for preparation of nitro compounds (16a–d)

A stirring mixture of an appropriate **15a–d** (20.0 mmol) and 2-fluoro-4-nitrophenol (24.1 mmol) in chlorobenzene (40 mL) was heated to 140 °C for about 20 h. The reaction was considered complete when less than 5% starting material remained. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure to yield a pale solid. The solid was dissolved in $CH_2Cl_2$ (80 mL), and washed with saturated $K_2CO_3$ aqueous solution (2 × 20 mL), then water (20 mL), and dried over anhydrous $Na_2SO_4$, concentrated under reduced pressure to afford a wheat solid, which was recrystallized from anhydrous ethanol (30 mL) to yield corresponding **16a–d**.

**7.1.7.1. 4-(2-Fluoro-4-nitrophenoxy)-6-methoxy-7-(3-morpholino-propoxy) quinoline (16a).** Light yellow solid, yield: 62.0%. Mp: 135–136 °C; MS (ESI) *m*/*z* (%): 458.1 ($M^+$).

**7.1.7.2. 4-(2-Fluoro-4-nitrophenoxy)-6-methoxy-7-(3-(piperidin-1-yl)propoxy) quinoline (16b).** Yellowish-white solid, yield: 80.4%. Mp: 137–138 °C; MS (ESI) *m*/*z* (%): 456.4 ($M^+$).

**7.1.7.3. 4-(2-Fluoro-4-nitrophenoxy)-6-methoxy-7-(3-(4-methylpiperidin-1-yl)propoxy)quinoline (16c).** Yellow solid; yield: 78.7%. Mp: 133–134 °C; MS (ESI) *m*/*z* (%): 470.6 ($M^+$).

**7.1.7.4. 4-(2-Fluoro-4-nitrophenoxy)-6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy) quinoline (16d).** Yellow solid, yield: 76.3%. Mp: 140–141 °C; MS (ESI) *m*/*z* (%): 442.2 ($M^+$).

### 7.1.8. General procedure for preparation of anilines (17a–d)

A mixture of **16a–d** (20.0 mmol), Fe (powder, 0.200 mol) and concentrated hydrochloric acid (36.5%, 1.00 mL) in ethanol/water (100 mL, 9:1 v/v) was refluxed with vigorous agitation for 2 h. The hot solution was filtered through celite and the filter cake was washed with hot ethanol. The combined filtrate was concentrated under reduced pressure to afford a yellow solid, which was recrystallized from anhydrous ethanol (60 mL) to yield corresponding anilines **17a–d**.

**7.1.8.1. 3-Fluoro-4-(6-methoxy-7-(3-morpholinopropoxy)quinolin-4-yloxy) aniline (17a).** White solid, yield: 92.0%. $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 8.48 (d, $J$ = 5.1 Hz, 1H), 7.58 (s, 1H), 7.44 (s, 1H), 7.04 (t, $J$ = 8.4 Hz, 1H), 6.54–6.59 (dd, $J_1$ = 12.0 Hz, $J_2$ = 2.4 Hz, 1H), 6.49–6.52 (m, 1H), 6.42 (d, $J$ = 5.1 Hz, 1H), 4.27 (t, $J$ = 6.6 Hz, 2H), 4.04 (s, 3H), 3.77–3.88 (br, 2H), 3.74 (t, $J$ = 4.5 Hz, 4H), 2.60 (t, $J$ = 6.9 Hz, 2H), 2.49–2.52 (m, 4H), 2.10–2.19 (m, 2H). Mp: 217–218 °C. MS (ESI) *m*/*z*: 427.1 ($M^+$).

**7.1.8.2. 3-Fluoro-4-(6-methoxy-7-(3-(piperdine-1-yl)propoxy)quinolin-4-yloxy) aniline (17b).** Gray solid, yield: 85.5%. Mp: 196–197 °C. MS (ESI) *m*/*z*: 426.3 ($M^+$).

**7.1.8.3. 3-Fluoro-4-(6-methoxy-7-(3-(4-methylpiperdine-1-yl)propoxy)quinolin-4-yloxy)aniline (17c).** White solid, yield: 77.4%. $^1H$ NMR (300 MHz, $CDCl_3$) 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, $J_1$ = 11.8, $J_2$ = 2.6 Hz, 1H), 6.50 (dd, $J_1$ = 9.0, $J_2$ = 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 (m, 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). Mp: 193–194 °C. MS (ESI) *m*/*z*: 440.2 ($M^+$).

**7.1.8.4. 3-Fluoro-4-(6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy)quinolin-4-yloxy) aniline (17d).** Light yellow solid, yield: 72.3%. Mp: 208–209 °C. MS (ESI) *m*/*z*: 412.5 ($M^+$).

### 7.1.9. General procedure for preparation of phenylcarbamates (18a–d)

To the mixture of **17a–d** (10.0 mmol) and anhydrous $K_2CO_3$ (2.76 g, 20.0 mmol) in dry acetone (60 mL), phenyl chloroformate (1.88 mL, 15.0 mmol) was added dropwise while maintaining the temperature between 0 °C and 5 °C. After the addition was completed, the mixture was warmed to room temperature for another 3 h, and the solvent was evaporated under reduced pressure. The residue was dissolved in $CH_2Cl_2$ (20 mL), and washed with water (3 × 10 mL), dried over anhydrous $Na_2SO_4$, concentrated under reduced pressure to afford corresponding phenylcarbamates **18a–d**, which were immediately used in the next step without further purification.

**7.1.9.1. Phenyl 3-fluoro-4-(6-methoxy-7-(3-morpholino-propoxy)-quinolin-4-yloxy)phenylcarbamate (18a).** Yellow oil, yield: 90.2%. Mp: 219–221 °C. $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 10.66 (s, 1H), 8.44 (d, $J$ = 5.1 Hz, 1H), 7.64–7.68 (m, 1H), 7.49 (s, 1H), 7.39–7.44 (m, 4H), 7.36 (s, 1H), 7.20–7.27 (m, 3H), 6.41 (d, $J$ = 5.1 Hz, 1H), 4.17 (t, $J$ = 6.3 Hz, 2H), 3.91 (s, 3H), 3.52–3.65 (br, 4H), 2.52–2.62 (br, 4H), 2.31–2.43 (br, 2H), 1.89–2.06 (m, 2H). MS (ESI) $m/z$: 548.3, 549.3 ($M^+$).

**7.1.9.2. Phenyl 3-fluoro-4-(6-methoxy-7-(3-(piperdine-1-yl)propoxy))-quinolin-4-yloxy) phenylcarbamate (18b).** Light yellow oil, yield: 83.1%. Mp: 210–212 °C. MS (ESI) $m/z$: 546.4 ($M^+$).

**7.1.9.3. Phenyl 3-fluoro-4-(6-methoxy-7-(3-(4-methylpiperdine-1-yl)propoxy))-quinolin-4-yloxy) phenylcarbamate (18c).** Yellow oil, yield: 82.3%. Mp: 226–228 °C. MS (ESI) $m/z$: 560.3 ($M^+$).

**7.1.9.4. Phenyl 3-fluoro-4-(6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy))-quinolin-4-yloxy) phenylcarbamate (18d).** Yellow oil, yield: 85.0%. Mp: 204–206 °C. MS (ESI) $m/z$: 532.2 ($M^+$).

**7.1.10. $N^1$-(3-fluoro-4-(6-methoxy-7-(3-morpholino-propoxy)quinolin-4-yloxy)phenyl)semicarbazide (19a)**

A mixture of **18a** (4.40 g, 8.01 mmol) and 80% hydrazine monohydrate (10 mL) in 1,4-dioxane (20 mL) was refluxed overnight with vigorous agitation. Most of the solvent was evaporated under reduced pressure when white solid appeared. After cooling to 10 °C, the resulting precipitate was filtered off, washed with water, and dried under vacuum to afford the title compound **19a** (1.80 g) as a white solid, yield: 46.7%. $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 9.03 (s, 1H), 8.47 (d, $J$ = 5.4 Hz, 1H), 7.83–7.88 (m, 1H), 7.63 (s, 1H), 7.53 (s, 1H), 7.44–7.48 (m, 1H), 7.40 (s, 1H), 7.33 (t, $J$ = 9.0 Hz, 1H), 6.43 (d, $J$ = 5.4 Hz, 1H), 4.32–4.59 (br, 2H), 4.20 (t, $J$ = 6.6 Hz, 2H), 3.95 (s, 3H), 3.58–3.61 (m, 4H), 2.45–2.48 (m, 2H), 2.33–2.44 (br, 4H), 1.94–2.03 (m, 2H). Mp: 188–190 °C. MS (ESI) $m/z$: 485.3 ($M^+$).

**7.1.11. $N^1$-(3-fluoro-4-(6-methoxy-7-(3-(piperidin-1-yl)propoxy)quinolin-4-yloxy)phenyl)semicarbazide (19b)**

The intermediate **19b**, which was purified by silica gel column chromatography (eluent, $CH_2Cl_2$/MeOH/$Et_3N$ = 100:1:1 to 100:10:1), was obtained from **18b** by the general procedure as a white solid, yield: 39.6%. $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 9.00 (s, 1H), 8.47 (d, $J$ = 5.1 Hz, 1H), 7.82–7.87 (m, 1H), 7.60 (s, 1H), 7.53 (s, 1H), 7.41–7.49 (m, 1H), 7.38 (s, 1H), 7.32 (t, $J$ = 9.0 Hz, 1H), 6.43 (d, $J$ = 5.1 Hz, 1H), 4.30–4.52 (br, 2H), 4.18 (t, $J$ = 6.3 Hz, 2H), 3.95 (s, 3H), 2.39–2.47 (m, 6H), 1.91–2.01 (m, 2H), 1.45–1.58 (m, 4H), 1.33–1.44 (m, 2H). Mp: 181–182 °C. MS (ESI) $m/z$: 484.3 ($M^+$).

**7.1.12. $N^1$-(3-fluoro-4-(6-methoxy-7-(3-(4-methylpiperidin-1-yl)propoxy)quinolin-4-yloxy)phenyl)semicarbazide (19c)**

The intermediate **19c**, which was purified by silica gel column chromatography (eluent, $CH_2Cl_2$/MeOH/$Et_3N$ = 100:1:1 to 100:10:1), was obtained from **18c** by the general procedure as a white solid, yield: 38.9%. $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 9.02 (s, 1H), 8.47 (d, $J$ = 5.1 Hz, 1H), 7.82–7.86 (m, 1H), 7.58 (s, 1H), 7.41 (s, 1H), 7.03 (t, $J$ = 8.7 Hz, 1H), 6.54–6.59 (dd, $J_1$ = 12.0 Hz, $J_2$ = 2.7 Hz, 1H), 6.48–6.52 (m, 1H), 6.41 (d, $J$ = 5.1 Hz, 1H), 4.32–4.49 (br, 2H), 4.25 (t, $J$ = 6.6 Hz, 2H), 4.03 (s, 3H), 2.89–2.98 (m, 2H), 2.57 (m, 2H), 2.11–2.20 (m, 2H), 1.94–2.02 (m, 2H), 1.58–1.68 (m, 2H), 1.21–1.36 (m, 3H), 0.94 (d, $J$ = 6.0 Hz, 3H). Mp: 191–193 °C. MS (ESI) $m/z$: 498.2 ($M^+$).

**7.1.13. $N^1$-(3-fluoro-4-(6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy)quinolin-4-yloxy)phenyl)semicarbazide (19d)**

White solid, yield: 43.9%. $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 9.03 (s, 1H), 8.47 (d, $J$ = 5.1 Hz, 1H), 7.83–7.87 (m, 1H), 7.63 (s, 1H), 7.53 (s, 1H), 7.44–7.47 (m, 1H), 7.38 (s, 1H), 7.33 (t, $J$ = 9.0 Hz, 1H), 6.42 (d, $J$ = 5.1 Hz, 1H), 4.29–4.57 (br, 2H), 4.20 (t, $J$ = 6.3 Hz, 2H), 3.95 (s, 3H), 2.58 (t, $J$ = 6.3 Hz, 2H), 2.46 (s, 4H), 1.94–2.03 (m, 2H), 1.70 (s, 4H). Mp: 177–178 °C. MS (ESI) $m/z$: 470.3 ($M^+$).

**7.1.14. General procedure for the synthesis of semicarbazones (20a–e, 21a–c, 22a–c, 23a–c, 24–42)**

To a solution of **19a**–**d** (0.200 g, 0.414 mmol) in isopropanol (2 mL), 1.1 equiv of aldehydes or ketones and acetic acid (1 drop) were added, and the mixture was refluxed for 5–6 h until TLC showed the completion of the reaction. After cooling to room temperature, the resultant precipitate was filtered and dried under vacuum.

**7.1.14.1. ($E$)-$N^1$-(3-Fluoro-4-(6-methoxy-7-(3-morpholino-propoxy)quinolin-4-yloxy)phenyl)-$N^4$-(benzylidene)semicarbazide (20a).** White solid, yield: 84.9%. Mp: 205–207 °C. $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 10.93 (s, 1H), 9.23 (s, 1H), 8.50 (d, $J$ = 5.1 Hz, 1H), 8.00 (s, 1H), 7.95 (dd, $J_1$ = 13.5 Hz, $J_2$ = 2.4 Hz, 1H), 7.86-7.90 (m, 2H), 7.65–7.68 (m, 1H), 7.55 (s, 1H), 7.39–7.48 (m, 5H), 6.47 (d, $J$ = 5.1 Hz, 1H), 4.21 (t, $J$ = 6.3 Hz, 2H), 3.96 (s, 3H), 3.59–3.62 (m, 4H), 2.27–2.49 (br, 6H), 1.95–2.04 (m, 2H). $^{13}$C NMR (600 MHz, DMSO-$d_6$) $\delta$ 159.9, 154.7, 153.5, 153.1, 152.4, 150.0, 149.3, 146.8, 141.9, 135.3, 135.2, 134.7, 130.0, 129.1, 127.6, 124.1, 116.9, 114.9, 109.0, 108.8, 108.7, 102.4, 99.5, 67.1, 66.7 (2C), 56.2, 55.3, 53.8 (2C), 26.2. MS (ESI) $m/z$: 574.2, 575.2 ($M^+$). Anal. Calcd for $C_{31}H_{32}FN_5O_5$ (%): C, 64.91; H, 5.62; N, 12.21. Found (%): C, 64.86; H, 5.60; N, 12.22.

**7.1.14.2. ($E$)-$N^1$-(3-Fluoro-4-(6-methoxy-7-(3-morpholino-propoxy)quinolin-4-yloxy)phenyl)-$N^4$-(4-fluorobenzylidene)semicarbazide (20b).** White solid, yield: 87.6%. Mp: 208–209 °C. $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 10.93 (s, 1H), 9.24 (s, 1H), 8.48 (d, $J$ = 5.1 Hz, 1H), 7.99 (s, 1H), 7.89–7.97 (m, 3H), 7.63–7.67 (m, 1H), 7.55 (s, 1H), 7.39–7.47 (m, 2H), 7.28 (t, $J$ = 8.7 Hz, 2H), 6.47 (d, $J$ = 5.1 Hz, 1H), 4.21 (t, $J$ = 6.3 Hz, 2H), 3.96 (s, 3H), 3.60–3.63 (m, 4H), 2.30–2.64 (br, 6H), 1.96–2.05 (m, 2H). MS (ESI) $m/z$: 592.2, 593.2 ($M^+$). Anal. Calcd for $C_{31}H_{31}F_2N_5O_5$ (%): C, 62.94; H, 5.28; N, 11.84. Found (%): C, 62.92; H, 5.29; N, 11.83.

**7.1.14.3. ($E$)-$N^1$-(3-Fluoro-4-(6-methoxy-7-(3-morpholino-propoxy)quinolin-4-yloxy)phenyl)-$N^4$-(4-chlorobenzylidene)semicarbazide (20c).** White solid, yield: 88.5%. Mp: 199–202 °C. $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 10.97 (s, 1H), 9.26 (s, 1H), 8.51 (d, $J$ = 5.1 Hz, 1H), 7.98 (s, 1H), 7.89–7.94 (m, 3H), 7.63–7.67 (m, 1H), 7.57 (s, 1H), 7.52 (d, $J$ = 8.4 Hz, 2H), 7.39–7.44 (m, 2H), 6.49 (d, $J$ = 5.1 Hz, 1H), 4.25 (t, $J$ = 6.3 Hz, 2H), 3.97 (s, 3H), 3.69–3.77 (br, 4H), 2.66–3.01 (br, 6H), 2.08–2.17 (m, 2H). MS (ESI) $m/z$: 607.3, 609.2 ($M^+$). Anal. Calcd for $C_{31}H_{31}ClFN_5O_5$ (%): C, 61.23; H, 5.14; N, 11.52. Found (%): C, 61.20; H, 5.16; N, 11.49.

**7.1.14.4. ($E$)-$N^1$-(3-Fluoro-4-(6-methoxy-7-(3-morpholino-propoxy)quinolin-4-yloxy)phenyl)-$N^4$-(4-trifluoromethoxybenzylidene)semicarbazide (20d).** White solid, yield: 82.1%. Mp: 210–214 °C. $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 11.02 (s, 1H), 9.27 (s, 1H), 8.50 (d, $J$ = 5.4 Hz, 1H), 8.01–8.04 (m, 3H), 7.89–7.94 (dd, $J_1$ = 13.5 Hz, $J_2$ = 2.4 Hz, 1H), 7.63–7.66 (m, 1H), 7.55 (s, 1H), 7.39–7.45 (m, 4H), 6.47 (d, $J$ = 5.1 Hz, 1H), 4.21 (t, $J$ = 6.3 Hz, 2H), 3.96 (s, 3H), 3.60 (br, 4H), 2.53–2.60 (m, 2H), 2.30–2.47 (br, 4H), 1.95–2.04 (m, 2H). MS (ESI) $m/z$: 658.2, 659.2 ($M^+$). Anal. Calcd for $C_{32}H_{31}F_4N_5O_6$ (%): C, 58.45; H, 4.75; N, 10.65. Found (%): C, 58.44; H, 4.73; N, 10.66.

**7.1.14.5. ($E$)-$N^1$-(3-Fluoro-4-(6-methoxy-7-(3-morpholino-propoxy)quinolin-4-yloxy)phenyl)-$N^4$-(4-trifluoromethylbenzylidene)semicarbazide (20e).** White solid, yield: 92.4%. Mp: 213–215 °C. $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 11.14 (s, 1H), 9.34

(s, 1H), 8.50 (d, $J$ = 5.4 Hz, 1H), 8.12 (d, $J$ = 8.1 Hz, 2H), 8.06 (s, 1H), 7.89–7.95 (dd, $J_1$ = 13.5 Hz, $J_2$ = 2.4 Hz, 1H), 7.81 (d, $J$ = 8.1 Hz, 2H), 7.64–7.67 (m, 1H), 7.55 (s, 1H), 7.40–7.46 (m, 2H), 6.48 (d, $J$ = 5.4 Hz, 1H), 4.21 (t, $J$ = 6.0 Hz, 2H), 3.96 (s, 3H), 3.60 (t, 4H), 2.46–2.49 (m, 2H), 2.32–2.44 (br, 4H), 1.95–2.03 (m, 2H). MS (ESI) $m/z$: 642.3, 643.3 ($M^+$). Anal. Calcd for $C_{32}H_{31}F_4N_5O_5$ (%): C, 59.90; H, 4.87; N, 10.92. Found (%): C, 59.86; H, 4.87; N, 10.89.

**7.1.14.6. (*E*)-$N^1$-(3-Fluoro-4-(6-methoxy-7-(3-(piperidin-1-yl)propoxy)quinolin-4-yloxy)phenyl)-$N^4$-(4-fluorobenzylidene)semicarbazide (21a).** White solid, yield: 86.1%. Mp: 211–213 °C. $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 10.77–11.18 (br, 1H), 9.12–9.43 (br, 1H), 8.49 (d, $J$ = 5.1 Hz, 1H), 7.99 (s, 1H), 7.89–7.97 (m, 3H), 7.63–7.68 (m, 1H), 7.54 (s, 1H), 7.38–7.44 (m, 2H), 7.28 (t, $J$ = 9.0 Hz, 2H), 6.47 (d, $J$ = 5.1 Hz, 1H), 4.19 (t, $J$ = 6.6 Hz, 2H), 3.96 (s, 3H), 2.43 (t, $J$ = 6.9 Hz, 2H), 2.26–2.40 (br, 4H), 1.89–2.01 (m, 2H), 1.44–1.56 (m, 4H), 1.31–1.44 (m, 2H). MS (ESI) $m/z$: 590.4, 591.3, 592.3 ($M^+$). Anal. Calcd for $C_{32}H_{33}F_2N_5O_4$ (%): C, 65.18; H, 5.64; N, 11.88. Found (%): C, 65.12; H, 5.60; N, 11.87.

**7.1.14.7. (*E*)-$N^1$-(3-Fluoro-4-(6-methoxy-7-(3-(piperidin-1-yl)propoxy)quinolin-4-yloxy)phenyl)-$N^4$-(benzylidene)semicarbazide (21b).** White solid, yield: 83.9%. Mp: 200–202 °C. $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 10.83–11.05 (br, 1H), 9.14–9.34 (br, 1H), 8.49 (d, $J$ = 5.1 Hz, 1H), 7.99 (s, 1H), 7.94 (dd, $J_1$ = 13.5 Hz, $J_2$ = 2.4 Hz, 1H), 7.86–7.89 (m, 2H), 7.64–7.68 (m, 1H), 7.55 (s, 1H), 7.38–7.48 (m, 5H), 6.47 (d, $J$ = 5.1 Hz, 1H), 4.19 (t, $J$ = 6.3 Hz, 2H), 3.96 (s, 3H), 2.43 (t, $J$ = 6.9 Hz, 2H), 2.25–2.39 (br, 4H), 1.92–2.01 (m, 2H), 1.46–1.55 (m, 4H), 1.32–1.45 (m, 2H). MS (ESI) $m/z$: 571.3, 572.4 ($M^+$). Anal. Calcd for $C_{32}H_{34}FN_5O_4$ (%): C, 67.23; H, 6.00; N, 12.25. Found (%): C, 67.16; H, 5.99; N, 12.23.

**7.1.14.8. (*E*)-$N^1$-(3-Fluoro-4-(6-methoxy-7-(3-(piperidin-1-yl)propoxy)quinolin-4-yloxy)phenyl)-$N^4$-(4-chlorobenzylidene)semicarbazide (21c).** White solid, yield: 89.4%. Mp: 214–217 °C. $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 10.88–11.39 (br, 1H), 9.34–9.61 (br, 1H), 8.49 (d, $J$ = 5.4 Hz, 1H), 7.98 (s, 1H), 7.88–7.95 (m, 3H), 7.61–7.65 (m, 1H), 7.54 (s, 1H), 7.51 (d, $J$ = 8.7 Hz, 2H), 7.38–7.44 (m, 2H), 6.46 (d, $J$ = 5.4 Hz, 1H), 4.19 (t, $J$ = 6.3 Hz, 2H), 3.96 (s, 3H), 2.43 (t, $J$ = 7.2 Hz, 2H), 2.30–2.40 (br, 4H), 1.92–2.01 (m, 2H), 1.45–1.55 (m, 4H), 1.36–1.42 (m, 2H). MS (ESI) $m/z$: 606.3, 608.3, 609.2 ($M^+$). Anal. Calcd for $C_{32}H_{33}ClFN_5O_4$ (%): C, 63.41; H, 5.49; N, 11.56. Found (%): C, 63.38; H, 5.48; N, 11.54.

**7.1.14.9. (*E*)-$N^1$-(3-Fluoro-4-(6-methoxy-7-(3-(4-methylpiperidin-1-yl)propoxy)quinolin-4-yloxy)phenyl)-$N^4$-(benzylidene)semicarbazide (22a).** White solid, yield: 84.4%. Mp: 213–216 °C. $^1$H NMR (300 MHz MHz, DMSO-$d_6$) $\delta$ 10.91 (s, 1H), 9.22 (s, 1H), 8.49 (d, $J$ = 5.4 Hz, 1H), 7.99 (s, 1H), 7.95 (dd, $J_1$ = 13.5 Hz, $J_2$ = 2.4 Hz, 1H), 7.89 (dd, $J_1$ = 8.1 Hz, $J_2$ = 1.5 Hz, 2H), 7.68 (m, 1H), 7.55 (s, 1H), 7.38–7.48 (m, 5H), 6.47 (d, $J$ = 5.4 Hz, 1H), 4.19 (t, $J$ = 6.3 Hz, 2H), 3.96 (s, 3H), 2.87 (d, $J$ = 11.7 Hz, 2H), 2.45 (t, $J$ = 7.2 Hz, 2H), 1.84–2.01 (m, 4H), 1.60 (d, $J$ = 11.7 Hz, 2H), 1.23–1.40 (m, 1H), 1.03–1.21 (m, 2H), 0.90 (d, $J$ = 6.3 Hz, 3H). MS (ESI) $m/z$: 586.4, 587.4 ($M^+$). Anal. Calcd for $C_{33}H_{36}FN_5O_4$ (%): C, 67.68; H, 6.20; N, 11.96. Found (%): C, 67.65; H, 6.17; N, 11.95.

**7.1.14.10. (*E*)-$N^1$-(3-Fluoro-4-(6-methoxy-7-(3-(4-methylpiperidin-1-yl)propoxy)quinolin-4-yloxy)phenyl)-$N^4$-(4-fluorobenzylidene)semicarbazide (22b).** White solid, yield: 87.7%. Mp: 215–218 °C. $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 10.96 (s, 1H), 10.28 (br, 1H), 9.30 (s, 1H), 8.58 (d, $J$ = 5.4 Hz, 1H), 8.00 (s, 1H), 7.91–7.97 (m, 2H), 7.65–7.68 (m, 1H), 7.62 (s, 1H), 7.53 (s, 1H), 7.44 (t, $J$ = 9.0 Hz, 1H), 7.28 (t, $J$ = 9.0 Hz, 2H), 6.60 (d, $J$ = 5.4 Hz, 1H), 4.29 (t, $J$ = 6.0 Hz, 2H), 3.99 (s, 3H), 3.49–3.53 (m, 2H), 3.19–3.25 (br, 2H), 2.88–2.94 (m, 2H), 2.28–2.38 (m, 2H), 1.77–1.82 (m, 2H), 1.46–1.71 (m, 3H), 0.95 (d, $J$ = 6.0 Hz, 3H). MS (ESI) $m/z$: 604.2, 605.2, 606.2 ($M^+$). Anal. Calcd for $C_{33}H_{35}F_2N_5O_4$ (%): C, 65.66; H, 5.84; N, 11.60. Found (%): C, 65.61; H, 5.81; N, 11.56.

**7.1.14.11. (*E*)-$N^1$-(3-Fluoro-4-(6-methoxy-7-(3-(4-methylpiperidin-1-yl)propoxy)quinolin-4-yloxy)phenyl)-$N^4$-(4-chlorobenzylidene)semicarbazide (22c).** White solid, yield: 86.5%. Mp: 216–218 °C. $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 10.99 (s, 1H), 9.27 (s, 1H), 8.49 (d, $J$ = 5.4 Hz, 1H), 7.98 (s, 1H), 7.89–7.94 (m, 3H), 7.63–7.66 (m, 1H), 7.55 (s, 1H), 7.52 (d, $J$ = 8.4 Hz, 2H), 7.38–7.44 (m, 2H), 6.47 (d, $J$ = 5.4 Hz, 1H), 4.19 (t, $J$ = 6.3 Hz, 2H), 3.96 (s, 3H), 2.86–2.95 (m, 2H), 2.52–2.57 (m, 2H), 1.94–2.04 (m, 4H), 1.57–1.62 (m, 2H), 1.27–1.43 (br, 1H), 1.06–1.23 (m, 2H), 0.90 (d, $J$ = 6.3 Hz, 3H). MS (ESI) $m/z$: 620.3, 622.4 ($M^+$). Anal. Calcd for $C_{33}H_{35}ClFN_5O_4$ (%): C, 63.92; H, 5.69; N, 11.29. Found (%): C, 63.88; H, 5.68; N, 11.26.

**7.1.14.12. (*E*)-$N^1$-(3-Fluoro-4-(6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy)quinolin-4-yloxy)phenyl)-$N^4$-(benzylidene)semicarbazide (23a).** White solid, yield: 83.8%. Mp: 195–196 °C. $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 10.92 (s, 1H), 9.23 (s, 1H), 8.49 (d, $J$ = 5.4 Hz, 1H), 8.00 (s, 1H), 7.95 (dd, $J_1$ = 13.5 Hz, $J_2$ = 2.4 Hz, 1H), 7.86–7.90 (m, 2H), 7.65–7.68 (m, 1H), 7.55 (s, 1H), 7.38–7.48 (m, 5H), 6.47 (dd, $J_1$ = 5.4 Hz, $J_2$ = 0.9 Hz, 1H), 4.21 (t, $J$ = 6.3 Hz, 2H), 3.96 (s, 3H), 2.58 (t, $J$ = 7.2 Hz, 2H), 2.40–2.48 (m, 4H), 1.95–2.01 (m, 2H), 1.65–1.73 (m, 4H). MS (ESI) $m/z$: 558.6, 559.6 ($M^+$). Anal. Calcd for $C_{31}H_{32}FN_5O_4$ (%): C, 66.77; H, 5.78; N, 12.56. Found (%): C, 66.69; H, 5.76; N, 12.53.

**7.1.14.13. (*E*)-$N^1$-(3-Fluoro-4-(6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy)quinolin-4-yloxy)phenyl)-$N^4$-(4-fluorobenzylidene)semicarbazide (23b).** White solid, yield: 85.1%. Mp: 211–213 °C. $^1$H NMR$^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 10.92 (s, 1H), 9.24 (s, 1H), 8.50 (d, $J$ = 5.1 Hz, 1H), 7.99 (s, 1H), 7.89–7.97 (m, 3H), 7.63–7.66 (m, 1H), 7.55 (s, 1H), 7.38–7.44 (t, $J$ = 9.0 Hz, 2H), 7.25–7.31 (t, $J$ = 9.0 Hz, 2H), 6.47 (d, $J$ = 5.1 Hz, 1H), 4.23 (t, $J$ = 6.0 Hz, 2H), 3.97 (s, 3H), 2.62–2.86 (m, 6H), 2.01–2.10 (m, 2H), 1.69–1.82 (m, 4H). $^{13}$C NMR (600 MHz, DMSO-$d_6$) $\delta$ 164.1, 162.5, 159.9, 154.7, 153.5, 153.1, 152.2, 149.4, 146.8, 140.8, 131.4, 129.8, 129.7, 124.2, 116.8, 116.1, 116.0, 115.0, 109.1, 108.7, 108.6, 102.4, 99.5, 66.8, 56.2, 53.7 (2C), 52.3, 27.1, 23.4 (2C). MS (ESI) $m/z$: 576.2, 577.2 ($M^+$). Anal. Calcd for $C_{31}H_{31}F_2N_5O_4$ (%): C, 64.69; H, 5.43; N, 12.17. Found (%): C, 64.66; H, 5.40; N, 12.16.

**7.1.14.14. (*E*)-$N^1$-(3-Fluoro-4-(6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy)quinolin-4-yloxy)phenyl)-$N^4$-(4-chlorobenzylidene)semicarbazide (23c).** White solid, yield: 79.7%. Mp: 210–212 °C. $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 11.00 (s, 1H), 9.28 (s, 1H), 8.49 (d, $J$ = 5.1 Hz, 1H), 7.98 (s, 1H), 7.89–7.94 (m, 3H), 7.63–7.67 (m, 1H), 7.55 (s, 1H), 7.48–7.52 (m, 2H), 7.38–7.44 (m, 2H), 6.47 (dd, $J_1$ = 5.4 Hz, $J_2$ = 0.9 Hz, 1H), 4.22 (t, $J$ = 6.3 Hz, 2H), 3.96 (s, 3H), 2.65–2.74 (m, 2H), 2.54–2.61 (br, 4H), 1.98–2.07 (m, 2H), 1.65–1.83 (br, 4H). MS (ESI) $m/z$: 592.1, 593.1, 595.1 ($M^+$). Anal. Calcd for $C_{31}H_{31}ClFN_5O_4$ (%): C, 62.89; H, 5.28; N, 11.83. Found (%): C, 62.88; H, 5.25; N, 11.79.

**7.1.14.15. (*E*)-$N^1$-(3-Fluoro-4-(6-methoxy-7-(3-(piperidin-1-yl)propoxy)quinolin-4-yloxy)phenyl)-$N^4$-(3,4-difluorobenzylidene)semicarbazide (24).** White solid, yield: 88.6%. Mp: 210–212 °C. $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 11.04 (s, 1H), 9.27 (s, 1H), 8.49 (d, $J$ = 5.4 Hz, 1H), 8.13–8.21 (m, 1H), 7.96 (s, 1H), 7.89 (dd, $J_1$ = 13.5 Hz, $J_2$ = 2.4 Hz, 1H), 7.61–7.66 (m, 2H), 7.55 (s, 1H), 7.48–7.52 (m, 1H), 7.40–7.45 (m, 2H), 6.47 (d, $J$ = 5.4 Hz, 1H), 4.19 (t, $J$ = 6.3 Hz, 2H), 3.96 (s, 3H), 2.43 (t, $J$ = 7.2 Hz, 2H), 2.36 (br, 4H), 1.92–2.01 (m, 2H), 1.48–1.55 (m, 4H), 1.34–1.44 (m, 2H). MS (ESI) $m/z$: 608.5, 609.5, 610.5 ($M^+$). Anal. Calcd for

$C_{32}H_{32}F_3N_5O_4$ (%): C, 63.25; H, 5.31; N, 11.53. Found (%): C, 63.23; H, 5.28; N, 11.50.

**7.1.14.16. (*E*)-$N^1$-(3-Fluoro-4-(6-methoxy-7-(3-(piperidin-1-yl)propoxy)quinolin-4-yloxy)phenyl)-$N^4$-(2-fluorobenzylidene)semicarbazide (25).** White solid, yield: 83.2%. Mp: 205–208 °C. $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 11.14 (s, 1H), 9.35 (s, 1H), 8.49 (d, $J$ = 5.4 Hz, 1H), 8.30–8.35 (m, 1H), 8.22 (s, 1H), 7.89–7.94 (dd, $J_1$ = 13.5 Hz, $J_2$ = 2.1 Hz, 1H), 7.63–7.66 (m, 1H), 7.55 (s, 1H), 7.38–7.43 (m, 3H), 7.25–7.32 (m, 2H), 6.47 (d, $J$ = 5.4 Hz, 1H), 4.20 (t, $J$ = 6.9 Hz, 2H), 3.96 (s, 3H), 2.47 (t, $J$ = 7.5 Hz, 2H), 2.31–2.44 (br, 4H), 1.94–2.02 (m, 2H), 1.49–1.56 (m, 4H), 1.38–1.46 (m, 2H). MS (ESI) $m/z$: 590.2, 591.2 ($M^+$). Anal. Calcd for $C_{32}H_{33}F_2N_5O_4$ (%): C, 65.18; H, 5.64; N, 11.88. Found (%): C, 65.14; H, 5.64; N, 11.85.

**7.1.14.17. (*E*)-$N^1$-(3-Fluoro-4-(6-methoxy-7-(3-(piperidin-1-yl)propoxy)quinolin-4-yloxy)phenyl)-$N^4$-(2,4-difluorobenzylidene)semicarbazide (26).** White solid, yield: 89.5%. Mp: 219–222 °C. $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 10.93–11.21 (br, 1H), 9.18–9.43 (br, 1H), 8.49 (d, $J$ = 5.1 Hz, 1H), 8.40–8.44 (m, 1H), 8.15 (s, 1H), 7.88–7.93 (dd, $J_1$ = 13.2 Hz, $J_2$ = 2.1 Hz, 1H), 7.62–7.65 (m, 1H), 7.54 (s, 1H), 7.40–7.45 (m, 2H), 7.30–7.39 (m, 1H), 7.19–7.25 (m, 1H), 6.47 (d, $J$ = 5.1 Hz, 1H), 4.19 (t, $J$ = 6.3 Hz, 2H), 3.96 (s, 3H), 2.43 (t, $J$ = 6.9 Hz, 2H), 2.30–2.38 (br, 4H), 1.92–2.00 (m, 2H), 1.47–1.55 (m, 4H), 1.34–1.42 (m, 2H). MS (ESI) $m/z$: 608.2, 609.2, 610.2 ($M^+$). Anal. Calcd for $C_{32}H_{32}F_3N_5O_4$ (%): C, 63.25; H, 5.31; N, 11.53. Found (%): C, 63.22; H, 5.30; N, 11.51.

**7.1.14.18. (*E*)-$N^1$-(3-Fluoro-4-(6-methoxy-7-(3-(4-methylpiperidin-1-yl)propoxy)quinolin-4-yloxy)phenyl)-$N^4$-(2-fluorobenzylidene)semicarbazide (27).** White solid, yield: 91.3%. Mp: 205–207 °C. $^1$H NMR$^1$H NMR$^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 11.06 (s, 1H), 9.27 (s, 1H), 8.49 (d, $J$ = 5.1 Hz, 1H), 8.31–8.36 (m, 1H), 8.22 (s, 1H), 7.89–7.94 (dd, $J_1$ = 13.2 Hz, $J_2$ = 2.4 Hz, 1H), 7.63–7.67 (m, 1H), 7.54 (s, 1H), 7.39–7.51 (m, 3H), 7.25–7.32 (m, 2H), 6.47 (d, $J$ = 5.1 Hz, 1H), 4.19 (t, $J$ = 6.6 Hz, 2H), 3.96 (s, 3H), 2.90 (m, 2H), 2.46 (m, 2H), 1.89–2.02 (m, 4H), 1.57–1.61 (m, 2H), 1.26–1.43 (br, 1H), 1.09–1.22 (m, 2H), 0.90 (d, $J$ = 6.3 Hz, 3H). MS (ESI) $m/z$: 604.2, 605.2, 606.1 ($M^+$). Anal. Calcd for $C_{33}H_{35}F_2N_5O_4$ (%): C, 65.66; H, 5.84; N, 11.60. Found (%): C, 65.60; H, 5.81; N, 11.57.

**7.1.14.19. (*E*)-$N^1$-(3-Fluoro-4-(6-methoxy-7-(3-(4-methylpiperidin-1-yl)propoxy)quinolin-4-yloxy)phenyl)-$N^4$-(2,4-difluorobenzylidene)semicarbazide (28).** White solid, yield: 82.1%. Mp: 206–208 °C. IR (KBr) $\upsilon_{max}$ ($cm^{-1}$) 3391.3 and 2924.9 (N–H), 1689.9 (C=O), 1617.4 (C=N). $^1$H NMR (600 MHz, DMSO-$d_6$) $\delta$ 11.12 (s, 1H), 9.33 (s, 1H), 8.49 (d, $J$ = 5.4 Hz, 1H), 8.40–8.44 (dd, $J_1$ = 15.0 Hz, $J_2$ = 8.4 Hz, 1H), 8.16 (s, 1H), 7.90–7.93 (dd, $J_1$ = 13.2 Hz, $J_2$ = 2.4 Hz, 1H), 7.66 (m, 1H), 7.55 (s, 1H), 7.43 (t, $J$ = 9.0 Hz, 1H), 7.41 (s, 1H), 7.35–7.83 (m, 1H), 7.21–7.25 (m, 1H), 6.47 (d, $J$ = 4.8 Hz, 1H), 4.20 (t, $J$ = 6.0 Hz, 2H), 3.97 (s, 3H), 2.83–3.08 (br, 2H), 2.53–2.71 (br, 2H), 1.86–2.09 (br, 4H), 1.61 (m, 2H), 1.31–1.42 (br, 1H), 1.11–1.25 (m, 2H), 0.90 (d, $J$ = 6.6 Hz, 3H). $^{13}$C NMR (600 MHz, DMSO-$d_6$) $\delta$ 159.9, 154.7, 153.2, 153.0, 152.4, 150.0, 149.3, 146.8, 136.6, 135.0, 133.8, 131.0, 129.2, 128.1, 124.2, 117.1, 114.9, 109.0, 108.9, 102.4, 99.5, 67.2, 56.2, 55.2, 53.9 (2C), 34.4 (2C), 30.8, 26.6, 22.3. MS (ESI) $m/z$: 622.5, 623.5, 624.5 ($M^+$). Anal. Calcd for $C_{33}H_{34}F_3N_5O_4$ (%): C, 63.76; H, 5.51; N, 11.27. Found (%): C, 63.75; H, 5.47; N, 11.24.

**7.1.14.20. (*E*)-$N^1$-(3-Fluoro-4-(6-methoxy-7-(3-(piperidin-1-yl)propoxy)quinolin-4-yloxy)phenyl)-$N^4$-(2-trifluoromethylbenzylidene)semicarbazide (29).** White solid, yield: 80.2%. Mp: 223–225 °C. $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 11.22 (s, 1H), 9.33 (s, 1H), 8.60 (d, $J$ = 8.1 Hz, 1H), 8.49 (d, $J$ = 5.4 Hz, 1H), 8.36 (m, 1H), 7.88–7.93 (dd, $J_1$ = 13.5 Hz, $J_2$ = 2.4 Hz, 1H), 7.74–7.80 (m, 2H), 7.59–7.66 (m, 2H), 7.55 (s, 1H), 7.40–7.45 (m, 2H), 6.47 (d, $J$ = 5.4 Hz, 1H), 4.19 (t, $J$ = 6.3 Hz, 2H), 3.96 (s, 3H), 2.43 (t, $J$ = 7.2 Hz, 2H), 2.35 (br, 4H), 1.92–2.01 (m, 2H), 1.48–1.55 (m, 4H), 1.32–1.43 (m, 2H). MS (ESI) $m/z$: 640.2, 641.2, 642.2 ($M^+$). Anal. Calcd for $C_{33}H_{33}F_4N_5O_4$ (%): C, 61.97; H, 5.20; N, 10.95. Found (%): C, 61.90; H, 5.17; N, 10.94.

**7.1.14.21. (*E*)-$N^1$-(3-Fluoro-4-(6-methoxy-7-(3-(piperidin-1-yl)propoxy)quinolin-4-yloxy)phenyl)-$N^4$-(2-cyanobenzylidene)semicarbazide (30).** Light yellow solid, yield: 83.1%. Mp: 214–216 °C. $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 11.19 (s, 1H), 9.34 (s, 1H), 8.50 (d, $J$ = 4.8 Hz, 1H), 7.98–8.15 (m, 3H), 7.85–7.95 (m, 3H), 7.63–7.66 (m, 1H), 7.55 (s, 1H), 7.40–7.45 (m, 2H), 6.47 (d, $J$ = 4.8 Hz, 1H), 4.20 (t, $J$ = 6.3 Hz, 2H), 3.96 (s, 3H), 2.29–2.47 (br, 6H), 1.91–2.01 (m, 2H), 1.47–1.59 (m, 4H), 1.34–1.45 (m, 2H). MS (ESI) $m/z$: 597.5, 598.5 ($M^+$). Anal. Calcd for $C_{33}H_{33}FN_6O_4$ (%): C, 66.43; H, 5.57; N, 14.09. Found (%): C, 66.37; H, 5.54; N, 14.06.

**7.1.14.22. (*E*)-$N^1$-(3-Fluoro-4-(6-methoxy-7-(3-(piperidin-1-yl)propoxy)quinolin-4-yloxy)phenyl)-$N^4$-(3-nitrobenzylidene)semicarbazide (31).** Yellow solid, yield: 90.9%. Mp: 217–220 °C. $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 11.16 (s, 1H), 9.42 (s, 1H), 8.68 (s, 1H), 8.50 (d, $J$ = 5.1 Hz, 1H), 8.36 (d, $J$ = 7.8 Hz, 1H), 8.25 (dd, $J_1$ = 8.1 Hz, $J_2$ = 1.5 Hz, 1H), 8.12 (s, 1H), 7.98–7.94 (dd, $J_1$ = 13.2 Hz, $J_2$ = 2.4 Hz, 1H), 7.74 (t, $J$ = 8.1 Hz, 1H), 7.63–7.67 (m, 1H), 7.55 (s, 1H), 7.40–7.46 (m, 2H), 6.47 (d, $J$ = 5.1 Hz, 1H), 4.19 (t, $J$ = 6.6 Hz, 2H), 3.96 (s, 3H), 2.42–2.47 (m, 2H), 2.28–2.40 (br, 4H), 1.92–2.02 (m, 2H), 1.46–1.57 (m, 4H), 1.35–1.45 (m, 2H). MS (ESI) $m/z$: 617.6, 618.6 ($M^+$). Anal. Calcd for $C_{32}H_{33}FN_6O_6$ (%): C, 62.33; H, 5.39; N, 13.63. Found (%): C, 62.29; H, 5.35; N, 13.60.

**7.1.14.23. (*E*)-$N^1$-(3-Fluoro-4-(6-methoxy-7-(3-(piperidin-1-yl)propoxy)quinolin-4-yloxy)phenyl)-$N^4$-(4-nitrobenzylidene)semicarbazide (32).** Yellow solid, yield: 89.4%. Mp: 215–218 °C. $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 11.27 (s, 1H), 9.40 (s, 1H), 8.50 (d, $J$ = 5.1 Hz, 1H), 8.29 (d, $J$ = 9.0 Hz, 2H), 8.17 (d, $J$ = 9.0 Hz, 2H), 8.09 (s, 1H), 7.89–7.94 (dd, $J_1$ = 13.2 Hz, $J_2$ = 2.1 Hz, 1H), 7.64–7.67 (m, 1H), 7.55 (s, 1H), 7.40–7.47 (m, 2H), 6.47 (d, $J$ = 5.1 Hz ,1H), 4.19 (t, $J$ = 6.6 Hz, 2H), 3.96 (s, 3H), 2.46 (t, $J$ = 6.9 Hz, 2H), 2.38 (br, 4H), 1.91–2.01 (m, 2H), 1.48–1.55 (m, 4H), 1.34–1.44 (m, 2H). MS (ESI) m/z: 617.5, 618.5 ($M^+$). Anal. Calcd for $C_{32}H_{33}FN_6O_6$ (%): C, 62.33; H, 5.39; N, 13.63. Found (%): C, 62.30; H, 5.35; N, 13.58.

**7.1.14.24. (*E*)-$N^1$-(3-Fluoro-4-(6-methoxy-7-(3-(piperidin-1-yl)propoxy)quinolin-4-yloxy)phenyl)-$N^4$-(2-nitrobenzylidene)semicarbazide (33).** Yellow solid, yield: 90.0%. Mp: 221–223 °C. $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 11.25 (s, 1H), 9.28 (s, 1H), 8.47–8.50 (m, 2H), 8.40 (s, 1H), 8.07 (d, $J$ = 8.1 Hz, 1H), 7.91 (dd, $J_1$ = 13.5 Hz, $J_2$ = 2.4 Hz, 1H), 7.79–7.84 (m, 1H), 7.61–7.68 (m, 2H), 7.54 (s, 1H), 7.40–7.46 (m, 2H), 6.47 (d, $J$ = 5.1 Hz, 1H), 4.19 (t, $J$ = 6.3 Hz, 2H), 3.96 (s, 3H), 2.43 (t, $J$ = 7.2 Hz, 2H), 2.30–2.39 (m, 4H), 1.92–2.01 (m, 2H), 1.45–1.55 (m, 4H), 1.43–1.45 (m, 2H). MS (ESI) $m/z$: 617.4, 618.3 ($M^+$). Anal. Calcd for $C_{32}H_{33}FN_6O_6$ (%): C, 62.33; H, 5.39; N, 13.63. Found (%): C, 62.32; H, 5.39; N, 13.59.

**7.1.14.25. (*E*)-$N^1$-(3-Fluoro-4-(6-methoxy-7-(3-(piperidin-1-yl)propoxy)quinolin-4-yloxy)phenyl)-$N^4$-(3-methoxybenzylidene)semicarbazide (34).** White solid, yield: 77.9%. Mp: 215–217 °C. $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 10.93 (s, 1H), 9.26 (s, 1H), 8.49 (d, $J$ = 5.1 Hz, 1H), 7.96 (s, 1H), 7.90–7.95 (m, 1H), 7.64–7.68 (m, 1H), 7.54 (s, 1H), 7.48 (m, 1H), 7.32–7.44 (m, 4H), 6.97–7.00 (m, 1H), 6.46 (d, $J$ = 5.1 Hz, 1H), 4.19 (t, $J$ = 6.6 Hz, 2H), 3.96 (s, 3H), 3.83 (s, 3H), 2.43 (t, $J$ = 6.9 Hz, 2H), 2.36 (br, 4H), 1.90–2.01

(m, 2H), 1.48–1.55 (m, 4H), 1.34–1.44 (m, 2H). MS (ESI) *m*/*z*: 602.5, 603.5 ($M^+$). Anal. Calcd for $C_{33}H_{36}FN_5O_5$ (%): C, 65.88; H, 6.03; N, 11.64. Found (%): C, 65.85; H, 6.01; N, 11.62.

**7.1.14.26. (*E*)-$N^1$-(3-Fluoro-4-(6-methoxy-7-(3-(piperidin-1-yl)propoxy)quinolin-4-yloxy)phenyl)-$N^4$-(2,5-dimethoxybenzylidene)semicarbazide (35).** White solid, yield: 83.7%. Mp: 206–209 °C. $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 10.89 (s, 1H), 9.27 (s, 1H), 8.47 (d, $J$ = 5.1 Hz, 1H), 8.31 (s, 1H), 7.90–7.95 (m, 1H), 7.76 (d, $J$ = 2.7 Hz, 1H), 7.63–7.66 (m, 1H), 7.54 (s, 1H), 7.37–7.43 (m, 2H), 6.96–7.04 (m, 2H), 6.46 (d, $J$ = 5.1 Hz, 1H), 4.19 (t, $J$ = 6.3 Hz, 2H), 3.96 (s, 3H), 3.80 (s, 6H), 2.43 (t, $J$ = 6.9 Hz, 2H), 2.27–2.39 (br, 4H), 1.92–2.00 (m, 2H), 1.45–1.57 (m, 4H), 1.33–1.44 (m, 2H). MS (ESI) *m*/*z*: 632.3, 633.2 ($M^+$). Anal. Calcd for $C_{34}H_{38}FN_5O_6$ (%): C, 64.65; H, 6.06; N, 11.09. Found (%): C, 64.63; H, 6.04; N, 11.05.

**7.1.14.27. (*E*)-$N^1$-(3-Fluoro-4-(6-methoxy-7-(3-(piperidin-1-yl)propoxy)quinolin-4-yloxy)phenyl)-$N^4$-(2,4,6-trimethylbenzylidene)semicarbazide (36).** White solid, yield: 92.3%. Mp: 208–211 °C. $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 10.78 (s, 1H), 8.93 (s, 1H), 8.48 (d, $J$ = 5.1 Hz, 1H), 8.29 (s, 1H), 7.86–7.91 (dd, $J_1$ = 13.5 Hz, $J_2$ = 2.4 Hz, 1H), 7.53–7.60 (m, 2H), 7.35–7.41 (m, 2H), 6.93 (s, 2H), 6.45 (d, $J$ = 5.1 Hz, 1H), 4.18 (t, $J$ = 6.3 Hz, 2H), 3.96 (s, 3H), 2.43 (t, $J$ = 7.5 Hz, 2H), 2.41 (s, 6H), 2.30–2.37 (br, 4H), 2.26 (s, 3H), 1.92–2.00 (m, 2H), 1.48–1.55 (m, 4H), 1.36–1.42 (m, 2H). MS (ESI) *m*/*z*: 614.5, 615.5 ($M^+$). Anal. Calcd for $C_{35}H_{40}FN_5O_4$ (%): C, 68.50; H, 6.57; N, 11.41. Found (%): C, 68.47; H, 6.55; N, 11.37.

**7.1.14.28. (*E*)-$N^1$-(3-Fluoro-4-(6-methoxy-7-(3-(piperidin-1-yl)propoxy)quinolin-4-yloxy)phenyl)-$N^4$-((pyridin-3-yl)methylene)semicarbazide (37).** Light yellow solid, yield: 74.7%. Mp: 217–219 °C. $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 10.76–11.60 (br, 1H), 9.25–9.70 (br, 1H), 9.03 (s, 1H), 8.59 (d, $J$ = 3.6 Hz, 1H), 8.49 (d, $J$ = 5.1 Hz, 1H), 8.32 (d, $J$ = 7.8 Hz, 1H), 8.02 (s, 1H), 7.95 (dd, $J_1$ = 13.5 Hz, $J_2$ = 1.8 Hz, 1H), 7.64–7.67 (m, 1H), 7.55 (s, 1H), 7.40–7.49 (m, 3H), 6.47 (d, $J$ = 5.1 Hz, 1H), 4.19 (t, $J$ = 6.3 Hz, 2H), 3.96 (s, 3H), 2.43 (t, $J$ = 7.2 Hz, 2H), 2.39 (br, 4H), 1.92–2.01 (m, 2H), 1.45–1.57 (m, 4H), 1.33–1.44 (m, 2H). MS (ESI) *m*/*z*: 573.4, 574.4 ($M^+$). Anal. Calcd for $C_{31}H_{33}FN_6O_4$ (%): C, 65.02; H, 5.81; N, 14.68. Found (%): C, 65.00; H, 5.78; N, 14.65.

**7.1.14.29. (*E*)-$N^1$-(3-Fluoro-4-(6-methoxy-7-(3-(piperidin-1-yl)propoxy)quinolin-4-yloxy)phenyl)-$N^4$-((furan-2-yl)methylene)semicarbazide (38).** Light yellow solid, yield: 71.9%. Mp: 195–199 °C. $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 10.90 (s, 1H), 9.16 (s, 1H), 8.49 (d, $J$ = 5.4 Hz, 1H), 7.87–7.92 (m, 2H), 7.82 (s, 1H), 7.58–7.61 (m, 1H), 7.55 (s, 1H), 7.36–7.42 (m, 2H), 6.98 (d, $J$ = 3.3 Hz, 1H), 6.63–6.65 (m, 1H), 6.47 (d, $J$ = 5.4 Hz, 1H), 4.22 (t, $J$ = 6.3 Hz, 2H), 3.96 (s, 3H), 2.62–2.87 (br, 6H), 2.07–2.16 (m, 2H), 1.61–1.70 (m, 4H), 1.41–1.51 (m, 2H). MS (ESI) *m*/*z*: 562.7, 563.7 ($M^+$). Anal. Calcd for $C_{30}H_{32}FN_5O_5$ (%): C, 64.16; H, 5.74; N, 12.47. Found (%): C, 64.13; H, 5.71; N, 12.45.

**7.1.14.30. (*E*)-$N^1$-(3-Fluoro-4-(6-methoxy-7-(3-(piperidin-1-yl)propoxy)quinolin-4-yloxy)phenyl)-$N^4$-((1H-pyrrol-2-yl)methylene)semicarbazide (39).** Light yellow solid, yield: 72.8%. Mp: 201–204 °C. $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 11.71 (br, 1H), 10.68 (s, 1H), 9.31 (s, 1H), 8.50 (d, $J$ = 5.4 Hz, 1H), 7.94–7.99 (dd, $J_1$ = 13.5 Hz, $J_2$ = 2.1 Hz, 1H), 7.79 (s, 1H), 7.64–7.68 (m, 1H), 7.56 (s, 1H), 7.39–7.45 (m, 2H), 7.01 (d, $J$ = 0.9 Hz, 1H), 6.48 (d, $J$ = 5.4 Hz, 1H), 6.40 (d, $J$ = 0.9 Hz, 1H), 6.11–6.13 (m, 1H), 4.23 (t, $J$ = 6.0 Hz, 2H), 3.96 (s, 3H), 2.57–2.90 (br, 6H), 2.05–2.18 (m, 2H), 1.55–1.70 (m, 4H), 1.40–1.52 (m, 2H). MS (ESI) *m*/*z*: 561.2, 562.2 ($M^+$). Anal. Calcd for $C_{30}H_{33}FN_6O_4$ (%): C, 64.27; H, 5.93; N, 14.99. Found (%): C, 64.18; H, 5.88; N, 14.92.

**7.1.14.31. (*E*)-$N^1$-(3-Fluoro-4-(6-methoxy-7-(3-(piperidin-1-yl)propoxy)quinolin-4-yloxy)phenyl)-$N^4$-(1-phenylethylidene)semicarbazide (40).** White solid, yield: 84.4%. Mp: 203–206 °C. $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 10.01 (s, 1H), 9.32 (s, 1H), 8.50 (d, $J$ = 5.4 Hz, 1H), 7.89–7.94 (m, 3H), 7.58–7.61 (m, 1H), 7.56 (s, 1H), 7.38–7.50 (m, 5H), 6.46 (d, $J$ = 5.4 Hz, 1H), 4.22 (t, $J$ = 6.0 Hz, 2H), 3.97 (s, 3H), 2.53–2.93 (br, 6H), 2.30 (s, 3H), 2.01–2.18 (br, 2H), 1.54–1.70 (br, 4H), 1.36–1.52 (br, 2H). MS (ESI) *m*/*z*: 586.6, 587.7 ($M^+$). Anal. Calcd for $C_{33}H_{36}FN_5O_4$ (%): C, 67.68; H, 6.20; N, 11.96. Found (%): C, 67.63; H, 6.16; N, 11.93.

**7.1.14.32. (E)-$N^1$-(3-Fluoro-4-(6-methoxy-7-(3-(piperidin-1-yl)propoxy)quinolin-4-yloxy)phenyl)-$N^4$-(1-phenylpropylidene)semicarbazide (41).** White solid, yield: 85.3%. Mp: 208–210 °C. $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta\delta$ 10.20 (s, 1H), 9.45 (br, 1H), 8.50 (d, $J$ = 5.4 Hz, 1H), 7.87–7.92 (m, 3H), 7.55–7.58 (m, 2H), 7.37–7.46 (m, 5H), 6.48 (d, $J$ = 5.4 Hz, 1H), 4.24 (t, $J$ = 6.3 Hz, 2H), 3.97 (s, 3H), 2.64–3.17 (br, 6H), 2.83 (q, $J$ = = 7.5 Hz, 2H), 2.12–2.26 (br, 2H), 1.62–1.77 (br, 4H), 1.41–1.57 (br, 2H), 1.07 (t, $J$ = 7.5 Hz, 3H). MS (ESI) *m*/*z*: 600.5, 601.5 ($M^+$). Anal. Calcd for $C_{34}H_{38}FN_5O_4$ (%): C, 68.10; H, 6.39; N, 11.68. Found (%): C, 68.05; H, 6.36; N, 11.65.

**7.1.14.33. (*E*)-$N^1$-(3-fluoro-4-(6-methoxy-7-(3-(piperidin-1-yl)propoxy)quinolin-4-yloxy)phenyl)-$N^4$-(2-methylpropylidene)semicarbazide (42).** White solid, yield: 68.7%. Mp: 177–179 °C. $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 10.41 (s, 1H), 8.91 (s, 1H), 8.47 (d, $J$ = 5.4 Hz, 1H), 7.84–7.89 (dd, $J_1$ = 13.5 Hz, $J_2$ = 2.1 Hz, 1H), 7.54–7.57 (m, 2H), 7.41 (s, 1H), 7. 36 (t, $J$ = 9.0 Hz, 1H), 7.23 (d, $J$ = 5.7 Hz, 1H), 6.45 (d, $J$ = 5.4 Hz, 1H), 4.21 (t, $J$ = 6.3 Hz, 2H), 3.96 (s, 3H), 2.54–2.74 (m, 6H), 1.96–2.11 (m, 2H), 1.52–1.65 (m, 4H), 1.37–1.47 (m, 2H), 1.00–1.18 (m, 1H), 1.08 (d, $J$ = 6.9 Hz, 6H). MS (ESI) *m*/*z*: 538.4, 539.4 ($M^+$). Anal. Calcd for $C_{29}H_{36}FN_5O_4$ (%): C, 64.79; H, 6.75; N, 13.03. Found (%): C, 64.75; H, 6.73; N, 13.01.

### 7.1.15. 4-(4-(7-(3-(Piperidin-1-yl)propoxy)-6-methoxyquinolin-4-yloxy)-3-fluorophenyl)thiosemicarbazide (44)

Intermediate **17b** (5.00 g, 11.7 mmol) was dissolved in $CHCl_3$ (50 mL) and sat. aq. $NaHCO_3$ (50 mL) was added. The resulting biphasic solution was cooled to 0 °C and thiophosgene (2.03 g, 17.6 mmol) was then carefully added via syringe. After the addition was completed, the reaction was allowed to warm to room temperature and stirred for 6 h. The organic layer was separated and the aqueous layer was extracted with $CHCl_3$ (2 × 20 mL). The combined organic layers were dried over $Na_2SO_4$, filtered, and concentrated under reduced pressure to afford intermediate **43** (4.82 g, 87.2%) as a yellow oil which was used in the next step as soon as possible without further purification.

To a solution of **43** (4.80 g, 10.2 mmol) in $CHCl_3$ (40 mL) was added 80% hydrazine monohydrate (40 mL), and the biphasic solution was vigorously stirred for 3 h at room temperature. The organic layer was separated and the aqueous layer was extracted with $CHCl_3$ (2 × 10 mL). The combined organic layers were dried over $Na_2SO_4$, filtered, and concentrated under reduced pressure to get a brown oil which was purified by silica gel column chromatography (eluent, $CH_2Cl_2$/MeOH/$Et_3N$ = 100:2:1 to 100:10:1) to afford **44** (2.84 g) as a yellow solid, yield: 53.2%. $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 8.96 (s, 1H), 8.47 (d, $J$ = 5.1 Hz, 1H), 7.80–7.86 (m, 1H), 7.58 (s, 1H), 7.52 (s, 1H), 7.40–7.49 (m, 1H), 7.40 (s, 1H), 7.31 (t, $J$ = 9.0 Hz, 1H), 6.46 (d, $J$ = 5.1 Hz, 1H), 4.32–4.48 (br, 2H), 4.19 (t, $J$ = 6.3 Hz, 2H), 3.96 (s, 3H), 2.39–2.47 (m, 6H), 1.91–2.03 (m, 2H), 1.43–1.57 (m, 4H), 1.31–1.43 (m, 2H). MS (ESI) *m*/*z*: 500.4, 501.4 ($M^+$).

#### 7.1.16. General procedure for the synthesis of thiosemicarbazide (45a–c)

To a solution of **44** (0.200 g, 0.404 mmol) in isopropanol (2 mL), 1.1 equiv of appropriate aldehyde and acetic acid (1 drop) were added, and the mixture was refluxed for 6–7 h until TLC showed the completion of the reaction. After cooling to 0 °C, the resultant precipitate was filtered and dried under vacuum.

**7.1.16.1. (*E*)-$N^1$-(3-Fluoro-4-(6-methoxy-7-(3-(piperidin-1-yl) propoxy)quinolin-4-yloxy)phenyl)-$N^4$-(2,4-difluorobenzylidene) thiosemicarbazide (45a).** Light yellow solid, yield: 85.7%. Mp: 123–126 °C. $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 12.12 (br, 1H), 10.34 (s, 1H), 8.45–8.53 (m, 2H), 8.38 (s, 1H), 7.88–7.93 (dd, $J_1$ = 13.2 Hz, $J_2$ = 2.4 Hz, 1H), 7.58–7.62 (m, 1H), 7.55 (s, 1H), 7.48 (t, $J$ = 8.7 Hz, 1H), 7.42 (s, 1H), 7.32–7.40 (m, 1H), 7.19–7.25 (m, 1H), 6.47 (d, $J$ = 5.4 Hz, 1H), 4.21 (t, $J$ = 6.3 Hz, 2H), 3.96 (s, 3H), 2.53–2.74 (br, 6H), 1.99–2.09 (m, 2H), 1.54–1.61 (m, 4H), 1.39–1.48 (m, 2H). MS (ESI) $m/z$: 624.3, 625.4, 626.3 ($M^+$). Anal. Calcd for $C_{32}H_{32}F_3N_5O_3S$ (%): C, 61.62; H, 5.17; N, 11.23. Found (%): C, 61.59; H, 5.13; N, 11.22.

**7.1.16.2. (*E*)-$N^1$-(3-Fluoro-4-(6-methoxy-7-(3-(piperidin-1-yl) propoxy)quinolin-4-yloxy)phenyl)-$N^4$-(2-nitrobenzylidene) thiosemicarbazide (45b).** Yellow solid, yield: 82.9%. Mp: 131–133 °C. $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 11.88–12.69 (br, 1H), 10.37 (s, 1H), 8.63 (s, 1H), 8.58 (d, $J$ = 8.1 Hz, 1H), 8.53 (dd, $J_1$ = 5.1 Hz, $J_2$ = 1.2 Hz, 1H), 8.10 (dd, $J_1$ = 8.1 Hz, $J_2$ = 1.2 Hz, 1H), 7.90–7.95 (m, 1H), 7.81 (t, $J$ = 7.5 Hz, 1H), 7.66–7.72 (m, 1H), 7.60–7.63 (m, 1H), 7.56 (s, 1H), 7.49 (t, $J$ = 6.0 Hz, 1H), 7.43 (s, 1H), 6.48 (d, $J$ = 5.1 Hz, 1H), 4.22 (t, $J$ = 6.0 Hz, 2H), 3.97 (s, 3H), 2.55–2.64 (m, 6H), 1.99–2.09 (m, 2H), 1.50–1.62 (m, 4H), 1.36–1.48 (m, 2H). MS (ESI) $m/z$: 633.3, 634.3 ($M^+$). Anal. Calcd for $C_{32}H_{33}FN_6O_5S$ (%): C, 60.75; H, 5.26; N, 13.28. Found (%): C, 60.74; H, 5.23; N, 13.24.

**7.1.16.3. (E)-$N^1$-(3-Fluoro-4-(6-methoxy-7-(3-(piperidin-1-yl)propoxy)quinolin-4-yloxy)phenyl)-$N^4$-((furan-2-yl)methylene)thiosemicarbazide (45c).** Light yellow solid, yield: 81.6%. Mp: 122–125 °C. $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 11.82–12.19 (br, 1H), 9.93–10.24 (br, 1H), 8.52 (d, $J$ = 5.1 Hz, 1H), 8.12 (s, 1H), 7.98 (dd, $J_1$ = 13.2 Hz, $J_2$ = 1.8 Hz, 1H), 7.89 (s, 1H), 7.59–7.66 (m, 1H), 7.54 (s, 1H), 7.41–7.50 (m, 2H), 7.12 (d, $J$ = 3.3 Hz, 1H), 6.68–6.69 (m, 1H), 6.47 (d, $J$ = 5.1 Hz, 1H), 4.19 (t, $J$ = 6.3 Hz, 2H), 3.96 (s, 3H), 2.43 (t, $J$ = 6.3 Hz, 2H), 2.24–2.39 (br, 4H), 1.89–2.01 (m, 2H), 1.44–1.55 (m, 4H), 1.33–1.43 (m, 2H). MS (ESI) $m/z$: 578.7, 579.6, 580.6 ($M^+$). Anal. Calcd for $C_{30}H_{32}FN_5O_4S$ (%): C, 62.37; H, 5.58; N, 12.12. Found (%): C, 62.34; H, 5.54; N, 12.09.

#### 7.1.17. $N^1$-(3-Fluoro-4-(6-methoxy-7-(3-(4-methylpiperidin-1-yl)propoxy)quinolin-4-yloxy)phenyl)-$N^4$-(2,4-difluorobenzyl)semicarbazide (46)

Sodium triacetoxyborohydride (0.102 g, 0.482 mmol) was added to a solution of **28** (0.100 g, 0.161 mmol) in 5:1 THF/AcOH (2 mL in total) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction mixture was then evaporated under reduced pressure, and the residue was dissolved in $CH_2Cl_2$ (5 mL), and washed with saturated sodium bicarbonate aqueous solution (2 × 5 mL), then water (5 mL), dried over $Na_2SO_4$ and concentrated in vacuo. The crude product was purified by column chromatography on silica gel (eluent, $CH_2Cl_2$/$CH_3OH$/$Et_3N$ = 100:2:1) to yield **46** (60.3 mg) as a white solid, yield: 62.1%. Mp: 165–167 °C. $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 11.09 (br, 1H), 9.29 (s, 1H), 8.49 (d, $J$ = 5.4 Hz, 1H), 8.36–8.44 (m, 1H), 7.88–7.93 (dd, $J_1$ = 13.2 Hz, $J_2$ = 2.4 Hz, 1H), 7.62–7.66 (m, 1H), 7.55 (s, 1H), 7.40–7.45 (m, 2H), 7.30–7.39 (m, 1H), 7.18–7.25 (m, 1H), 6.47 (d, $J$ = 5.4 Hz, 1H), 5.34 (m, 1H), 4.20 (t, $J$ = 6.3 Hz, 2H), 3.96 (s, 3H), 3.79 (br, 2H), 2.81–3.04 (br, 2H), 2.53–2.65 (br, 2H), 1.85–2.18 (br, 4H), 1.55–1.67 (m, 2H), 1.29–1.45 (br, 1H), 1.10–1.25 (m, 2H), 0.91 (d, $J$ = 6.3 Hz, 3H). MS (ESI) $m/z$: 624.6, 625.5 ($M^+$). Anal. Calcd for $C_{33}H_{36}F_3N_5O_4$ (%): C, 63.55; H, 5.82; N, 11.23. Found (%): C, 63.53; H, 5.80; N, 11.22.

## Acknowledgments

This work was supported by a grant from National S&T Major Project (No. 2011ZX09102-001-006) and National Natural Science Foundation of China (NSFC No. 21002065).

## Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmc.2013.06.026.

## References and notes

1. Gherardi, E.; Stoker, M. *Nature* **1990**, *346*, 228.
2. Naldini, L.; Weidner, K. M.; Vinga, E.; Gaudino, G.; Bardelli, A.; Ponzetto, C.; Narsimhan, R. P.; Hartmann, G.; Zarnegar, R.; Michalopoulos, G. K. *EMBO J.* **1991**, *10*, 2876.
3. Huh, C. G.; Factor, V. M.; Sánchez, A.; Uchida, K.; Conner, E. A.; Thorgeirsson, S. S. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 4477.
4. Boccaccio, C.; Comoglio, P. M. *Nat. Rev. Cancer* **2006**, *6*, 637.
5. Parr, C.; Watkins, G.; Mansel, R. E.; Jiang, W. G. *Clin. Cancer Res.* **2004**, *10*, 202.
6. Takayama, H.; LaRochelle, W. J.; Sharp, R.; Otsuka, T.; Kriebel, P.; Anver, M.; Aaronson, S. A.; Merlino, G. *Proc. Natl. Acad. Sci. U.S.A.* **1997**, *94*, 701.
7. Durante, C.; Russo, D.; Verrienti, A.; Filetti, S. *Expert Opin. Invest. Drugs* **2011**, *20*, 407.
8. Porter, J. *Expert Opin. Ther. Pat.* **2010**, *20*, 159.
9. Liu, X.; Newton, R. C.; Scherle, P. A. *Trends Mol. Med.* **2010**, *16*, 37.
10. Underiner, T. L.; Herbertz, T.; Miknyoczki, S. J. *Anti-Cancer Agents Med. Chem.* **2010**, *10*, 7.
11. Schroeder, G. M.; An, Y.; Cai, Z. W.; Chen, X. T.; Clark, C.; Cornelius, L. A.; Dai, J.; Gullo-Brown, J.; Gupta, A.; Henley, B.; Hunt, J. T.; Jeyaseelan, R.; Kamath, A.; Kim, K.; Lippy, J.; Lombardo, L. J.; Manne, V.; Oppenheimer, S.; Sack, J. S.; Schmidt, R. J.; Shen, G.; Stefanski, K.; Tokarski, J. S.; Trainor, G. L.; Wautlet, B. S.; Wei, D.; Williams, D. K.; Zhang, Y.; Zhang, Y.; Fargnoli, J.; Borzilleri, R. M. *J. Med. Chem.* **2009**, *52*, 1251.
12. Cui, J. J.; Tran-Dubé, M.; Shen, H.; Nambu, M.; Kung, P. P.; Pairish, M.; Jia, L.; Meng, J.; Funk, L.; Botrous, I.; McTigue, M.; Grodsky, N.; Ryan, K.; Padrique, E.; Alton, G.; Timofeevski, S.; Yamazaki, S.; Li, Q.; Zou, H.; Christensen, J.; Mroczkowski, B.; Bender, S.; Kania, R. S.; Edwards, M. P. *J. Med. Chem.* **2011**, *54*, 6342.
13. Albrecht, B. K.; Harmange, J. C.; Bauer, D.; Berry, L.; Bode, C.; Boezio, A. A.; Chen, A.; Choquette, D.; Dussault, I.; Fridrich, C.; Hirai, S.; Hoffman, D.; Larrow, J. F.; Kaplan-Lefko, P.; Lin, J.; Lohman, J.; Long, A. M.; Moriguchi, J.; O'Connor, A.; Potashman, M. H.; Reese, M.; Rex, K.; Siegmund, A.; Shah, K.; Shimanovich, R.; Springer, S. K.; Teffera, Y.; Yang, Y.; Zhang, Y.; Bellon, S. F. *J. Med. Chem.* **2008**, *51*, 2879.
14. D'Angelo, N. D.; Bellon, S. F.; Booker, S. K.; Cheng, Y.; Coxon, A.; Dominguez, C.; Fellows, I.; Hoffman, D.; Hungate, R.; Kaplan-Lefko, P.; Lee, M. R.; Li, C.; Liu, L.; Rainbeau, E.; Reider, P. J.; Rex, K.; Siegmund, A.; Sun, Y.; Tasker, A. S.; Xi, N.; Xu, S.; Yang, Y.; Zhang, Y.; Burgess, T. L.; Dussault, I.; Kim, T. S. *J. Med. Chem.* **2008**, *51*, 5766.
15. Mannion, M.; Raeppel, S.; Claridge, S.; Zhou, N.; Saavedra, O.; Isakovic, L.; Zhan, L.; Gaudette, F.; Reappel, F.; Déziel, R.; Beaulieu, N.; Nguyen, H.; Chute, I.; Beaulieu, C.; Dupont, I.; Robert, M. F.; Lefebvre, S.; Dubay, M.; Rahil, J.; Wang, J.; Ste-Croix, H.; Macleod, A. R. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 6552.
16. Yasunari, F.; Terufumi, S.; Tsuyoshi, N.; Tatsushi, O.; Atsushi, M.; Kazuhide, N. WO2003000660A1, **2003**.
17. Peterson, Q. P.; Hsu, D. C.; Goode, D. R.; Novotny, C. J.; Totten, R. K.; Hergenrother, P. J. *J. Med. Chem.* **2009**, *52*, 5721.
18. Liang, Z.; Zhang, D.; Ai, J.; Chen, L.; Wang, H.; Kong, X.; Zheng, M.; Liu, H.; Luo, C.; Geng, M.; Jiang, H.; Chen, K. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 3749.
19. Liu, T.; Sun, C.; Xing, X.; Jing, L.; Tan, R.; Luo, Y.; Huang, W.; Song, H.; Li, Z.; Zhao, Y. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 3122.
20. Wilson, J.; Zuberi, S.; Naganathan, S.; Goldman, E.; Kanter, J. WO2010056960, **2010**.
21. Fetscher, C. A. *Org. Synth.* **1963**, *4*, 735.
22. Hernández, S.; Moreno, I.; SanMartin, R.; Gómez, G.; Herrero, M. T.; Domínguez, E. *J. Org. Chem.* **2010**, *75*, 434.
23. Thirumurugan, R.; Sriram, D.; Saxena, A.; Stables, J.; Yogeeswari, P. *Bioorg. Med. Chem.* **2006**, *14*, 3106.
24. Raheem, I. T.; Thiara, P. R.; Peterson, E. A.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2007**, *129*, 13404.
25. Karabatsos, G. J.; Taller, R. A. *J. Am. Chem. Soc.* **1963**, *85*, 3624.
26. Tiedt, R.; Degenkolbe, E.; Furet, P.; Appleton, B. A.; Wagner, S.; Schoepfer, J.; Buck, E.; Ruddy, D. A.; Monahan, J. E.; Jones, M. D.; Blank, J.; Haasen, D.;

Drueckes, P.; Wartmann, M.; McCarthy, C.; Sellers, W. R.; Hofmann, F. *Cancer Res.* **2011**, *71*, 5255.
27. Nakagawa, T.; Tohyama, O.; Yamaguchi, A.; Matsushira, T.; Takahashi, K.; Funasaka, S.; Shirotori, S.; Asada, M.; Obaishi, H. *Cancer Sci.* **2010**, *101*, 210.
28. Ted, L. U.; Torsten, H.; Sheila, J. M. *Anti-Cancer Agents Med.* **2010**, *10*, 7.
29. Liu, L.; Siegmund, A.; Xi, N.; Kaplan-Lefko, P.; Rex, K.; Chen, A.; Lin, J.; Moriguchi, J.; Berry, L.; Huang, L.; Teffera, Y.; Yang, Y.; Zhang, Y.; Bellon, S. F.; Lee, M.; Shimanovich, R.; Bak, A.; Dominguez, C.; Norman, M. H.; Harmange, J. C.; Dussault, I.; Kim, T. S. *J. Med. Chem.* **2008**, *51*, 3688.
30. Peach, M. L.; Tan, N.; Choyke, S. J.; Giubellino, A.; Athauda, G.; Burke, T. R., Jr.; Nicklaus, M. C.; Bottaro, D. P. *J. Med. Chem.* **2009**, *52*, 943.
31. Qian, F.; Engst, S.; Yamaguchi, K.; Yu, P.; Won, K. A.; Mock, L.; Lou, T.; Tan, J.; Li, C.; Tam, D.; Lougheed, J.; Yakes, F. M.; Bentzien, F.; Xu, W.; Zaks, T.; Wooster, R.; Greshock, J.; Joly, A. H. *Cancer Res.* **2009**, *69*, 8009.
32. Kataoka, Y.; Mukohara, T.; Tomioka, H.; Funakoshi, Y.; Kiyota, N.; Fujiwara, Y.; Yashiro, M.; Hirakawa, K.; Hirai, M.; Minami, H. *Invest. New Drugs* **2012**, *30*, 1352.
33. Walsh, D. A.; Franzyshen, S. K.; Yanni, J. M. *J. Med. Chem.* **1989**, *32*, 105.