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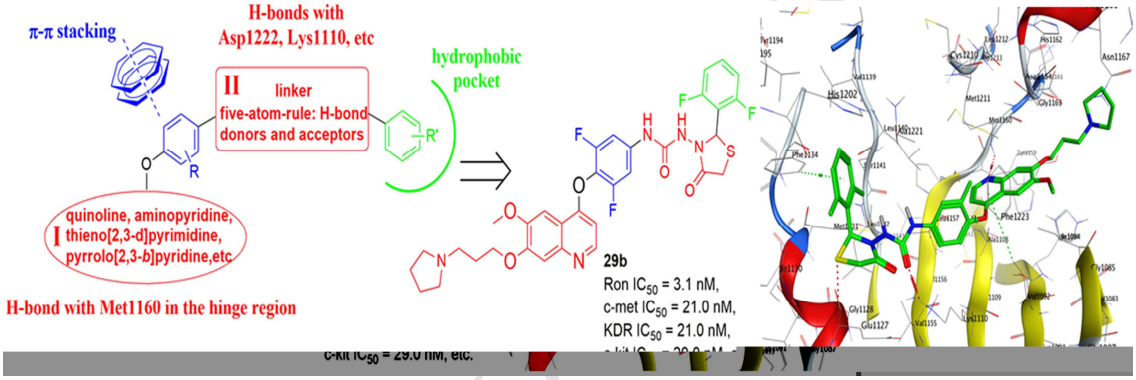
Graphical Abstract



Identification of novel N^1-(2-aryl-1, 3-thiazolidin-4-one)-N^3-aryl ureas showing potent multi-tyrosine kinase inhibitory activities

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Abstract

A total of 29 novel compounds bearing N^1-(2-aryl-1, 3-thiazolidin-4-one)-N^3-aryl ureas were designed, synthesized and evaluated for their biological activities. The structure-activity relationships (SARs) and binding modes of this series of compounds were clarified together. Compound **29b** was identified possessing high potency against multi-tyrosine kinases including Ron, c-Met, c-Kit, KDR, Src and IGF-1R, etc. *In vitro* antiproliferation and cytotoxicity of compound **29b** against A549 cancer cell line were confirmed by IncuCyte live-cell imaging.

Keywords: 1, 3-thiazolidin-4-one; urea; anticancer; tyrosine kinase; inhibitors

1 Introduction

C-Met, also referred to as hepatocyte growth factor receptor (HGFR), is a heterodimeric transmemeric receptor tyrosine kinase composed of an extracellular α-chain and a membrane spanning β-chain that are connected through a disulfide bond [1]. Aberrant c-Met signaling, resulting from MET genomic amplification, c-Met overexpression, or c-Met mutations, could be found in a variety of human cancers and often correlated with poor clinical outcomes [2]. Some literature disclosed that constitutive c-Met activation due to MET amplification was found to be a driver of proliferation and survival of several gastric and lung cancer cell lines, and has been linked to acquired resistance of lung cancers to epidermal growth factor receptor (EGFR) inhibitors [3-5]. Thus, developing novel c-Met kinase inhibitors have been actively pursued by researchers, especially small-molecule inhibitors targeting the catalytic domains of kinase [6, 7].

Cabozantinib, a typical multi-kinase inhibitor bearing quinoline pharmacophore, was approved for the treatment of patients with progressive metastatic medullary thyroid cancer (MTC) [8]. In recent years, a variety of small-molecule inhibitors bearing quinoline pharmacophores have emerged continually as shown in Fig. 1 [9-12]. However, the majority of studies have been limited to *in vitro* experiments due to unfavorable pharmacologic and/or pharmacokinetic properties, as well as intolerable toxicity [2].

(**Fig. 1** should be listed here.)

As shown in Fig. 2, reported SARs [13-16] of quinoline-based inhibitors suggested that regions I and II, which could form H-bonds with the backbone of c-Met kinase, are crucial for inhibitory activity. The substituted phenyl ring (ring A) connecting region I and II was responsible for forming π-π stacking. In addition, hydrophobic interaction was generated by terminal aryl ring reaching into the hydrophobic pocket formed by amino acid residues.

(**Fig. 1** should be listed here.)

1, 3-Thiazolidin-4-one and its derivatives have attracted much attention over the years since they were promising scaffolds that have occupied a prominent position in medicinal chemistry [17, 18]. The detailed literature survey of 1, 3-thiazolidin-4-one and its derivatives demonstrated a wide broad-spectrum pharmacological properties such as antioxidant, antimalarial, anti-HIV, anti-inflammatory, antibacterial and anticancer, *etc* [19-22]. Published data indicated that anticancer activity of 1, 3-thiazolidin-4-ones may be associated with their affinity to diverse targets including non-membrane protein tyrosine phosphatase (SHP-2), JNK-stimulating phosphatase-1 (JSP-1), tumor necrosis factor TNF-α, anti-apoptotic biocomplex Bcl-XL-BH3 and inregrin, *etc* [23].

Hence, based on the above SARs and the structural charactiristics of c-Met kinase inhibitors bearing quinoline pharmacophores, we designed and synthesized hydrid compounds by linking the main structural unit of 4-phenoxy-6, 7-disubstituted quinolines with 1, 3-thiazolidin-3-one scaffolds in attempt to maximize their anticancer activity (Fig. 2). In this report, i*n vitro* antiproliferation and cytotoxicity against A549 cancer cell line were further confirmed by Incucyte real-time imaging.

2 Results and discussion

2.1 Chemistry

(**Scheme 1** should be listed here.)

Target compounds **11a-u** were synthesized according to the routes outlined in Scheme 1 [24]. Commercially available 4-hydroxy-3-methoxyacetophenone was alkylated with 1-bromo-3-chloropropane under basic condition to provide **1**. Regioselective nitration and subsequent aminomethylenation with *N*, *N*-dimethylformamide dimethylacetal (DMF-DMA) afforded intermediate **3**. The intramolecular cyclization in the presence of iron powder and acetic acid afforded **4**, which underwent a nucleophilic substitution with morpholine to give access to **5**. The resultant hydroxyl moiety **5** was converted to **6** by nucleophilic substitution with 4-fluoronitrobenzene under Cs_2CO_3 in MeCN. Intermediate **6** was reduced to provide aniline **7** in excellent yields. By further treatment with 4-nitrophenyl carbonochloridate, the intermediate **7** was converted into amides **8** which was treated with hydrazine hydrate directly to furnish semicarbazide **9**. Intermediates **10a-u** were available via the condensation of **9** with appropriate aldehydes. Finally, the target compounds **11a-u** were obtained via the cyclization with mercaptoacetic acid under $SiCl_4$ [25].

(**Scheme 2** should be listed here.)

As shown in Scheme 2, the resultant hydroxyl moiety **5** obtained previously was converted to the corresponding chloride **12** on exposure to phosphorus oxychloride. Nucleophilic displacement of chlorine atom in the **12** with 4-hydroxybenzaldehyde afforded **13** [26]. Finally, the intermediate **13** was condensed with *N*-(2-fluorophenyl)hydrazinecarboxamide or *N*-(2, 4-difluorophenyl)hydrazine-carboxamide to afford semicarbazones **14a** and **14b**, respectively. At last, the target compounds **15a-b** were obtained according to the same method (vide supra).

As illustrated in Scheme 3 and Scheme 4, the synthesis of compounds **22a-d** and **29a-b** were done in accordance with previously described procedures prepared for **11a-u**.

(**Scheme 3** should be listed here.)

(**Scheme 4** should be listed here.)

2.2 Enzymatic Assay and SARs

Taking Cabozantinib and Staurosporine as references, all the newly synthesized compounds (**11a-u**, **15a-b**, **22a-d** and **29a-b**) were evaluated for their ability to inhibit c-Met kinase using enzyme-linked immunosorbent assays (ELISAs). The results are summarized in Table 1, 2, 3 and 4.

A series of compounds (**11a-u**) with different R_1 were synthesized and evaluated for their inhibition of c-Met kinase (Table 1). All compounds exhibited moderate to potent inhibitory activities against c-Met kinase with IC_{50} values ranging from 0.05 to 0.688 μmol·L^{-1}.

Firstly, a phenyl ring (ring B) was introduced at the C-2 of 1, 3-thiazolidin-4-one and compound **11a** was obtained. Satisfyingly, it displayed promising inhibition of c-Met kinase (IC_{50} = 0.097 μmol·L^{-1}). Replacement of the phenyl ring by a cyclohexyl ring led to an approximate 5-fold drop in potency (**11u** vs **11a**). The introduction of pyridinyl ring **11p** into R_1 was detrimental to enzymatic potency (3.3-fold loss in potency). In order to know if the "five-atom-rule" [16] was applicable for the designed compounds, benzyl **11s** and phenethyl **11t** were synthesized. In addition, loss of c-Met inhibition was observed compared **11s** (IC_{50} = 0.205 μmol·L^{-1}) and **11t** (IC_{50} = 0.331 μmol·L^{-1}) with **11a** (IC_{50} = 0.097 μmol·L^{-1}). It suggested that the presence of a phenyl ring directly attached to the C-2 of 1, 3-thiazolidin-4-one was of significance to inhibitory potency. The bulky effect of the substituents likely weakened inhibitory potency, since the more steric analogues 4-dimethylaminophenyl **11q** and naphthyl **11r** showed 4.4- and 6.7-fold lower potency than phenyl **11a**. Subsequently, a series of compounds (**11b-o**) with diversified small substituents at the phenyl ring were explored. IC_{50} values indicated that it was well tolerated when the substituents were at the ortho-position of phenyl ring, with following rank order: -CF_3 < -Cl < -F. From the results above, we could confirm that minor changes at R_1 could influence c-Met kinase inhibitory activity in different extent.

(**Table 1** should be listed here.)

In the following work, the 1, 3-thiazolidin-4-one moiety was moved to 4-position of phenyl ring A. Unfortunately, the obtained compounds **15a** (IC_{50} = 4.10 μmol·L^{-1}) and **15b** (IC_{50} = 3.35 μmol·L^{-1}) were significantly less potent compared to **11b** (IC_{50} = 0.061 μmol·L^{-1}) and **11e** (IC_{50} = 0.141 μmol·L^{-1}) accordingly (Table 2).

(**Table 2** should be listed here.)

Having identified well tolerated group on R_1 (2, 6-F-Ph-) and the position of 1, 3-thiazolidin-4-one moiety, our attention was turned to the investigation of R_3 and four compounds (**22a-d**) were prepared (Table 3)**.** To our delight, the pyrrolyl derivative **22d** exhibited optimal c-Met inhibition (IC_{50} = 0.037

$\mu mol \cdot L^{-1}$).

(**Table 3** should be listed here.)

Encouraged by the prominent activity of compound **22d,** it was selected for further investigation focused on the phenyl ring A. The IC_{50} values showed that the substitution by fluorine atom on the phenyl ring A resulted a slight boost in c-Met inhibitory activity. The 3-fluoro analogue **29b** displayed a better enzymatic potency than the 2-fluoro analogue **29a**, suggesting that 3-fluoro substitution is superior to 2-fluoro substitution (Table 4).

(**Table 4** should be listed here.)

2.3 Molecular docking study

In order to elucidate the binding mode of this series of compounds with the active site of c-Met kinase, docking simulation studies of selected compound **29b** were carried out by Molecular Operating Environment (MOE, Chemical Computing Group Inc., Canada). As depicted in Fig.3A, compound **29b** adopted an extend conformation as type II kinase inhibitors [27] was buried into the binding pocket of c-Met kinase completely. It occupied the ATP-binding site and formed two strong H-bonds (the quinoline-N and Met1160, the urea-O and Lys1110) and one weak H-bond (the thiazolidinone-S and Glu1127). The terminal 2, 6-difluorophenyl ring (ring B) inserted into a hydrophobic pocket formed by Phe1134, Phe1200 and Ala1221, etc, and notable arene-H interaction with Phe1134 was observed. In addition, π-π stacking was formed between the central fluorophenyl ring (ring A) and the phenyl ring of Phe1223 (Fig. 3B and 3C).

(**Fig. 3** should be listed here.)

2.4 IncuCyte live-cell imaging

In vitro antitumor activity was evaluated by IncuCyte live-cell imaging preliminarily. Taking Cabozantinib as positive control, antiproliferation and cytotoxicity of compound **29b** against non-small cell lung cancer A549 were confirmed.

Time-lapse imaging of the negative control showed a standard growth curve up to approximate 55% cell confluence level by day 3 (green curve, Fig.4A), while compound **29b** treatment efficiently suppressed cell proliferation depending on both concentration and time. As shown in Fig. 4A (the curves of phase object confluence) and 4B (phase contrast images), compound **29b** exhibited significant antiproliferation against A549 cells after 72 h at the concentration of 0.041 μM (confluence: from 16% to 35%), which was superior to that of Cabozantinib at the concentration of 3.33 μM (confluence: from 18% to 48%).

(**Fig. 4** should be listed here.)

In addition, real-time cytotoxicity study of compound **29** against A549 cells was carried on meantime. To our delight, compound **29b** performed excellent cytotoxicity at the concentration of 10μM compared with

Cabozantinib at the same concentration after 72 h (Fig. 5A and 5B). The cytotoxicity at lower concentration was evaluated (data not all showed), and the results indicated that the cytotoxicity of compound **29b** (1.11μM) was almost equipotent to Cabozantinib (10μM).

(**Fig. 5** should be listed here.)

2.5 Kinase profile of compound 29b

Compared with the c-Met IC_{50} values of compound **29b** (0.021 μmol·L^{-1}) and Cabozantinib (0.019 μmol·L^{-1}), similar *in vitro* anticancer activities should be diaplayed. However, the results were not the case (vide supra). It suggested that compound **29b** might act through other mechanisms rather than only by inhibiting c-Met kinase. In order to know the details, compound **29b** was tested on a panel of eight other kinases including c-Kit, Ron, KDR, RET, EGFR, Src, IGF-1R and AXL. As can be seen in **Table 5**, compound **29b** showed potent inhibitory activities against c-Kit, Ron, EGFR and Src with 1.8-, 22.2-, 3.8- and 2.9-fold more potent than Cabozantinib, respectively. In addition, compound **29b** demonstrated moderate inhibition of IGF-1R, with at least 2 times more effective than Cabozantinib. Further studies on the mechanism of these compounds are in progress.

(**Table 5** should be listed here.)

3 Conclusion

In summary, we described the pharmacophore hybrid design, synthesis and examination of a series of N^1-(2-aryl-1, 3-thiazolidin-4-one)-N^3-aryl urea derivatives in an attempt to develop effective anticancer agents. Compound **29b** was found to have promising multi-tyrosine kinase inhibitory activities with IC_{50} values ranging from 3.1 nM to 4.67 μM, including c-Met, c-Kit, Ron, EGFR, Src and IGF-1R. The results of IncuCyte live-cell imaging study showed that compound **29b** performed excellent antiproliferation and cytotoxicity against non-small cell lung cancer A549 cells in comparison to Cabozantinib. Further studies comprising improvement of activity, mechanism and *in vivo* anticancer activity are currently ongoing in our group, and the results will be reported in a due course.

4 Experimental

4.1 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. ^{1}H NMR and ^{13}C NMR spectra were generated on a Bruker ARX-400 spectrometers (Bruker Bioscience, Billerica, MA, USA). Chemical shifts are given in parts per million (ppm) relative to TMS as internal standards. 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).

4.1.1 4-(3-Chloropropoxy)-3-methoxyacetophenone (1)

Anhydrous K_2CO_3 (165.6 g, 1.2 mol) and 1-bromo-3-chloropropane (105.4 g, 0.66 mol) was added to a solution of 4-hydroxy-3-methoxy-acetophenone (100.0 g, 0.60 mol) in DMF (500 mL). The reaction mixture was then stirred at rt for 6 h. The mixture was then poured into cold water (1500 mL) with

vigorously agitating for 15 min, and the resulting precipitate was filtered off, washed with water, and dried under vacuum to afford **1** as white solid, yield: 91.9% (133.8 g). MS (ESI) m/z 242.9 $[M+H]^+$.

4.1.2 4-(3-Chloropropoxy)-5-methoxy-2-nitroacetophenone (2)

A stirred solution of **1** (113.8 g, 0.46 mol) in CH_2Cl_2 (675 mL) was cooled to -20 °C, and fuming nitric acid (56.5 mL) was added at a rate such that the temperature maintained at -15 to -10 °C. The reaction mixture was allowed to stir at about -10 °C for 5 h, then poured into cold water (250 mL). The organic layer was separated and washed with saturated aqueous sodium bicarbonate solution (2 × 200 mL) and water (200 mL) orderly, then concentrated under reduced pressure to afford **2** as light yellow solid, yield: 88.3% (117.5 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (s, 1H), 6.76 (s, 1H), 4.26 (t, *J* = 8.0 Hz, 2H), 3.96 (s, 3H), 3.77 (t, *J* = 8.8 Hz, 2H), 2.50 (s, 3H), 2.29-2.37 (m, 2H). MS (ESI) m/z 288.1 $[M+H]^+$.

4.1.3 1-(4-(3-Chloropropoxy)-5-methoxy-2-nitrophenyl)-3-(dimethylamino)prop-2-en-1-one (3)

DMF-DMA (217.5 mL, 1.61 mol) was added to a solution of **2** (116.3 g, 0.40 mol) in xylene (560 mL) and the reaction was refluxed for 14 h. The solvent was evaporated under reduced pressure, and another 150 mL xylene was added. After stirred for 30 min at rt, the product was collected by filtration and then dried under vacuum to yield **3** as yellow solid, yield: 79.6 % (109.1 g). MS (ESI) m/z 343.0 $[M+H]^+$.

4.1.4 6-Methyloxy-7-(4-(3-chloropropoxy))-4-4-hydroxyquioline (4)

Fe (88.9 g, 1.56 mmol) was added to a solution of **12** (108.8 g, 0.31 mol) in acetic acid (545 mL) at 60 °C in batches, then the mixture was stirred at 100 °C with vigorous agitation for 3 h. The hot solution was filtered through celite and washed with hot acetic acid (100 mL). The combined filtrate was cooled to rt, and the resultant solid was collected by filtration which was recrystallized from acetic acid (3000 mL) to afford **4** as light yellow solid, yield: 67.5% (56.5 g). MS (ESI) m/z 268.1 $[M+H]^+$.

4.1.5 General procedure for preparation of 4-hydroxyquinoline derivates (5 and 16a-d)

To a stirring solution of **4** in acetonitrile (V: m = 8:1) was added different amines (5 eqiv.), and the resulting reaction mixture was refluxed for 8 h. The solvent was removed under reduced pressure to get a crude product which was purified by column chromatography on silica gel using DCM: MeOH 15:1 to give the corresponding 4-hydroxyquinolines **5** and **16a-d.**

4.1.5.1 6-Methyloxy-7-(4-(3-morpholinopropoxy))-4-quiolin-ol (5)

Light yellow solid, yield: 95.1% (21.2 g). MS (ESI) m/z 318.1 $[M+H]^+$.

4.1.5.2 6-Methoxy-7-(3-thiomorpholinopropoxy)quinolin-4-ol (16a)

Light yellow solid, yield: 92.4% (3.5 g). MS (ESI) m/z 335.1 $[M+H]^+$.

4.1.5.3 6-Methoxy-7-(3-(2-methylpiperidin-1-yl)propoxy)quinolin-4-ol (16b)

White solid, yield: 90.8% (3.0 g). MS (ESI) m/z 331.3 $[M+H]^+$.

4.1.5.4 7-(3-(3, 5-dimethylpiperidin-1-yl)propoxy)-6-methoxyquinolin-4-ol (16c)

White solid, yield: 89.9% (3.4 g). MS (ESI) m/z 345.1 $[M+H]^+$.

4.1.5.5 6-Methoxy-7-(3-(pyrrolidin-1-yl)propoxy)quinolin-4-ol (16d)

Yellow solid, yield: 88.6% (7.8 g). MS (ESI) m/z 303. 3$[M+H]^+$.

4.1.6 4-(4-nitrophenoxy)-6-methoxy-7-(3-morpholinopropoxy)quinoline (6)

To a round bottom flask was added **5** (21g, 66.0 mmol), acetonitrile (200 mL) and cesium carbonate (43.0 g, 0.13 mol). The mixture was stirred at rt for 30 min at which time 4-fluoronitrobenzene (11.2g, 79.2 mmol) was added over a 10 min period. Refluxed for 2 h, the reaction was complete at which time about 75% of the MeCN was removed under reduced pressure and the resulting solution was poured into ice water

(150 mL). The solid was filtered and dried to afford **6** as yellow solid, yield: 61.2% (17.8 g). MS (ESI) m/z 440.1 $[M+H]^+$.

4.1.7 4-(6-methoxy-7-(3-morpholinopropoxy)quinolin-4-yloxy)aniline (7)

A mixture of **6** (17.5 g, 39.8 mmol), Fe (11.1 g, 0.20 mol) and conc. HCl (1.0 mL) in ethanol-water (265 mL, 9:1 v/v) was refluxed with vigorous agitation for 3 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 ethanol (120 mL) to afford **7** as white solid, yield: 91.4% (14.9 g). MS (ESI) m/z 410.3 $[M+H]^+$.

4.1.8 *N*^{1}-(3-fluoro-4-(6-methoxy-7-(3-morpholino-propoxy)quinolin-4-yloxy)phenyl)semicarbazide (9)

To the mixture of **7** (14.5 g, 35.4 mmol) and dry pyridine (14.2 g, 0.18 mmol) in dry DCM (145 mL), phenyl chloroformate (13.3 mL, 0.11 mol) was added dropwise at 0 °C. After the addition was completed, the mixture was warmed to rt for 3 h. 50 mL saturated aqueous sodium bicarbonate solution was added and the organic phase was washed with water (2 × 30 mL), dried over anhydrous Na_2SO_4, concentrated under reduced pressure to afford corresponding phenylcarbamate **8**, which were immediately used in the next step without further purification.

A mixture of **8** and 80% hydrazine monohydrate (80 mL) in xylene (80 mL) was stirred at 70 °C for 3 h with vigorous agitation. After cooling to rt, the resulting precipitate was filtered off, washed with water, and dried under vacuum to afford **9** as white solid, total yield: 53.9% (8.9 g). MS (ESI) m/z 468.2 $[M+H]^+$.

4.1.9 General procedure for the synthesis of semicarbazones (10a-u)

To a solution of **9** (0.46 g, 1 mmol) in isopropanol (5 mL), 1.1 equiv of aldehydes 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 to afford **10a-u**, yield: 88.1% to 94.3%.

4.1.10 General procedure for the synthesis of target compounds (11a-u)

To a solution of **10a-u** (0.8 mmol) in mercaptoacetic (2 mL), $SiCl_4$ (3 drops) was added. The mixture was stirred at 50 °C for approximate 6 h. CH_2Cl_2 (20 mL) and cold water (1 mL) was added to the reaction mixture, and the solution was adjusted to pH 8 with the addition of 10% aq. NaOH. The organic phase was separated and washed with water (2 × 10 mL), dried over anhydrous Na_2SO_4, concentrated under reduced pressure to afford yellow oil which was further columned with a biotage system with 10:1 DCM/MeOH.

4.1.10.1

1-(4-((6-methoxy-7-(3-morpholinopropoxy)quinolin-4-yl)oxy)phenyl)-3-(4-oxo-2-phenylthiazolidin-3-yl)urea (11a)

White solid, yield: 49.8%, m.p. > 300 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ9.03 (s, 1H), 8.67 (s, 1H), 8.45 (d, *J* = 5.2 Hz, 1H), 7.58-7.67 (m, 1H), 7.56 (d, *J* = 9.2 Hz, 2H), 7.52 (s, 1H), 7.42-7.47 (m, 1H), 7.38 (s, 1H), 7.25-7.34 (m, 3H), 7.17 (d, *J* = 9.2 Hz, 2H), 6.40 (d, *J* = 5.2 Hz, 1H), 6.07 (s, 1H), 4.19 (t, *J* = 6.4 Hz, 2H), 3.94 (s, 3H), 3.78-3.90 (m, 2H), 3.58-3.60 (m, 4H), 2.43-2.49 (m, 2H), 2.35-2.44 (br, 4H), 1.94-2.00 (m, 2H). MS (ESI) m/z 629.2 $[M+H]^+$.

4.1.10.2

1-(2-(2-fluorophenyl)-4-oxothiazolidin-3-yl)-3-(4-((6-methoxy-7-(3-morpholinopropoxy)quinolin-4-yl) oxy)phenyl)urea (11b)

White solid, yield: 49.0%, m.p. > 300 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.99-9.07 (br, 1H), 8.68 (s, 1H), 8.45 (d, *J* = 5.2 Hz, 1H), 7.58-7.68 (m, 1H), 7.55 (d, *J* = 9.2 Hz, 2H), 7.50 (s, 1H), 7.42-7.47 (m, 1H), 7.38 (s, 1H), 7.24-7.30 (m, 2H), 7.19 (d, *J* = 9.2 Hz, 2H), 6.41 (d, *J* = 5.2 Hz, 1H), 6.07 (s, 1H), 4.19 (t, *J* = 6.4 Hz, 2H), 3.93 (s, 3H), 3.78-3.90 (m, 2H), 3.58-3.60 (m, 4H), 2.45-2.49 (m, 2H), 2.34-2.43 (br, 4H), 1.94- 2.01 (m, 2H). ^{13}C NMR (400 MHz, DMSO-d_6) δ 169.90, 162.07, 160.55, 159.61, 154.25, 152.28, 149.83, 149.27, 148.89, 146.83, 137.19, 131.39, 131.30, 129.89, 125.34, 121.97, 120.55, 116.37, 116.16, 115.47, 108.95, 103.28, 99.63, 67.09, 66.68 (2C), 56.79, 56.17, 55.29, 53.84 (2C), 29.60, 26.15. MS (ESI) m/z 648.1 $[M+H]^+$.

4.1.10.3

1-(2-(3-fluorophenyl)-4-oxothiazolidin-3-yl)-3-(4-((6-methoxy-7-(3-morpholinopropoxy)quinolin-4-yl) oxy)phenyl)urea (11c)

White solid, yield: 49.2%, m.p. > 300 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.05-9.18 (br, 1H), 8.67 (s, 1H), 8.44 (d, *J* = 5.2 Hz, 1H), 7.53 (d, *J* = 9.2 Hz, 2H), 7.51 (s, 1H), 7.44-7.49 (m, 1H), 7.34-7.42 (m, 2H), 7.19 (d, *J* = 9.2 Hz, 2H), 6.41 (d, *J* = 5.2 Hz, 1H), 5.86 (s, 1H), 4.19 (t, *J* = 6.4 Hz, 2H), 3.91-3.95 (m, 4H), 3.79 (d, *J* = 15.6 Hz, 1H), 3.58-3.60 (m, 4H), 2.45-2.49 (m, 2H), 2.35- 2.43 (br, 4H), 1.95-2.01 (m, 2H). MS (ESI) m/z 648.1 $[M+H]^+$.

4.1.10.4

1-(2-(4-fluorophenyl)-4-oxothiazolidin-3-yl)-3-(4-((6-methoxy-7-(3-morpholinopropoxy)quinolin-4-yl) oxy)phenyl)urea (11d)

White solid, yield: 51.6%, m.p. > 300 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.95-9.06 (br, 1H), 8.55 (s, 1H), 8.46 (d, *J* = 5.2 Hz, 1H), 7.51-7.58 (m, 5H), 7.39 (s, 1H), 7.17-7.27 (m, 4H), 6.42 (d, *J* = 5.2 Hz, 1H), 5.86 (s, 1H), 4.21 (t, *J* = 6.0 Hz, 2H), 3.94 (s, 3H), 3.76-3.91 (m, 2H), 3.57-3.67 (br, 4H), 2.59-2.64 (m, 2H), 2.32-2.50 (br, 4H), 1.96- 2.07 (m, 2H). MS (ESI) m/z 648.2 $[M+H]^+$.

4.1.10.5

1-(2-(2,4-difluorophenyl)-4-oxothiazolidin-3-yl)-3-(4-((6-methoxy-7-(3-morpholinopropoxy)quinolin-4 -yl)oxy)phenyl)urea (11e)

White solid, yield: 52.9%, m.p. > 300 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.02-9.09 (br, 1H), 8.68 (s, 1H), 8.45 (d, *J* = 5.2 Hz, 1H), 7.67-7.76 (m, 1H), 7.55 (d, *J* = 8.8 Hz, 2H), 7.51 (s, 1H), 7.38 (s, 1H), 7.30-7.36 (m, 1H), 7.14-7.22 (m, 3H), 6.42 (d, *J* = 5.2 Hz, 1H), 6.04 (s, 1H), 4.20 (t, *J* = 6.4 Hz, 2H), 3.94 (s, 3H), 3.78-3.91 (m, 2H), 3.58-3.61 (m, 4H), 2.45-2.49 (m, 2H), 2.34-2.44 (br, 4H), 1.95-2.01 (m, 2H). MS (ESI) m/z 648.1 $[M+H]^+$.

4.1.10.6

1-(2-(3,4-difluorophenyl)-4-oxothiazolidin-3-yl)-3-(4-((6-methoxy-7-(3-morpholinopropoxy)quinolin-4 -yl)oxy)phenyl)urea (11f)

White solid, yield: 52.0%, m.p. > 300 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.09 (s, 1H), 8.65 (s, 1H), 8.46 (d, *J* = 5.2 Hz, 1H), 7.67-7.74 (m, 1H), 7.54 (d, *J* = 8.8 Hz, 2H), 7.50 (s, 1H), 7.35-7.38 (m, 1H), 7.29-7.34 (m, 1H), 7.14-7.21 (m, 3H), 6.43 (d, *J* = 5.2 Hz, 1H), 5.95 (s, 1H), 4.19 (t, *J* = 6.4 Hz, 2H), 3.93 (s, 3H), 3.78-3.88 (m, 2H), 3.56-3.61 (m, 4H), 2.45-2.51 (m, 2H), 2.34- 2.42 (m, 4H), 1.94-2.01 (m, 2H). MS (ESI) m/z 666.2 $[M+H]^+$.

4.1.10.7

1-(2-(2,6-difluorophenyl)-4-oxothiazolidin-3-yl)-3-(4-((6-methoxy-7-(3-morpholinopropoxy)quinolin-4

-yl)oxy)phenyl)urea (11g)

White solid, yield: 50.5%, m.p. > 300 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.03 (s, 1H), 8.83 (s, 1H), 8.45 (d, *J* = 5.2 Hz, 1H), 7.47-7.55 (m, 4H), 7.38 (s, 1H), 7.16-7.21 (m, 4H), 6.42 (d, *J* = 5.2 Hz, 1H), 6.17 (s, 1H), 4.19 (t, *J* = 6.4 Hz, 2H), 3.94 (s, 3H), 3.80-3.84 (br, 2H), 3.58-3.60 (m, 4H), 2.45- 2.49 (m, 2H), 2.33-2.44 (br, 4H), 1.95-2.01 (m, 2H). MS (ESI) m/z 666.2 $[M+H]^+$.

4.1.10.8

1-(4-((6-methoxy-7-(3-morpholinopropoxy)quinolin-4-yl)oxy)phenyl)-3-(4-oxo-2-(3,4,5-trifluorophenyl)thiazolidin-3-yl)urea (11h)

White solid, yield: 56.0%, m.p. > 300 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.57-9.76 (br, 1H), 9.02-9.19 (br, 1H), 8,44 (d, *J* = 5.2 Hz, 1H),7.52-7.62 (m, 4H), 7.51 (s, 1H), 7.38 (s, 1H), 7.19 (d, *J* = 8.8 Hz, 2H), 6.41 (d, *J* = 5.2Hz, 1H), 5.86 (s, 1H), 4.19 (t, *J* = 6.4 Hz, 2H), 3.95-3.97 (m, 1H), 3.94 (s, 3H), 3.73-3.77 (m,1H), 3.54-3.64 (m, 4H), 2.47 (t, *J* = 7.2 Hz, 2H), 2.34-2.44 (br, 4H), 1.95-2.01 (m, 2H). MS (ESI) m/z 684.1 $[M+H]^+$.

4.1.10.9

1-(4-((6-methoxy-7-(3-morpholinopropoxy)quinolin-4-yl)oxy)phenyl)-3-(4-oxo-2-(2,4,6-trifluorophenyl)thiazolidin-3-yl)urea (11i)

White solid, yield: 47.3%, m.p. > 300 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.04 (s, 1H), 8.79 (s, 1H), 8.45 (d, *J* = 5.2 Hz, 1H), 7.55 (d, *J* = 8.8 Hz, 2H), 7.51 (s, 1H), 7.38 (s, 1H), 7.28-7.33 (m, 2H), 7.20 (d, *J* = 8.8 Hz, 2H), 6.42 (d, *J* = 5.2 Hz, 1H), 6.12 (s, 1H), 4.19 (t, *J* = 6.4 Hz, 2H), 3.94 (s, 3H), 3.79-3.86 (m, 2H), 3.58-3.61 (m, 4H), 2.45- 2.49 (m, 2H), 2.35-2.43 (br, 4H), 1.95-2.01 (m, 2H). MS (ESI) m/z 684.1 $[M+H]^+$.

4.1.10.10

1-(2-(4-chlorophenyl)-4-oxothiazolidin-3-yl)-3-(4-((6-methoxy-7-(3-morpholinopropoxy)quinolin-4-yl)oxy)phenyl)urea (11j)

White solid, yield: 56.9%, m.p. > 300 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.94-9.11 (br, 1H), 8.60 (s, 1H), 8.45 (d, *J* = 5.2 Hz, 1H), 7.47-7.54 (m, 7H), 7.38 (s, 1H), 7.19 (d, *J* = 8.8 Hz, 2H), 6.41 (d, *J* = 5.2 Hz, 1H), 5.85 (s, 1H), 4.19 (t, *J* = 6.4 Hz, 2H), 3.93 (s, 3H), 3.76-3.92 (m, 2H), 3.58-3.60 (m, 4H), 2.45- 2.48 (m, 2H), 2.28-2.43 (br, 4H), 1.94-2.01 (m, 2H). MS (ESI) m/z 664.2 $[M+H]^+$.

4.1.10.11

1-(2-(2-chlorophenyl)-4-oxothiazolidin-3-yl)-3-(4-((6-methoxy-7-(3-morpholinopropoxy)quinolin-4-yl)oxy)phenyl)urea (11k)

White solid, yield: 54.0%, m.p. > 300 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.12 (s, 1H), 8.78 (s, 1H), 8.45 (d, *J* = 5.2 Hz, 1H), 7.66-7.68 (m, 1H), 7.52-7.60 (m, 4H), 7.39-7.47 (m, 2H), 7.38 (s, 1H), 7.20 (d, *J* = 8.8 Hz, 2H), 6.42 (d, *J* = 5.2 Hz, 1H), 6.17 (s, 1H), 4.19 (t, *J* = 6.4 Hz, 2H), 3.93 (s, 3H), 3.78-3.90 (m, 2H), 3.58-3.60 (m, 4H), 2.45- 2.49 (m, 2H), 2.33-2.44 (br, 4H), 1.94-2.01 (m, 2H). MS (ESI) m/z 664.2 $[M+H]^+$.

4.1.10.12

1-(2-(3,5-dichlorophenyl)-4-oxothiazolidin-3-yl)-3-(4-((6-methoxy-7-(3-morpholinopropoxy)quinolin-4-yl)oxy)phenyl)urea (11l)

White solid, yield: 51.7%, m.p. > 300 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.97-9.05 (br, 1H), 8.64 (s, 1H), 8.45 (d, *J* = 5.2 Hz, 1H), 7.74-7.80 (m, 4H), 7.54 (d, *J* = 8.8 Hz, 2H), 7.50 (s, 1H), 7.38 (s, 1H), 7.19 (d, *J* = 8.8 Hz, 2H), 6.41 (d, *J* = 5.2 Hz, 1H), 5.95 (s, 1H), 4.19 (t, *J* = 6.4 Hz, 2H), 3.93 (s, 3H), 3.79-3.96

(m, 2H), 3.58-3.61 (m, 4H), 2.46- 2.49 (m, 2H), 2.34-2.44 (br, 4H), 1.95-2.01 (m, 2H). MS (ESI) m/z 698.2 $[M+H]^+$.

4.1.10.13

1-(4-((6-methoxy-7-(3-morpholinopropoxy)quinolin-4-yl)oxy)phenyl)-3-(4-oxo-2-(4-(trifluoromethyl) phenyl)thiazolidin-3-yl)urea (11m)

White solid, yield: 43.9%, m.p. > 300 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.06-9.20 (br, 1H), 8.74 (s, 1H), 8.45 (d, *J* = 5.2 Hz, 1H), 7.61-7.63 (m, 3H), 7.56 (d, *J* = 8.8 Hz, 2H), 7.38 (s, 1H), 7.20 (d, *J* = 8.8 Hz, 2H), 6.41 (d, *J* = 5.2 Hz, 1H), 5.87 (s, 1H), 4.19 (t, *J* = 6.4 Hz, 2H), 3.94 (s, 3H), 3.75-3.99 (m, 2H), 3.58-3.60 (m, 4H), 2.43- 2.49 (m, 2H), 2.31-2.41 (br, 4H), 1.95-2.01 (m, 2H). ^{13}C NMR (400 MHz, DMSO-d_6) δ 170.03, 162.11, 160.55, 159.63, 154.13, 152.28, 149.83, 149.27, 148.85, 146.83, 137.22, 131.44, 131.38, 129.04, 126.09, 123.20, 121.95, 120.52, 116.35, 116.18, 115.47, 108.95, 103.27, 99.62, 67.09, 66.68 (2C), 56.79, 56.17, 55.29, 53.84 (2C), 29.60, 26.15. MS (ESI) m/z 698.2 $[M+H]^+$.

4.1.10.14

1-(4-((6-methoxy-7-(3-morpholinopropoxy)quinolin-4-yl)oxy)phenyl)-3-(4-oxo-2-(2-(trifluoromethyl) phenyl)thiazolidin-3-yl)urea (11n)

White solid, yield: 40.4%, m.p. > 300 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.06 (s, 1H), 8.70 (s, 1H), 8.44 (d, *J* = 5.2 Hz, 1H), 7.92-7.94 (m, 1H), 7.80-7.84 (m, 1H), 7.74-7.76 (m, 1H), 7.58-7.62 (m, 1H), 7.53 (d, *J* = 8.8 Hz, 2H), 7.50 (s, 1H), 7.38 (s, 1H), 7.19 (d, *J* = 8.8 Hz, 2H), 6.42 (d, *J* = 5.2 Hz, 1H), 6.14 (s, 1H), 4.19 (t, *J* = 6.4 Hz, 2H), 3.93 (s, 3H), 3.82-3.98 (m, 2H), 3.58-3.60 (m, 4H), 2.45- 2.49 (m, 2H), 2.33-2.43 (br, 4H), 1.94-2.01 (m, 2H). MS (ESI) m/z 698.2 $[M+H]^+$.

4.1.10.15

1-(4-((6-methoxy-7-(3-morpholinopropoxy)quinolin-4-yl)oxy)phenyl)-3-(4-oxo-2-(3-(trifluoromethyl) phenyl)thiazolidin-3-yl)urea (11o)

White solid, yield: 43.7%, m.p. > 300 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.99-9.10 (br, 1H), 8.65 (s, 1H), 8.45 (d, *J* = 5.2 Hz, 1H), 7.90-7.95 (br, 1H), 7.82-7.84 (m, 1H), 7.73-7.75 (m, 1H), 7.58-7.62 (m, 1H), 7.63-7.67 (m, 1H), 7.54 (d, *J* = 8.8 Hz, 2H), 7.50 (s, 1H), 7.38 (s, 1H), 7.18 (d, *J* = 8.8 Hz, 2H), 6.40 (d, *J* = 5.2 Hz, 1H), 6.14 (s, 1H), 4.19 (t, *J* = 6.4 Hz, 2H), 3.93 (s, 3H), 3.78-3.97 (m, 2H), 3.58-3.60 (m, 4H), 2.45-2.49 (m, 2H), 2.32-2.43 (br, 4H), 1.94-2.01 (m, 2H). MS (ESI) m/z 698.2 $[M+H]^+$.

4.1.10.16

1-(4-((6-methoxy-7-(3-morpholinopropoxy)quinolin-4-yl)oxy)phenyl)-3-(4-oxo-2-(pyridin-4-yl)thiazol idin-3-yl)urea (11p)

White solid, yield: 50.1%, m.p. > 300 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.03-9.13 (br, 1H), 8.73 (s, 1H), 8.63 (d, *J* = 6.0 Hz, 2H), 8.45 (d, *J* = 5.2 Hz, 1H), 7.51-7.55 (m, 5H), 7.38 s, 1H), 7.19 (d, *J* = 8.8 Hz, 2H), 6.41 (d, *J* = 5.2 Hz, 1H), 5.86 (s, 1H), 4.19 (t, *J* = 6.4 Hz, 2H), 3.76-3.96 (m, 5H), 3.58-3.60 (m, 4H), 2.45-2.49 (m, 2H), 2.27-2.42 (br, 4H), 1.91-2.01 (m, 2H). MS (ESI) m/z 631.2 $[M+H]^+$.

4.1.10.17

1-(2-(4-(dimethylamino)phenyl)-4-oxothiazolidin-3-yl)-3-(4-((6-methoxy-7-(3-morpholinopropoxy)qui nolin-4-yl)oxy)phenyl)urea (11q)

White solid, yield: 40.6%, m.p. > 300 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.83-8.98 (br, 1H), 8.45 (d, *J* = 9.2 Hz, 1H), 8.38 (s, 1H), 7.53 (d, *J* = 9.2 Hz, 2H), 7.50 (s, 1H), 7.38 (s, 1H), 7.28-7.30 (m, 2H), 7.18 (d, *J* = 9.2 Hz, 2H), 6.72 (d, *J* = 8.8 Hz, 2H), 6.40 (d, *J* = 5.2 Hz, 1H), 5.72 (s, 1H), 4.19 (t, *J* = 6.4 Hz, 2H),

3.93 (s, 3H), 3.71-3.82 (m, 2H), 3.58-3.60 (m, 4H), 2.91 (s, 6H), 2.46-2.49 (m, 2H), 2.33-2.43 (br, 4H), 1.94-2.01 (m, 2H). MS (ESI) m/z 673.2 $[M+H]^+$.

4.1.10.18

1-(4-((6-methoxy-7-(3-morpholinopropoxy)quinolin-4-yl)oxy)phenyl)-3-(2-(naphthalen-2-yl)-4-oxothiazolidin-3-yl)urea (11r)

White solid, yield: 50.6%, m.p. > 300 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.99-9.09 (br, 1H), 8.69 (s, 1H), 8.43 (d, *J* = 5.2 Hz, 1H), 7.90-8.02 (m, 4H), 7.66- 7.71 (m, 1H), 7.55-7.58 (m, 2H), 7.53 (d, *J* = 8.8 Hz, 1H), 7.50 (s, 1H), 7.38 (s, 1H), 7.17 (d, *J* = 8.8 Hz, 2H), 6.40 (d, *J* = 5.2Hz, 1H), 6.00 (s, 1H), 4.19 (t, *J* = 6.4 Hz, 2H), 3.94-3.99 (m, 2H), 3.93 (s, 3H), 3.85 (d, *J* = 16.0 Hz, 1H), 3.56-3.63 (m, 4H), 2.45- 2.49 (m, 2H), 2.32-2.43 (br, 4H), 1.91-2.01 (m, 2H). MS (ESI) m/z 680.3 $[M+H]^+$.

4.1.10.19

1-(2-benzyl-4-oxothiazolidin-3-yl)-3-(4-((6-methoxy-7-(3-morpholinopropoxy)quinolin-4-yl)oxy)phenyl)urea (11s)

White solid, yield: 59.4%, m.p. > 300 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.25 (s, 1H), 8.77 (s, 1H), 8.46 (d, *J* = 5.2 Hz, 1H), 7.63 (d, *J* = 9.2 Hz, 2H), 7.52 (s, 1H), 7.38 (s, 1H), 7.25-7.35 (m, 5H), 7.23 (d, *J* = 9.2 Hz, 2H), 6.44 (d, *J* = 5.2 Hz, 1H), 4.94-5.01 (m, 1H), 4.19 (t, *J* = 6.4 Hz, 2H), 3.94 (s, 3H), 3.58-3.60 (m, 4H), 3.35-3.50 (m, 2H), 3.25-3.29 (m, 1H), 2.90-2.95 (m, 1H), 2.45-2.52 (m, 2H), 2.32-2.44 (br, 4H), 1.95-2.01 (m, 2H). MS (ESI) m/z 644.2 $[M+H]^+$.

4.1.10.20

1-(4-((6-methoxy-7-(3-morpholinopropoxy)quinolin-4-yl)oxy)phenyl)-3-(4-oxo-2-phenethylthiazolidin-3-yl)urea (11t)

White solid, yield: 58.9%, m.p. > 300 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.15-9.26 (br, 1H), 8.68 (s, 1H), 8.46 (d, *J* = 5.2 Hz, 1H), 7.60 (d, *J* = 8.8 Hz, 2H), 7.51 (s, 1H), 7.38 (s, 1H), 7.18-7.31 (m, 7H), 6.43 (d, *J* = 5.2 Hz, 1H), 7.75-7.77 (m, 1H), 4.19 (t, *J* = 6.4 Hz, 2H), 3.93 (s, 3H), 3.58- 3.69 (m, 6H), 2.66-2.75 (m, 2H), 2.45-2.49 (m, 2H), 2.38-2.43 (br, 4H), 2.22-2.31 (m, 1H), 1.94-2.03 (m, 3H). ^{13}C NMR (400 MHz, DMSO-d_6) δ 169.69, 162.14, 160.56, 159.67, 154.51, 152.29, 149.84, 149.29, 148.86, 146.84, 141.38, 137.39, 128.90 (2C), 128.82 (2C), 126.47, 121.94, 120.72, 115.49, 108.96, 103.30, 99.64, 67.10, 66.69 (2C), 60.82, 56.18, 55.30, 53.85 (2C), 36.86, 30.43, 28.92, 26.16. MS (ESI) m/z 657.2 $[M+H]^+$.

4.1.10.21

1-(2-cyclohexyl-4-oxothiazolidin-3-yl)-3-(4-((6-methoxy-7-(3-morpholinopropoxy)quinolin-4-yl)oxy)phenyl)urea (11u)

White solid, yield: 56.6%, m.p. > 300 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.09 (s, 1H), 8.79 (s, 1H), 8.46 (d, *J* = 5.2 Hz, 1H), 7.61 (d, *J* = 9.2 Hz, 2H), 7.52 (s, 1H), 7.38 (s, 1H), 7.21 (d, *J* = 9.2 Hz, 2H), 6.43 (d, *J* = 5.2 Hz, 1H), 4.73-4.77 (br , 1H), 4.20 (t, *J* = 6.4 Hz, 2H), 3.94 (s, 3H), 3.58-3.61 (m, 4H), 3.54 (s, 2H), 2.46-2.49 (m, 2H), 2.34-2.43 (br, 4H), 1.92-2.02 (m, 3H), 1.70-1.80 (m, 2H), 1.61-1.69 (m, 2H), 1.51-1.59 (m, 1H), 0.98-1.37 (m, 5H). ^{13}C NMR (400 MHz, DMSO-d_6) δ 169.91, 162.09, 160.57, 159.70, 154.41, 152.29, 149.84, 149.29, 148.82, 146.85, 137.42, 121.96, 120.61, 115.49, 108.97, 103.29, 99.65, 67.10, 66.70 (2C), 66.16, 56.19, 55.31, 53.86 (2C), 28.96, 28.67, 26.41, 26.18 (2C), 26.15, 25.47, 24.78. MS (ESI) m/z 636.3 $[M+H]^+$.

4.1.11 4-Chloro-6-methyloxy-7-(4-(3-morpholinopropoxy))quinolone (12)

Phosphorus oxychloride (24 mL) was added to **5** (3.0 g, 9.4 mmol) and the mixture heated to reflux for 3

h. The contents were concentrated under reduced pressure and the pale residue was poured into ice-water (50 mL) with vigorous agitation. The solution was treated with solid sodium bicarbonate to achieve pH to 8, 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 **12** as offwhite solid, yield: 94.4% (3.0 g). MS (ESI) m/z 337.1 $[M+H]^+$.

4.1.12 4-((6-methoxy-7-(3-morpholinopropoxy)quinolin-4-yl)oxy)benzaldehyde (13)

A solution of **12** (3.0 g, 8.9 mmol) and 4-hydroxybenzaldehyde (1.3 g, 10.7 mmol) in chlorobenzene (30 mL) was refluxed for 13 h. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure to yield dark brown solid which was purified by silica gel column chromatography (eluent, DCM:MeOH:Et_3N = 100:2:1 to 100:5:1) to afford **13** as white solid, yield: 64.3% (2.4 g). MS (ESI) m/z 423.2$[M+H]^+$.

4.1.13

1-(4-fluorophenyl)-3-(2-(4-((6-methoxy-7-(3-morpholinopropoxy)quinolin-4-yl)oxy)phenyl)-4-oxothiazolidin-3-yl)urea (15a)

Compound **15a** was prepared with similar procedure as compound **11a**. White solid, yield: 60.1%, m.p. > 300 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ^{13}C NMR (400 MHz, DMSO-d_6) δ 8.99-9.05 (br, 1H), 8.68 (s, 1H), 8.46 (d, *J* = 5.2 Hz, 1H), 7.58-7.66 (m, 1H), 7.57 (d, *J* = 9.2 Hz, 2H), 7.52 (s, 1H), 7.42-7.48 (m, 1H), 7.36 (s, 1H), 7.24-7.31 (m, 2H), 7.19 (d, *J* = 9.2 Hz, 2H), 6.43 (d, *J* = 5.2 Hz, 1H), 6.01 (s, 1H), 4.19 (t, *J* = 6.4 Hz, 2H), 3.95 (s, 3H), 3.78-3.90 (m, 2H), 3.58-3.62 (m, 4H), 2.45-2.52 (m, 2H), 2.34-2.42 (br, 4H), 1.94- 2.01 (m, 2H). MS (ESI) m/z 648.2 $[M+H]^+$.

4.1.14

1-(2,4-difluorophenyl)-3-(2-(4-((6-methoxy-7-(3-morpholinopropoxy)quinolin-4-yl)oxy)phenyl)-4-oxothiazolidin-3-yl)urea (15b)

Compound **15b** was prepared with similar procedure as compound **11a**. White solid, yield: 58.7%, m.p. > 300 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ^{13}C NMR (400 MHz, DMSO-d_6) δ 9.00-9.06 (br, 1H), 8.67 (s, 1H), 8.44 (d, *J* = 5.2 Hz, 1H), 7.67-7.75 (m, 1H), 7.54 (d, *J* = 8.8 Hz, 2H), 7.50 (s, 1H), 7.36 (s, 1H), 7.31-7.36 (m, 1H), 7.14-7.21 (m, 3H), 6.43 (d, *J* = 5.2 Hz, 1H), 5.97 (s, 1H), 4.21 (t, *J* = 6.4 Hz, 2H), 3.96 (s, 3H), 3.79-3.93 (m, 2H), 3.58-3.62 (m, 4H), 2.43-2.49 (m, 2H), 2.34-2.43 (br, 4H), 1.95-2.00 (m, 2H). MS (ESI) m/z 666.2 $[M+H]^+$.

4.1.15 General procedure for the synthesis of target compounds (22a-d)

Compound **22a-d** was prepared with similar procedure as compound **11a**.

4.1.15.1

1-(2-(2,6-difluorophenyl)-4-oxothiazolidin-3-yl)-3-(4-((6-methoxy-7-(3-thiomorpholinopropoxy)quinolin-4-yl)oxy)phenyl)urea (22a)

White solid, yield: 50.9%, m.p. > 300 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.06 (s, 1H), 8.83 (s, 1H), 8.45 (d, *J* = 5.2Hz, 1H), 7.47-7.55 (m, 4H), 7.38 (s, 1H), 7.16-7.23 (m, 4H), 6.42 (d, *J* = 5.2 Hz, 1H), 6.17 (s, 1H), 4.18 (t, *J* = 6.4 Hz, 2H), 3.94 (s, 3H), 3.84 (s, 2H), 2.57-2.73 (m, 8H), 2.45-2.49 (m, 2H), 1.93-1.99 (m, 2H). MS (ESI) m/z 682.1 $[M+H]^+$.

4.1.15.2

1-(2-(2,6-difluorophenyl)-4-oxothiazolidin-3-yl)-3-(4-((6-methoxy-7-(3-(2-methylpiperidin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl)urea (22b)

White solid, yield: 49.0%, m.p. > 300 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.14 (s, 1H), 8.87 (s, 1H), 8.45 (d, *J* = 5.2 Hz, 1H), 7.47-7.55 (m, 4H), 7.38 (s, 1H), 7.16- 7.21 (m, 4H), 6.42 (d, *J* = 5.2 Hz, 1H), 6.17 (s, 1H), 4.18 (t, *J* = 6.4 Hz, 2H), 3.93 (s, 2H), 2.83-2.96 (m, 2H), 2.32-2.47 (m, 2H), 2.17-2.28 (br, 1H), 1.88-1.99 (m, 2H), 1.52-1.65 (m, 3H), 1.38-1.51 (m, 1H), 1.19-1.31 (m, 2H), 1.05 (d, *J* = 6.4 Hz, 3H). MS (ESI) m/z 677.3 $[M+H]^+$.

4.1.15.3

1-(2-(2,6-difluorophenyl)-4-oxothiazolidin-3-yl)-3-(4-((7-(3-(3,5-dimethylpiperidin-1-yl)propoxy)-6-methoxyquinolin-4-yl)oxy)phenyl)urea (22c)

White solid, yield: 51.5%, m.p. > 300 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.02 (s, 1H), 8.79 (s, 1H), 8.45 (d, *J* = 5.2 Hz, 1H), 7.47- 7.55 (m, 4H), 7.37 (s, 1H), 7.16- 7.21 (m, 4H), 6.42 (d, *J* = 5.2 Hz, 1H), 6.17 (s, 1H), 4.18 (t, *J* = 6.4 Hz, 2H), 3.94 (s, 3H), 3.84 (s, 2H), 2.84-2.87 (m, 2H), 2.41-2.48 (m, 2H), 1.93-2.03 (m, 2H), 1.54-1.70 (m, 3H), 1.37-1.49 (m, 2H), 0.82-0.83 (m, 6H), 0.45-0.54 (m, 1H). MS (ESI) m/z 692.3 $[M+H]^+$.

4.1.15.4

1-(2-(2,6-difluorophenyl)-4-oxothiazolidin-3-yl)-3-(4-((6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl)urea (22d)

White solid, yield: 47.3%, m.p. > 300 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.01 (s, 1H), 8.80 (s, 1H), 8.45 (d, *J* = 5.2 Hz, 1H), 7.47-7.55 (m, 4H), 7.38 (s, 1H), 7.16-7.21 (m, 4H), 6.42 (d, *J* = 5.2 Hz, 1H), 6.17 (s, 1H), 4.20 (t, *J* = 4.8 Hz, 2H), 3.95 (s, 3H), 3.84 (s, 2H), 2.62-2.73 (m, 2H), 2.56-2.63 (m, 4H), 1.97-2.05 (m, 2H), 1.68-1.76 (br, 4H). MS (ESI) m/z 650.2 $[M+H]^+$.

4.1.16 General procedure for the synthesis of target compounds (29a-b)

Compound **29a-b** was prepared with similar procedure as compound **11a**.

4.1.16.1

1-(2-(2,6-difluorophenyl)-4-oxothiazolidin-3-yl)-3-(3-fluoro-4-((6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl)urea (29a)

White solid, yield: 46.6%, m.p. > 300 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.94 (s, 1H), 8.74 (s, 1H), 8.47 (d, *J* = 5.2 Hz, 1H), 8.01-8.05 (m, 1H), 7.49-7.56 (m, 1H), 7.48 (s, 1H), 7.39 (s, 1H), 7.31-7.34 (m, 1H), 7.19-7.23 (m, 2H), 7.06-7.09 (m, 1H), 6.52 (d, *J* = 5.2 Hz, 1H), 6.19 (s, 1H), 4.20 (t, *J* = 4.8 Hz, 2H), 3.93 (s, 3H), 3.85 (s, 2H), 2.64-2.72 (m, 2H), 2.53-2.64 (br, 4H), 1.97-2.05 (m, 2H), 1.68-1.78 (br, 4H). MS (ESI) m/z 668.2 $[M+H]^+$.

4.1.16.2

1-(2-(2,6-difluorophenyl)-4-oxothiazolidin-3-yl)-3-(2-fluoro-4-((6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy)quinolin-4-yl)oxy)phenyl)urea (29b)

White solid, yield: 45.9%, m.p. > 300 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.29 (s, 1H), 9.02 (s, 1H), 8.46 (d, *J* = 5.2 Hz, 1H), 7..63-7.67 (m, 1H), 7.53 (s, 1H), 7.47-7.54 (m, 1H), 7.39 (s, 1H), 7.35-7.37 (m, 1H), 7.26-7.29 (m, 2H), 7.16-7.20 (m, 2H), 6.42 (d, *J* = 5.2 Hz, 1H), 6.15 (s, 1H), 4.20 (t, *J* = 4.8 Hz, 2H), 3.95 (s, 3H), 3.84 (s, 2H), 2.62-2.71 (m, 2H), 2.56-2.62 (m, 4H), 1.98-2.05 (m, 2H), 1.68-1.77 (br, 4H). ^{13}C NMR (400 MHz, DMSO-d_6) δ 168.96, 162.49, 160.00, 159.87, 155.24, 154.24, 152.32, 149.97, 148.91, 146.80, 138.85, 138.75, 135.10, 134.93, 132.18, 124.58, 121.95, 115.63, 115.25, 114.90, 108.97, 102.35, 99.50, 67.09, 66.68 (2C), 56.79, 56.16, 55.29, 53.84 (2C), 29.60, 26.15. MS (ESI) m/z 668.2 $[M+H]^+$.

4.2 ELISA Kinase Assay

Kinase activities were evaluated according to the reported protocol [14, 28]. Shortly, in an ELISAs, 20 μg/mL poly (Glu, Tyr) 4:1 was precoated as substrate in 384-well plates. 50 μL of 10 μmol·L^{-1} ATP solution diluted in kinase reaction buffer (50 mmol·L^{-1} HEPES, pH 7.4, 50 mmol·L^{-1} $MgCl_2$, 0.5 mmol·L^{-1} $MnCl_2$, 0.2 mmol·L^{-1} Na_3VO_4, 1 mmol·L^{-1} DTT) was added to each well. Compounds were tested from 1 μmol·L^{-1}, 3-fold dilution, 10 points, in duplicate. The kinase reaction was initiated by addition of purified tyrosine kinase protein diluted in 40 μL of kinase reaction buffer solution. After incubation for 1 h at 37 °C, the plate was washed 3 times with phosphate buffered saline (PBS). 100 μL of antiphosphotyrosine (PY99) antibody was added. After 0.5 h of incubation at 37 °C, the plate was washed 3 times with PBS. A solution of 100 μL of horseradish peroxidase-conjugated goat anti-mouse IgG was added. The plate was reincubated at 37 °C for 0.5 h and washed. 100 μL of a solution containing 0.03% H_2O_2 and 2 mg/mL *o*-phenylenediamine in 0.1 mmol·L^{-1} citrate buffer, pH 5.5, was added and samples were incubated at rt until color appeared. The reaction was terminated by addition of 2 mol·L^{-1} H_2SO_4 (50 μL), and the plate was read using a multiwell spectrophotometer at 490 nm. IC_{50} values were calculated from the inhibition curves.

4.3 IncuCyte live-cell imaging assays

A total of 5×10^3 A549 cells grown in 100μL Dulbecco's Modified Eagle Media (DMEM) with serum (10 % FBS) were seeded in 96-well plates respectively and incubated in a tissue culture incubator at 37 °C and 5% CO_2 in an IncuCyte (Essen BioScience). Assay was performed according to the manufacturer's protocol. All samples consisted of three replicates. Images were captured every 2 h over 72 h to monitor proliferation and cytotoxicity.

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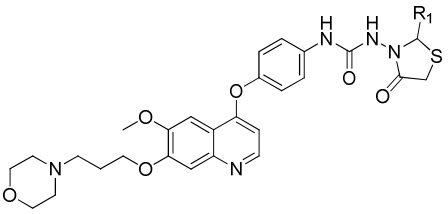
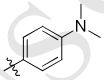
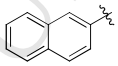
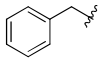
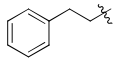
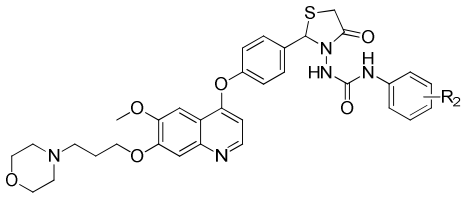
Table 1 c-Met kinase inhibitory activities of compounds **11a-u**.



Compd.	R_1	c-Met IC_{50} (μmol·L^{-1})[a]	Compd.	R_1	c-Met IC_{50} (μmol·L^{-1})
11a	Ph-	0.097	**11m**	4-CF_3-Ph-	0.495
11b	2-F-Ph-	0.061	**11n**	2-CF_3-Ph-	0.358
11c	3-F-Ph-	0.308	**11o**	3-CF_3-Ph-	0.415
11d	4-F-Ph-	0.196	**11p**		0.320
11e	2, 4-F-Ph-	0.141	**11q**		0.427
11f	3, 4-F-Ph-	0.337	**11r**		0.659
11g	2, 6-F-Ph-	0.050	**11s**		0.205
11h	3, 4, 5-F-Ph-	0.580	**11t**		0.331
11i	2, 4, 6-F-Ph-	0.094	**11u**		0.688
11j	4-Cl-Ph-	0.348	**Cabozantinib**	-	0.019
11k	2-Cl-Ph-	0.169	**Staurosporine**	-	0.128
11l	3, 5-Cl-Ph-	0.658			

[a] Values are expressed as the mean of two independent experiments.

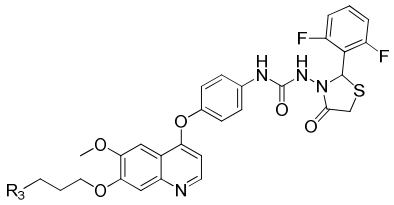
Table 2 c-Met kinase inhibitory activities of compounds **15a-b**.

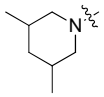


Compd.	R_2	c-Met IC_{50}[a] (μmol·L^{-1})
15a	2-F-Ph-	4.10
15b	2, 4-F-Ph-	3.35
Cabozantinib	-	0.019
Staurosporine	-	0.128

[a)] Values are expressed as the mean of two independent experiments.

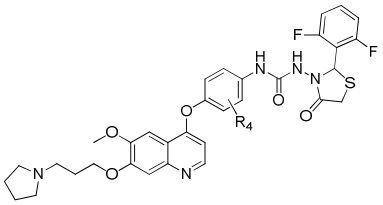
Table 3 c-Met kinase inhibitory activities of compounds **22a-d**.



Compd.	R_3	c-Met IC_{50}[a] (μmol·L^{-1})
22a		0.154
22b		0.046
22c		0.114
22d		0.037
Cabozantinib	-	0.019
Staurosporine	-	0.128

[a] Values are expressed as the mean of two independent experiments.

Table 4 c-Met kinase inhibitory activities of compounds **29a-b**.



Compd.	R_4	c-Met IC_{50}[a] (μmol·L^{-1})
29a	2-F	0.030
29b	3-F	0.021
Cabozantinib	-	0.019
Staurosporine	-	0.128

[a)] Values are expressed as the mean of two independent experiments.

Table 5 Kinase profile of compound **29b**.

Compd.	Kinase (IC_{50}[a], μmol·L^{-1})							
	c-Kit	Ron	KDR	RET	AXL	EGFR	IGF-1R	Src
29b	0.029	0.0031	0.021	0.152	0.062	0.812	4.67	0.061
Cabozantinib	0.053	0.069	0.00048	0.037	0.0095	3.11	>10	0.178

[a] Values are expressed as the mean of two independent experiments.

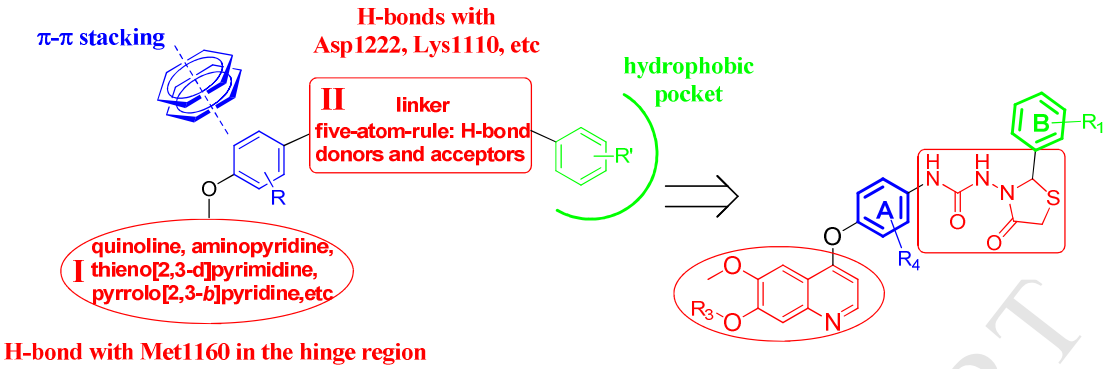


Fig. 2 The reported SARs of c-Met kinase inhibitors and the design of target compounds.

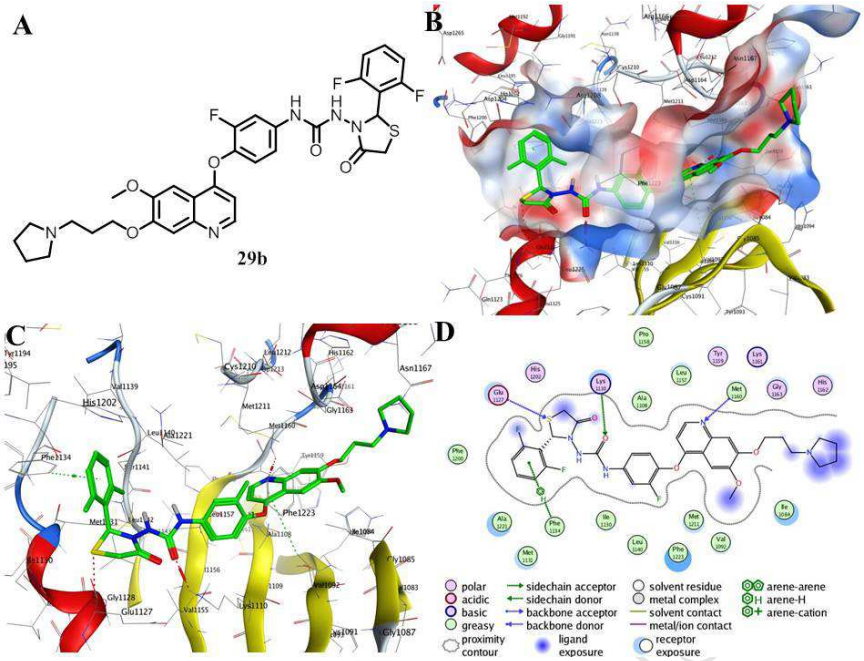


Fig.3 The proposed binding mode of compound **29b** with c-Met kinase (PBD ID: 3LQ8). A) The structure of compound 29b. B) Binding pocket of c-Met. C) The interactions between compound **29b** and c-Met. The compound was shown by green sticks, the H-bonds were represented by red dotted lines, and the arene-H interaction was shown by green dotted lines. D) 2D depiction of the ligand-protein interaction.

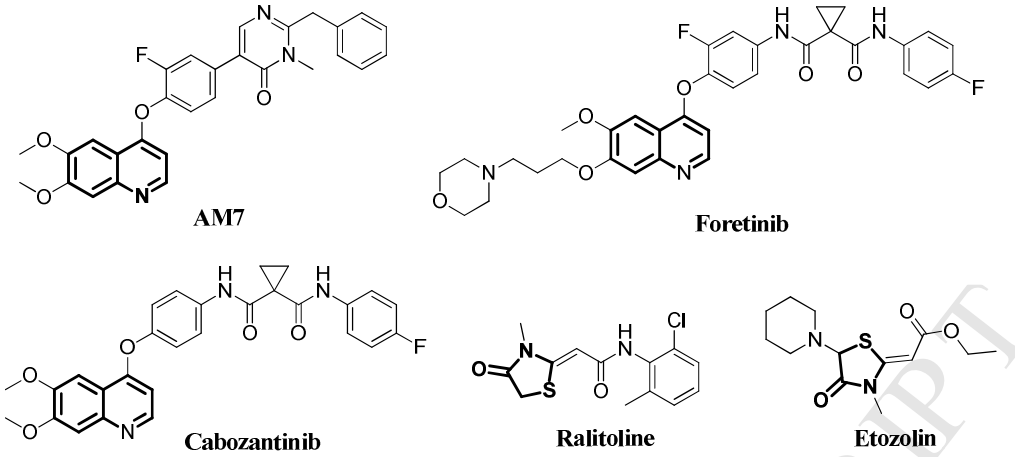


Fig. 1 The representative c-Met kinase inhibitors bearing quinoline pharmacophores and drugs bearing thiazolidinone scaffolds.

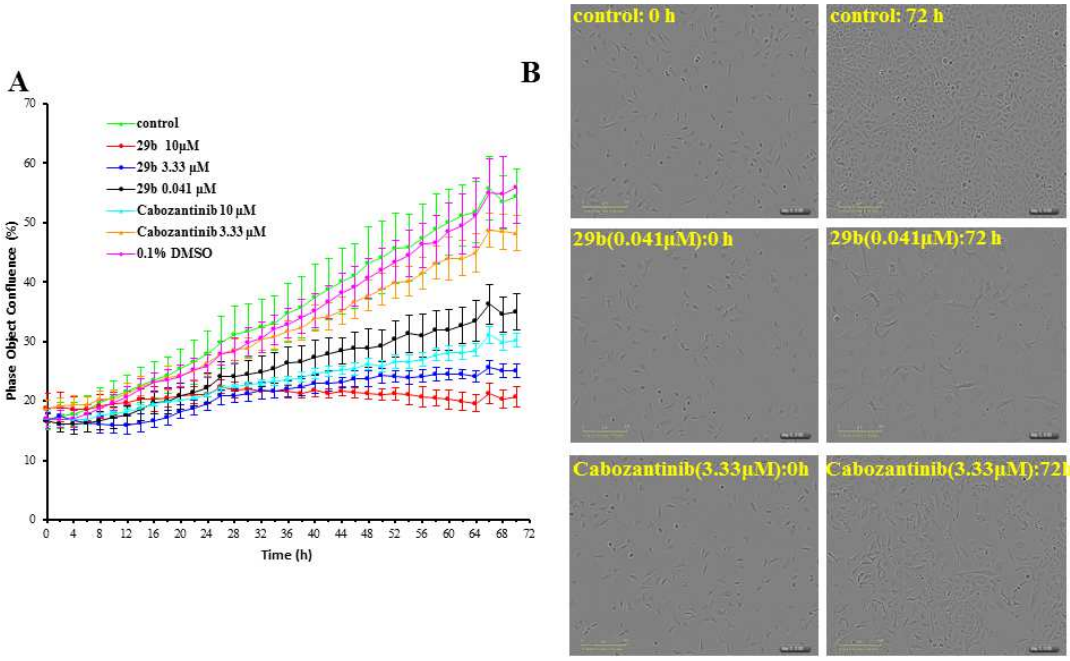


Fig. 4 Real-time cell confluence study in non-small cell lung cancer A549. A) The cell population was monitored for 72 h using an IncuCyte ZOOM system in an incubator (5% CO_2 and 37 °C). A549 cells were incubated with 0.1% DMSO or exposed to compound **29b** or Cabozantinib at different concentration. Error bars: ± SD from n = 3 and all SD values are below 0.05. B) Phase contrast images (white light) of A549 cells after 3 days of treatment with compound **29b**, Cabozantinib or not.

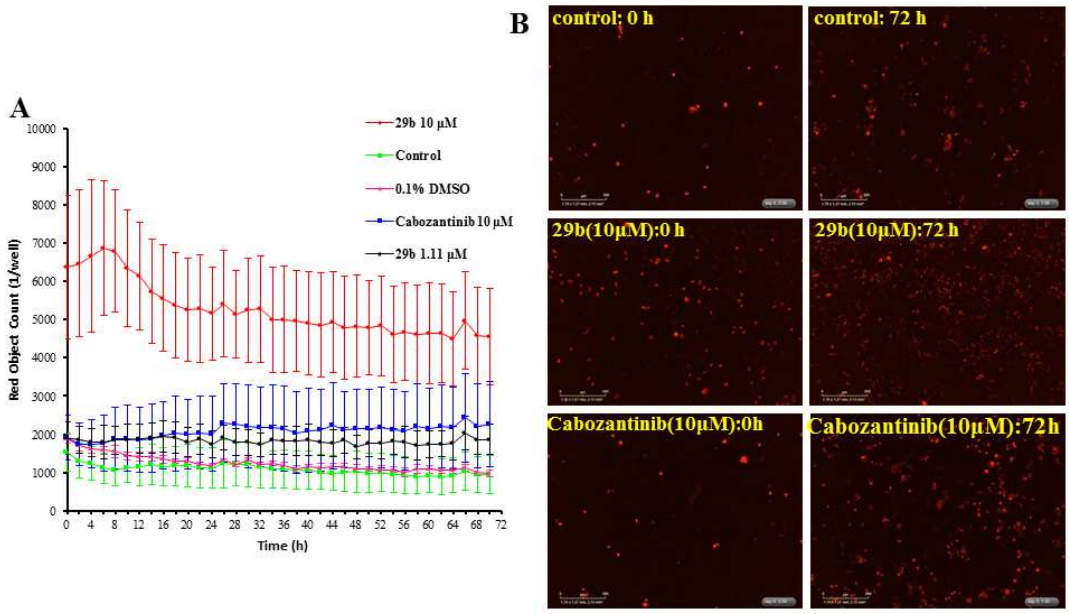
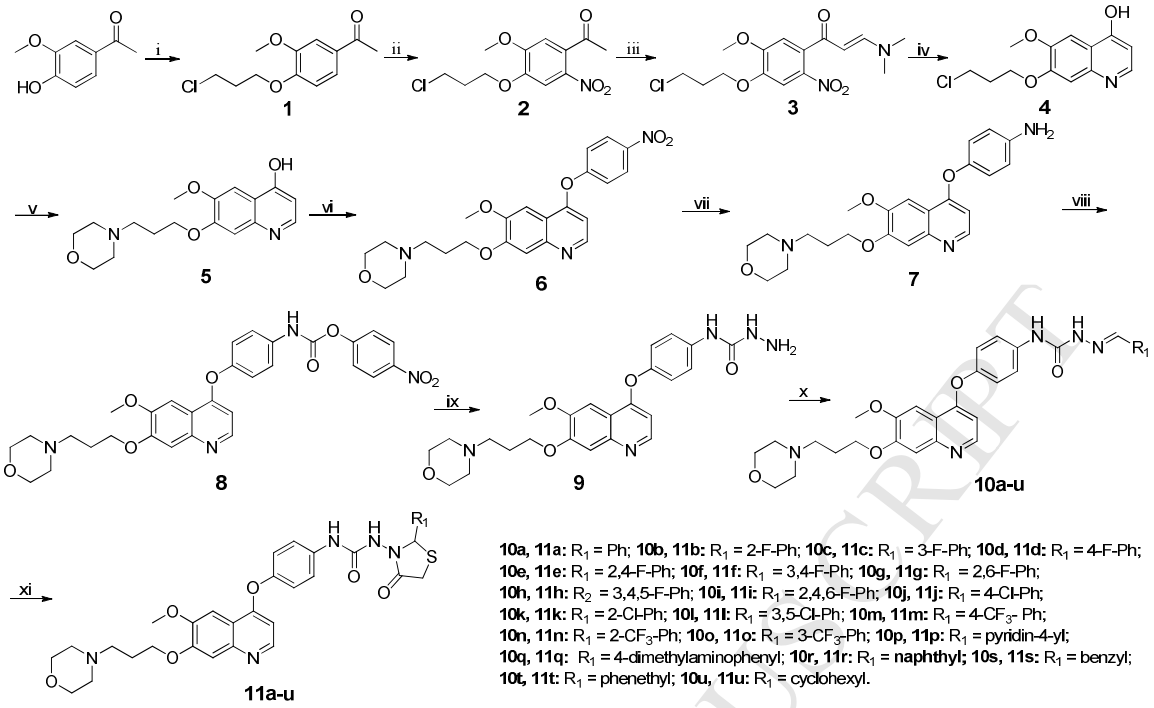
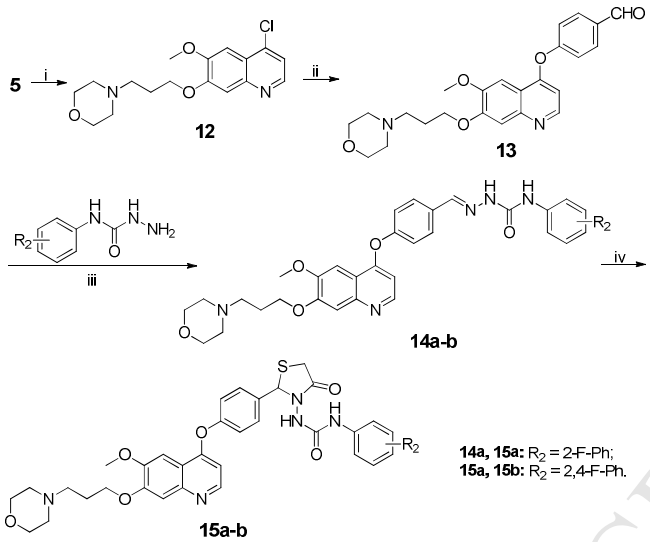


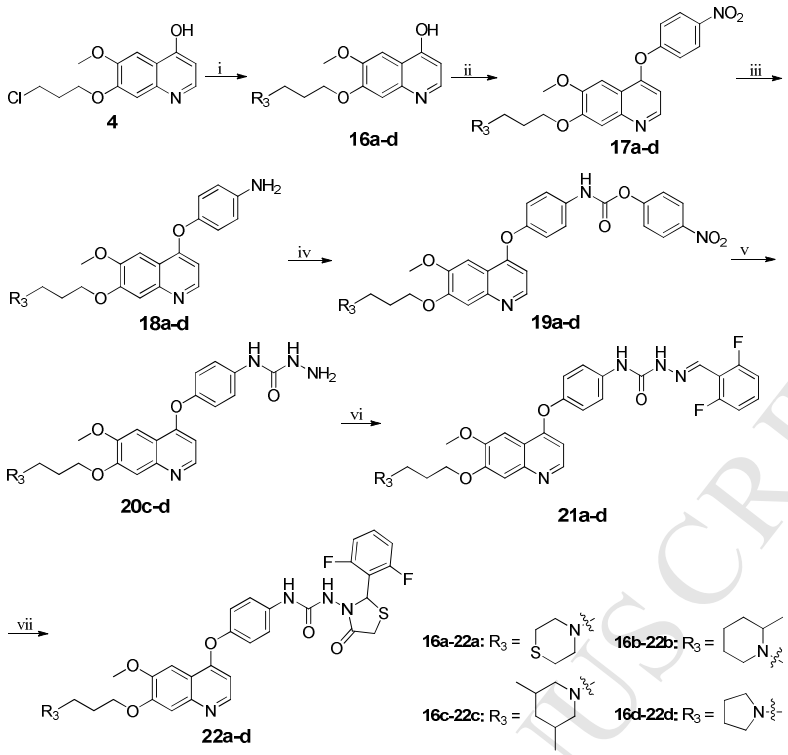
Fig. 5 Real-time cytotoxicity study in non-small cell lung cancer A549. A) The dead cell population was monitored for 72 h using an IncuCyte ZOOM system in an incubator (5% CO_2 and 37 °C). Error bars: ± SD from n = 3 and all SD values are below 0.05. B) Phase-contrast images (red light) of cells after 3 days of treatment with 10 µM of compound **29b**, 10 µM Cabozatinib or negative control. Red fluorescent cell was counted as dead cell.



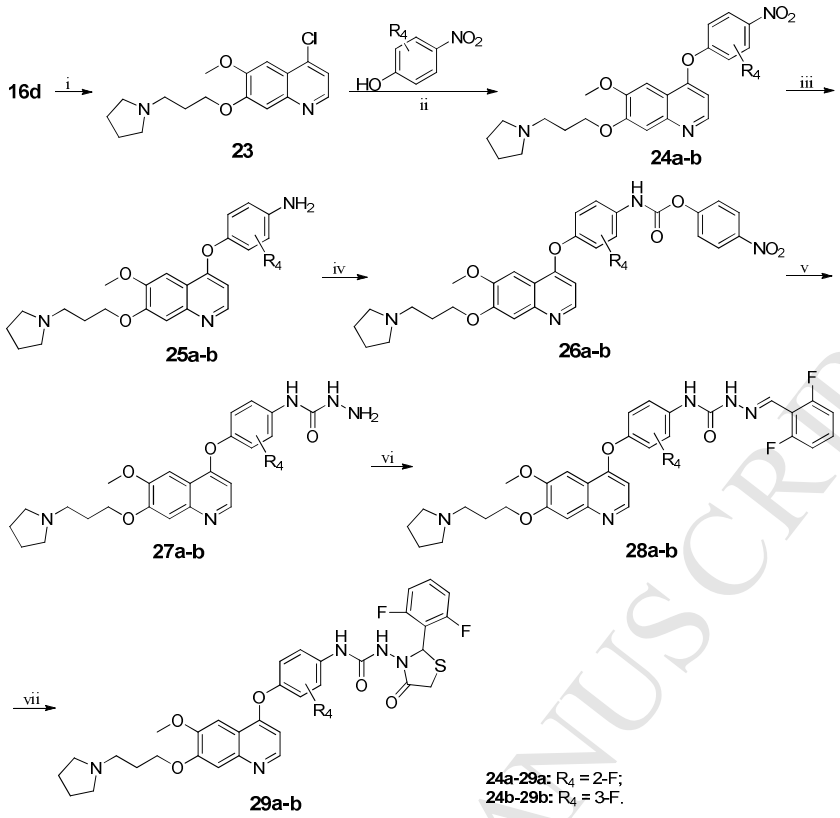
Scheme 1. Synthesis of compounds **11a-u**. Reagents and conditions: i) 1-bromo-3-chloropropane, K_2CO_3, DMF, rt; ii) fuming HNO_3, CH_2Cl_2, -10°C; iii) DMF-DMA, xylene, reflux; iv) Fe, AcOH, 100 °C; v) morpholine, CH_3CN, reflux; vi) 4-fluoronitrobenzene, Cs_2CO_3, CH_3CN, reflux; vii) Fe, conc. HCl, 95% EtOH-H_2O, reflux; viii) 4-nitrophenyl carbonochloridate, CH_2Cl_2, pyridine, rt; ix) $NH_2NH_2 \cdot H_2O$, xylene, 70°C; x) aldehyde, *i*-PrOH, HOAc, reflux; xi) $SiCl_4$, mercaptoacetic acid, 50 °C.



Scheme 2. Synthesis of compounds **15a-b**. Reagents and conditions: i) $POCl_3$, reflux; ii) 4-hydroxybenzaldehyde, PhCl, reflux; iii) *i*-PrOH, HOAc, reflux; iv) $SiCl_4$, mercaptoacetic acid, 50 °C.



Scheme 3. Synthesis of compounds **22a-d**. Reagents and conditions: i) R_3, CH_3CN, reflux; ii) 4-fluoronitrobenzene, Cs_2CO_3, CH_3CN, reflux; iii) Fe, conc. HCl, 95% EtOH-H_2O, reflux; iv) 4-nitrophenyl carbonochloridate, CH_2Cl_2, pyridine, rt; v) $NH_2NH_2 \cdot H_2O$, xylene, 70°C; vi) 2, 6-difluorobenzaldehyde, *i*-PrOH, HOAc, reflux; vii) $SiCl_4$, mercaptoacetic acid, 50 °C.



Scheme 4. Synthesis of compounds **29a-b**. Reagents and conditions: i) $POCl_3$, reflux; ii) PhCl, reflux; iii) Fe, conc. HCl, 95% EtOH-H_2O, reflux; iv) 4-nitrophenyl carbonochloridate, CH_2Cl_2, pyridine, rt; v) $NH_2NH_2 \cdot H_2O$, xylene, 70°C; vi) 2, 6-difluorobenzaldehyde, *i*-PrOH, HOAc, reflux; vii) $SiCl_4$, mercaptoacetic acid, 50 °C.

Identification of novel N^1-(2-aryl-1, 3-thiazolidin-4-one)-N^3-aryl ureas showing potent multi-tyrosine kinase inhibitory activities

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Research highlights

► Novel N^1-(2-aryl-1, 3-thiazolidin-4-one)-N^3-aryl ureas were obtained.

► Compound **29b** was identified possessing high potency against multi-tyrosine kinases.

► *In vitro* antiproliferation and cytotoxicity were confirmed by IncuCyte live-cell imaging.