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Original article

Discovery of novel type II c-Met inhibitors based on BMS-777607

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ABSTRACT

Twenty-two new analogs based on the structure of BMS-777607 were designed, synthesized, and evaluated to determine their biological activities. Compounds bearing a cyclic sulfonamide or α-chloropiperidone scaffold exhibited good activity, which may provide a new basis for further structural optimization. Quinoline-containing analogs exhibited better results than did their counterparts with an aminopyrimidine, aminopyridine, or pyrrolopyridine unit. Two analogs, **22d** and **22e**, stood out as the most potent c-Met inhibitors with IC_{50}s of 0.9 and 1.7 nM, respectively. These two compounds were more potent than BMS-777607 in enzymatic inhibition and cell proliferation studies.

1. Introduction

c-Met is a prototype member of a subfamily of heterodimeric receptor tyrosine kinases (RTKs). The c-Met pathway is frequently deregulated in a wide variety of human cancers and plays critical roles in cancer formation, progression, and dissemination, as well as the resistance to approved therapies [1–4]. Therefore, the inhibition of increased c-Met signaling may have a significant impact on the treatment of human cancers in which the c-Met pathway is aberrantly activated. In fact, recent clinical trials of c-Met pathway-targeted agents have yielded convincing evidence to support the potential utility of this class of agents in the treatment of various human cancers [5–7]. To date, the development of small molecular c-Met kinase inhibitors has made remarkable progress, resulting in more than ten candidates reaching clinical trials [8]. These known small molecular inhibitors have been categorized into two types based on their binding mode in the DFG motif (aspartate-phenylalanine-glycine) of the c-Met activation loop. Type I inhibitors bind the DFG-in conformation with a U-shaped geometry and are defined as ATP-competitive inhibitors of the activated kinase. In contrast to type I inhibitors, those that bind the inactivated DFG-out conformation are defined as type II inhibitors. This type of compounds binds to the same area occupied by the type I inhibitors but also exploits hydrogen bonding and hydrophobic interactions with the allosteric site [9,10].

As disclosed recently, certain mutations near the active site of c-Met may cause resistance of type I inhibitors. In contrast, type II inhibitors are postulated to be more effective against these mutations because their binding interactions extend beyond the entrance to c-Met's active site [11–13]. Initiated by Kirin Brewery Company in 2003 [14], numerous type II inhibitors with different structures have been reported in the past ten years, and some of these are currently in clinical trials or pre-clinical development (Fig. 1) [9]. A good example of these type II inhibitors is BMS-777067, which inhibits the kinase activity of c-Met (IC_{50} = 3.9 nM), as well as that of Axl (IC_{50} = 1.1 nM), Ron (IC_{50} = 1.8 nM), and Tyro3 (IC_{50} = 4.3 nM) [15]. This compound is now in phase 2 trial because of its excellent *in vivo* efficacy and favorable pharmacokinetic and preclinical safety profiles.

As displayed in Fig 1, most of the type II inhibitors may be disconnected into four units according to their structures and subunit functions. Moiety A is a phenyl ring or *para*-substituted (usually fluorine) phenyl ring. As disclosed by the crystal structure of the c-Met kinase domain in complex with BMS-777607 [15], this aromatic ring occupies a deep hydrophobic pocket defined by three residues (F1134, L1195, and F1200). The main chain of moiety B is usually constituted by five atoms (i.e., six chemical

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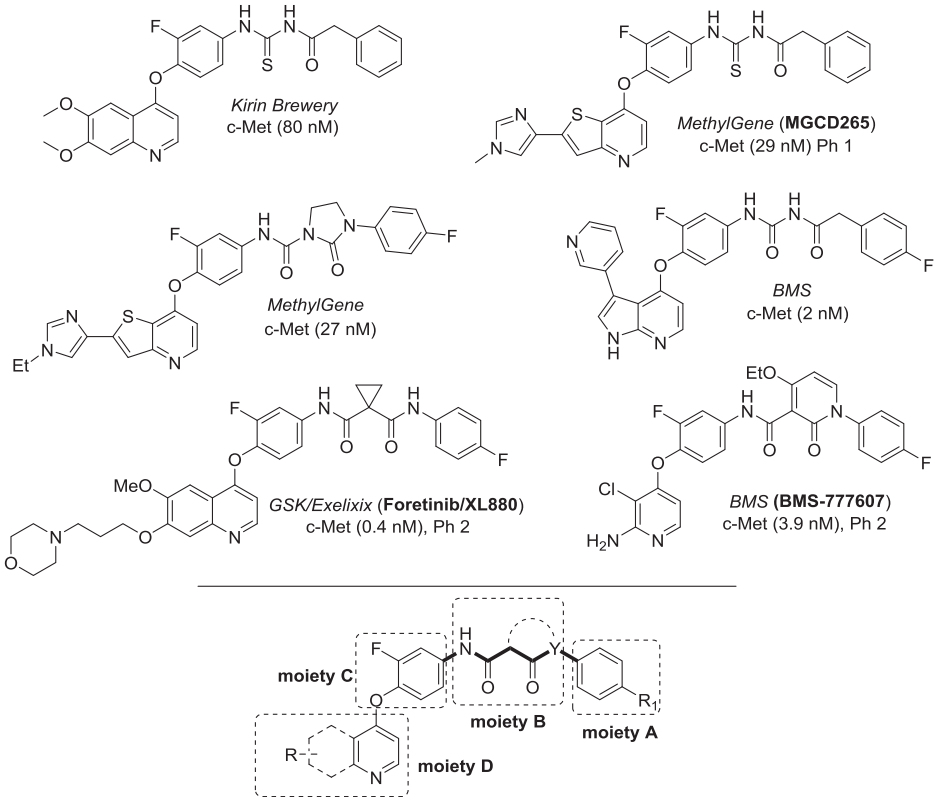


Fig. 1. Some representative type II c-Met inhibitors and their structural characteristics.

bonds, as summarized recently by Gong et al. [16,17]), bearing at least one amide bond, with or without a ring on the side chain. In the compound BMS-777607, the carbonyl group in this moiety forms a hydrogen bond with residue D1222. The structure of moiety C is comparatively conserved, bearing a phenyl ring π-stacked with residue F1223 of the DFG motif. In contrast, the structure of moiety D is alterable, and fused pyridine derivates (substituted quinoline, pyrrolopyridine, and thienopyridine) and a simple substituted pyridine are tolerant. The role of the pyridine nitrogen is an anchor to the hinge region through its interaction with M1160 [15].

Based on the unique structure of BMS-777607, we designed and prepared two series of new analogs in this study (Fig. 2). In series 1, moieties D and C in the parent compound were fixed, whereas the pyridone fragment in moiety B was replaced with sulfonamide (cyclic or linear) or substituted piperidone. In addition, several minor modifications were performed on the phenyl ring of moiety A. In the second series, moieties A and C were fixed, and moiety D was replaced with other aromatic rings. Moiety B also underwent several modifications in this series.

2. Chemistry

Substituted *N*-phenyl sulfamoyl acetamides **7a**–**f** were prepared according to the sequence outlined in Scheme 1. Commercially available ethyl 2-(chlorosulfonyl)acetate **1** and substituted anilines **2a**–**c** were coupled in the presence of triethylamine to yield the corresponding linear sulfonamides **3a**–**c**, respectively. The six-membered cyclic sulfamoyl acetamide esters **3d**–**f** were obtained through the treatment of **3a**–**c** with 1-bromo-3-chloropropane. The hydrolysis of **3a**–**f** gave **4a**–**f**, and the coupling of these compounds with amine **5** [15] under standard conditions yielded the key intermediates **6a**–**f**. Finally, a Hoffman rearrangement resulted in **7a**–**f** at high yields.

For the preparation of isomeric sulfamoyl acetamides (**11a**–**c**) and isomeric six-membered sulfamoyl acetamides (**11d**–**f**) derivates, chloroacetyl chloride was first coupled with substituted anilines (**2a**–**c**) to give compounds **8a**–**c**, which were then converted to sulfochlorides **9a**–**c** in the presence of sodium sulfite followed by phosphorous pentachloride. The coupling of amine **5** with sulfochlorides **9a**–**c** produced sulfamoyl acetamide analogs **10a**–**c**, respectively. The treatment of **10a**–**c** with 1,3-bromocholoropropane in the presence of potassium carbonate provided the cyclic sulfamoyl acetamide analogs **10d**–**f**. Finally, a Hoffman rearrangement delivered aminopyridines **11a**–**f** from the amide precursors **10a**–**f**, and these reactions were mediated by $PhI(OAc)_2$ (Scheme 2).

The synthesis of piperidone analogs is displayed in Scheme 3. The coupling of 2-piperidone acid **16a** with amine **5** smoothly produced the corresponding 2-piperidone analog **17a**. The treatment of **17a** with $PhI(OAc)_2$ gave the desired aminopyridine **18a**. In contrast, the coupling of α-bromo-2-piperidone acid **16b** with amine **5** in the presence of EDC·HCl (2.5 eq) and DMAP afforded the halo-exchanged α-chloro product **17b**. A similar procedure as that described above gave the final product **18b**.

For the preparation of the series 2 compounds, two building blocks (**19**, **20**) were prepared through known procedures [15,18,19]. Carboxylic acid **19a** was activated with $SOCl_2$ and then coupled with aromatic amine **20a**. The removal of the protecting group resulted in the desired analog **21a** at good yield. Compounds **21b** and **21c** were obtained using similar procedure without the deprotection step. For compounds **22a**–**e**, the substitution on the pyridone motif was transformed after the coupling of the building blocks **19b** and **20a**–**c** (Scheme 4).

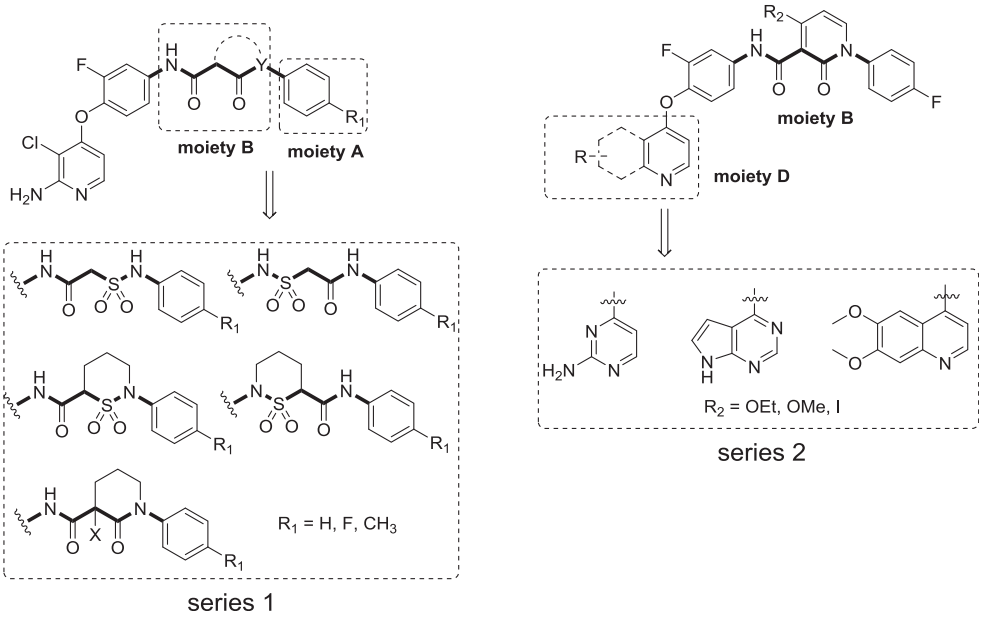
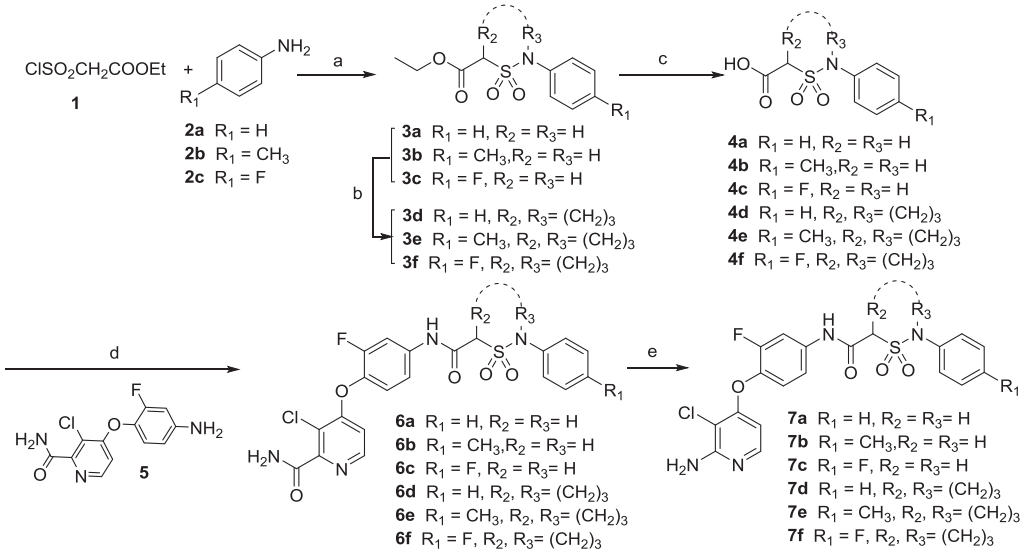


Fig. 2. Design of two series of novel c-Met inhibitors.

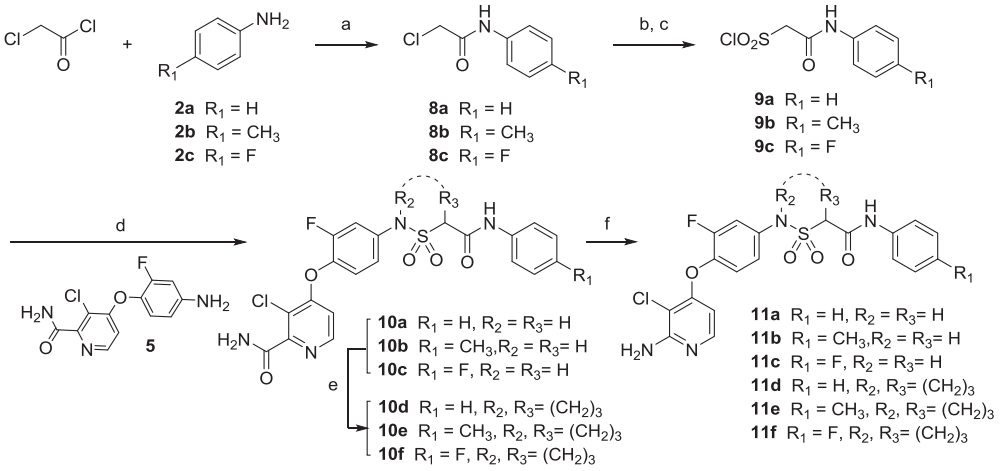
3. Biology

3.1. c-Met kinase assay

The effects of the indicated compound on the activities of c-Met kinases were determined using enzyme-linked immunosorbent assays (ELISAs) with purified recombinant proteins. Briefly, 96-well plates were pre-coated with 20 μg/mL poly (Glu,Tyr)$_{4:1}$ (Sigma) as the substrate. A 50-μL aliquot of 10 μmol/L ATP solution diluted in kinase reaction buffer (50 mmol/L HEPES [pH 7.4], 50 mmol/L $MgCl_2$, 0.5 mmol/L $MnCl_2$, 0.2 mmol/L Na_3VO_4, and 1 mmol/L DTT) was added to each well, and 1 μL of various concentrations of Yhhu3813 diluted in 1% DMSO (v/v) (Sigma) were then added to each reaction well. DMSO (1%, v/v) was used as the negative control. The kinase reaction was initiated by the addition of purified c-Met tyrosine kinase proteins diluted in 49 μL of kinase reaction buffer. After incubation for 60 min at 37 °C, the plate was washed three times with phosphate-buffered saline (PBS) containing 0.1% Tween 20 (T-PBS). Anti-phosphotyrosine (PY99) antibody (100 μL; 1:500, diluted in 5 mg/mL BSA T-PBS) was then added. After a 30-min incubation at 37 °C, the plate was washed three times, and 100 μL of horseradish peroxidase-conjugated goat anti-mouse IgG (1:2000, diluted in 5 mg/mL BSA T-PBS) was added. The plate was then incubated at 37 °C for 30 min and washed three times. A 100-μL aliquot of a solution containing 0.03% H_2O_2 and 2 mg/mL o-phenylenediamine in 0.1 mol/L citrate buffer (pH 5.5) was added. The reaction was terminated by the addition of 50 μL of 2 mol/L H_2SO_4 when the color changed, and the plate was analyzed using a multi-well spectrophotometer (SpectraMAX 190, Molecular Devices) at 490 nm. The inhibition rate (%) was calculated using the following equation: [1 − (A490/A490 control)] × 100%. The IC_{50} values were calculated from the inhibition curves obtained from two separate experiments.



Scheme 1. Reagents and conditions: a) Et_3N, toluene; b) 1-bromo-3-chloropropane, K_2CO_3, DMF; c) NaOH, EtOH; d) EDC·HCl, DMAP; e) $PhI(OAc)_2$.



Scheme 2. Reagents and conditions: a) Et_3N, CH_2Cl_2; b) Na_2SO_3, EtOH, H_2O; c)PCl_5; d) DIPEA, THF; e) 1-bromo-3-chloropropane, K_2CO_3, DMF; f) $PhI(OAc)_2$.

3.2. Western blot analysis

MKN45 cells were treated with an increasing dose of the indicated compound for 2 h at 37 °C and then lysed in 1× SDS sample buffer. The cell lysates were subsequently resolved by 10% SDS-PAGE and transferred to nitrocellulose membranes. The membranes were probed with the appropriate primary antibodies and then with horseradish peroxidase-conjugated anti-rabbit or anti-mouse IgG. The immunoreactive proteins were detected using an enhanced chemiluminescence detection reagent (Thermo Fisher).

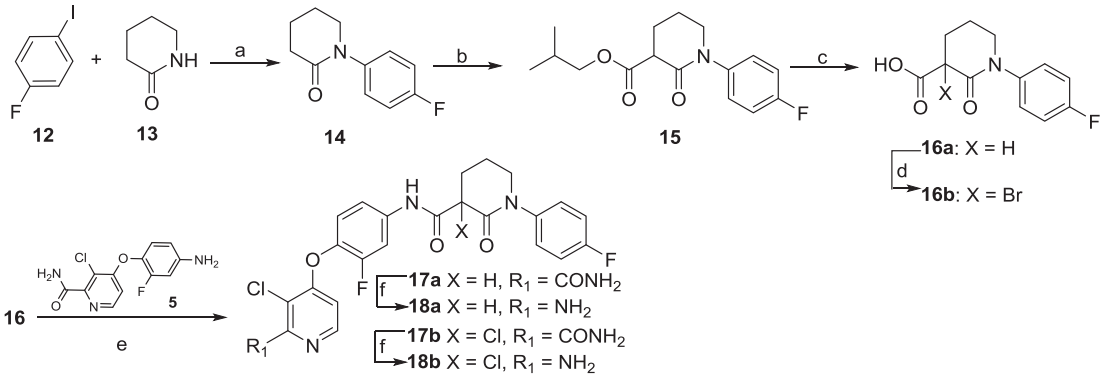
3.3. Cell proliferation assay

Cells were seeded in 96-well tissue culture plates. The following day, the cells were exposed to various concentrations of the compounds and further cultured for 72 h. The cell proliferation was then determined using the sulforhodamine B (SRB, Sigma) or the thiazolyl blue tetrazolium bromide (MTT, Sigma) assay. The IC_{50} values were calculated through fitting of the concentration–response curve using the four-parameter method.

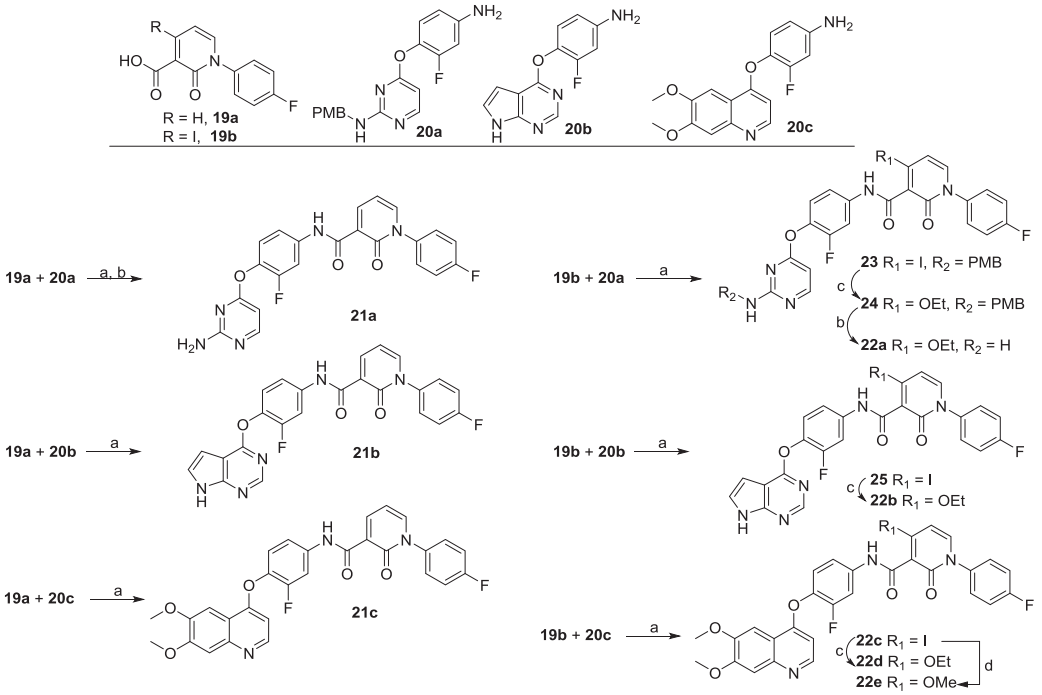
4. Results and discussion

As illustrated in Table 1, most of the designed compounds belonging to series 1 (**7a**–**f**, **11a**–**f**, **18a**–**b**) showed moderate to good inhibition of the c-Met enzyme. The compounds (**7a**–**c**) bearing a linear sulfonamide motif in the right site of moiety B (near moiety A) showed IC_{50}s ranging from 290 to 500 nM, whereas the presence of sulfonamide in a six-member ring (**7d**–**7f**) resulted in a 1.7–5.3-fold enhancement of the activity (**7d** vs. **7a**, **7e** vs. **7b**, and **7f** vs. **7c**). The replacement of the amide bond near moiety C with linear sulfonamide (**11a**–**c**) slightly decreased the enzyme inhibition. However, the presence of cyclic sulfonamide at this position (**11d**–**f**) caused a loss of activity. The analog bearing saturated pyridone (i.e., piperidone) (**18a**) showed weaker activity compared to that bearing cyclic sulfonamide (**7d**–**f**). However, the substitution of the α-position of piperidone with chlorine (**18b**) resulted in a 5-fold enhancement in the activity (**18b** vs. **18a**). The investigation of different groups (H, Me, or F) at the *para*-site of the phenyl ring in moiety A indicated that *para*-fluoride gave slightly better results (**7c**, **7f**, and **11c**). Although all of the compounds (**7a**–**f**, **11a**–**f**, and **18a**–**b**) belonging to series 1 that did not contain a pyridone moiety showed weaker activities compared to the positive control BMS-777607, the novel designed cyclic sulfonamide (**7f**) and α-chloropiperidone (**18b**) scaffolds lead to the development other new analogs with improved activity.

Most of the compounds belonging to series 2 (**21a**–**c**, **22a**–**e**) exhibited good to excellent inhibition against c-Met kinase. Of these, three compounds (**22c**–**e**) showed better activity than the positive control. If moiety B was fixed as un-substituted pyridone (**21a**–**c**), the analogs bearing pyrimidine (**21a**) or pyrrolopyridine



Scheme 3. Reagents and conditions: a) CuI, K_3PO_4, DMF, 90%; b) ^tBuLi, isobutyl chloroformate, 82%; c) LiOH, 87%; d) Br_2, Et_2O, 92%; e) EDC·HCl, DMAP, 76% for **17a**, 68% for **17b**; f) $PhI(OAc)_2$, 72% for **18a**, 76% for **18b**.



Scheme 4. Reagents and conditions: a) $SOCl_2$, DIPEA, THF; b) TFA; c) NaH, EtOH/THF; d) NaH, MeOH/THF.

(**21b**) showed better results (IC_{50} = 20–39 nM) than their counterpart containing a quinoline scaffold (**21c**). However, the weak activity of **21c** may be caused by its poor solubility. A compound bearing the same scaffold (**22d**) displayed much better activity than its counterparts (**22a**, **22b**), i.e., its activity was as low as 0.9 nM, which is 4-fold stronger than that of BMS-777607. In general, quinoline moiety-containing compounds gave better results (**22d** vs. **22a**, **22b**, and BMS-777607). The investigation of compounds with a quinoline unit in moiety D revealed that the substitution of pyridone in moiety B with iodide (**22c**) or methoxylation (**22e**) at the 4-position gave good results.

We then evaluated the inhibitory effect of increasing concentrations (0.1, 1, and 10 μM) of the promising compounds on proliferation of BaF3/TPR-Met cells, which stably express a constitutively active c-Met due to a chromosomal rearrangement. As shown in Fig. 3, five compounds (**21b**, **22b**, **22c**, **22d**, and **22e**) displayed significant inhibitory activity against cell proliferation (>80%) at a concentration of 10 μM, and three compounds (**22c**, **22d**, and **22e**) showed strong activity at a concentration of 1 μM. In addition, compounds **22d** and **22e** continued to show significant inhibitory effects even at a concentration of 0.1 μM, which indicates that these two compounds are more potent than BMS-777607. The IC_{50} values of **22d** and **22e** with respect to the cell proliferation of the c-Met-constitutively activated MKN45 and BaF3/TPR-Met cells are shown in Table 2. Indeed, these two compounds showed approximately 5–9-fold higher potency than BMS-777607.

Based on the data above, **22d** and **22e** were proven to be potent c-Met inhibitors through both c-Met enzymatic and cell proliferation assays. To further determine whether the c-Met kinase inhibition of these two compounds in a cell-free system can be recapitulated *in vitro*, the cellular c-Met-targeting signal pathway of **22d** in c-Met constitutively activated MKN45 cancer cells was investigated. The results showed that **22d** inhibited c-Met phosphorylation in MKN45 cells in a dose-dependent manner, with complete abolishment at 0.1 μM (Fig. 4). In addition, Erk1/2 and AKT, the key downstream molecules of c-Met that play important roles in c-Met functioning, were also significantly inhibited as a result of **22d** treatment (Fig. 4). These data support the finding that **22d** inhibits c-Met signaling and, in turn, suppresses c-Met-dependent cell proliferation.

5. Conclusion

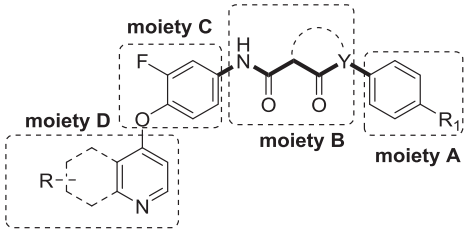
In summary, two series of analogs based on BMS-777607 were designed, synthesized, and evaluated to determine their effect on c-Met inhibition. Modifications at moiety B revealed that the novel designed cyclic sulfonamide and α-chloropiperidone scaffolds may provide a new basis for further optimization. The quinoline moiety-containing analogs gave better result than their counterparts bearing aminopyrimidine, aminopyridine, or pyrrolopyridine. Two analogs, namely compounds **22d** and **22e**, stood out as the most potent c-Met inhibitors with IC_{50}s of 0.9 and 1.7 nM, respectively. These two compounds exhibited approximately 5–9-fold higher potency than did BMS-777607 with respect to the inhibition of cell proliferation. Further studies on the structural optimization of these derivatives are currently underway in our laboratory.

6. Experimental protocols

6.1. Chemistry

All chemical reagents were used as supplied unless indicated. Solvents used in organic reactions were distilled under an inert atmosphere. Unless otherwise noted, all reactions were carried out at room temperature and were performed under a positive pressure of argon. Flash column chromatography was performed on silica gel (200–300 mesh, Qingdao, China). Analytical thin layer chromatography (TLC) was performed on glass plates pre-coated with a 0.25 mm thickness of silica gel. ^1H NMR and ^{13}C NMR spectra were taken on a Jeol JNM-ECP 600 or a Bruker Avance III 400 spectrometer at rt. Chemical shifts of the ^1H NMR spectra are

Table 1
c-Met enzymatic activity of the designed compounds.



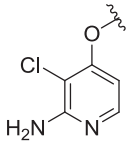
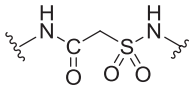
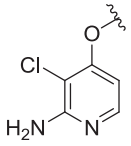
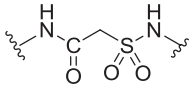
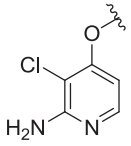
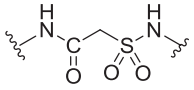
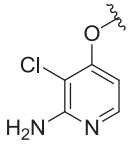
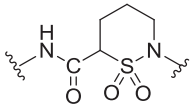
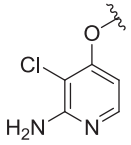
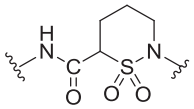
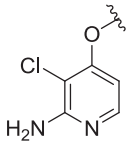
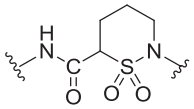
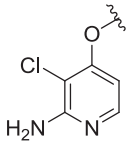
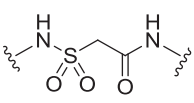
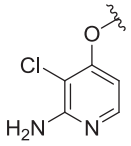
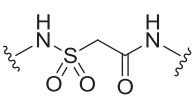
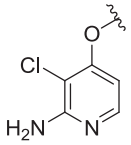
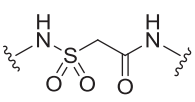
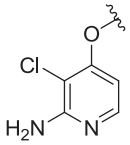
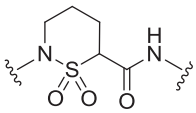
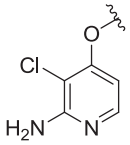
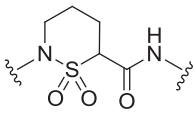
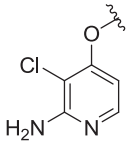
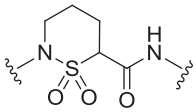
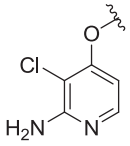
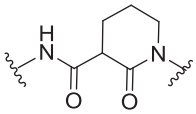
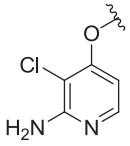
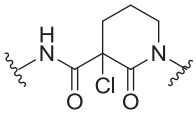
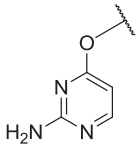
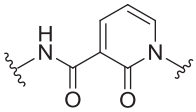
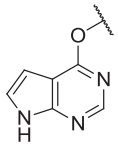
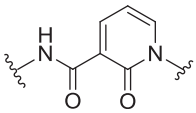
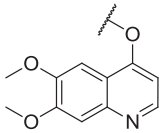
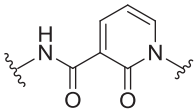
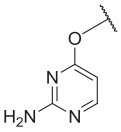
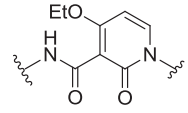
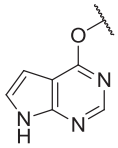
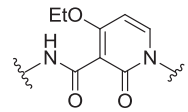
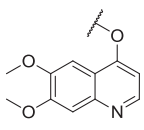
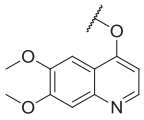
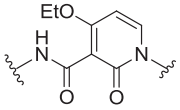
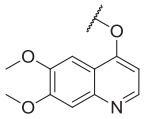
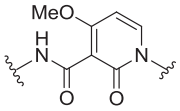
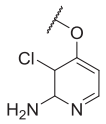
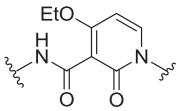
Cmpd	Moiety D	Moiety B	R_1	c-Met IC_{50} (nM)
7a			H	290.5 ± 18.6
7b			CH_3	494.7 ± 145.4
7c			F	373.2 ± 28.5
7d			H	168.7 ± 26.4
7e			CH_3	165.5 ± 30.1
7f			F	70.2 ± 3.1
11a			H	100.8 ± 15.7
11b			CH_3	1044 ± 108.9
11c			F	432.9 ± 27.0

Table 1 (*continued*)

Cmpd	Moiety D	Moiety B	R_1	c-Met IC_{50} (nM)
11d			H	Not detected
11e			CH_3	Not detected
11f			F	Not detected
18a			F	427.0 ± 6.1
18b			F	81.0 ± 7.6
21a			F	39.0 ± 0.2
21b			F	20.0 ± 1.0
21c			F	29.7% @ 10 μM
22a			F	26.9 ± 3.9
22b			F	49.6 ± 3.0
22c			F	0.7 ± 0.1

(*continued on next page*)

Table 1 (*continued*)

Cmpd	Moiety D	Moiety B	R_1	c-Met IC_{50} (nM)
22d			F	0.9 ± 0.1
22e			F	1.7 ± 0.4
BMS-777607			F	3.7 ± 1.3 3.9 ± 0.5 (lit.)

The IC_{50} values are shown as the means ± SD (nM) from two separate experiments.

expressed in ppm relative to the solvent residual signal 7.26 in $CDCl_3$ or to tetramethylsilane ($\delta = 0.00$). Chemical shifts of the ^{13}C NMR spectra are expressed in ppm relative to the solvent signal 77.00 in $CDCl_3$ or to tetramethylsilane ($\delta = 0.00$) unless otherwise noted. Electrospray (ESI) mass spectra were recorded on a Global Q-TOF mass spectrometer.

6.2. General methods for preparation of linear sulfonamide **3a–c**

Sulfonyl chloride **1** (33 mmol) in THF (10 mL) was added dropwise to a solution of aromatic amine **2** (33 mmol) and triethylamine (4.4 mL, 35 mmol) in 100 mL THF at 0 °C. Upon completion of the addition, the reaction mixture was stirred at room temperature for 1 h before concentrated in vacuo. The residue was dissolved in EtOAc (100 mL), washed with saturated brine (3 × 20 mL), dried over Na_2SO_4, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel to give compounds **3a–c**.

6.2.1. Ethyl 2-(N-phenylsulfamoyl)acetate (**3a**)

Yellow oil; yield 65%; ^1H NMR ($CDCl_3$, 600 MHz) δ 7.31–7.38 (m, 4H, ArH), 7.25–7.22 (m, 1H, ArH), 7.13 (s, 1H, NH), 4.26 (q, 2H, CH_2O), 3.94 (s, 2H, $COCH_2SO_2$), 1.30 (t, 3H, $J = 7.1$ Hz, OCH_2CH_3).

6.2.2. Ethyl 2-(N-p-tolylsulfamoyl)acetate (**3b**)

Yellow solid; yield 72%; ^1H NMR ($CDCl_3$, 600 MHz) δ 7.21–7.20 (m, 2H, ArH), 7.16 (d, 2H, $J = 8.4$ Hz, ArH), 6.96 (s, 1H, NH), 4.26 (q, 2H, CH_2O), 3.91 (s, 2H, $COCH_2SO_2$), 2.33 (s, 3H, CH_3), 1.31 (t, 3H, $J = 7.1$ Hz, OCH_2CH_3).

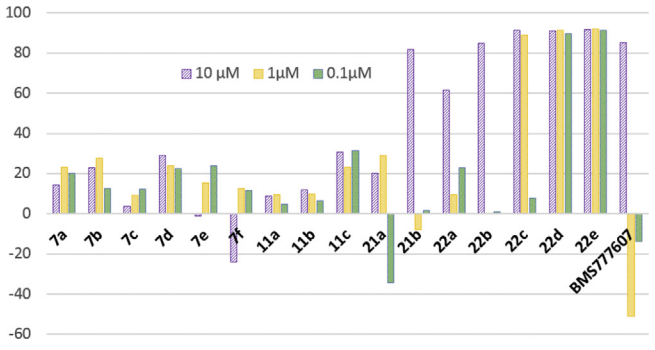


Fig. 3. Effect of the promising compounds on BF3/TPR-Met cell proliferation.

6.2.3. Ethyl 2-(N-4′-fulorophenylsulfamoyl)acetate (**3c**)

Yellow solid; yield 65%; ^1H NMR ($CDCl_3$, 600 MHz) δ 7.33–7.31 (m, 2H, ArH), 7.09 (s, 1H, NH), 7.07–7.04 (m, 2H, ArH), 4.26 (q, 2H, CH_2O), 3.91 (s, 2H, $COCH_2SO_2$), 1.31 (t, 3H, $J = 7.2$ Hz, OCH_2CH_3).

6.3. General methods for preparation of cyclic sulfonamide **3d–f**

A solution of 1-bromo-3-chloropropane (600 μL, 930 mg, 6 mmol) in DMF (60 mL) was added during 1.5 h to a mixture of sulfonamide **3a–c** (5 mmol) and potassium carbonate (2.07 g, 15 mmol) in DMF (60 mL) at 60 °C. This reaction mixture was stirred until the end of the reaction (checked by TLC). The reaction mixture was then diluted with water (150 mL), acidified with conc. HCl to pH = 1, and extracted with dichloromethane (3 × 50 mL). The organic phase was washed with 2% HCl (3 × 10 mL), dried over sodium sulfate, and evaporated to dryness. The product was recrystallized from a mixture of diethyl ether and hexane.

6.3.1. Ethyl 2-phenyl-1,2-thiazinane-1,1-dioxide-6-carboxylate (**3d**)

Yellow solid; yield: 75%; ^1H NMR (600 MHz, $CDCl_3$) δ 7.41–7.30 (m, 4H, ArH), 7.30–7.24 (m, 1H, ArH), 4.35–4.19 (m, 2H, CH_2O), 4.04 (dd, 1H, $J = 9.9$, 4.1 Hz, CH), 4.02–3.92 (m, 1H, C*H*H), 3.77–3.67 (m, 1H, CH*H*), 2.65–2.54 (m, 1H, CH*H*), 2.54–2.46 (m, 1H, CH*H*), 2.15–2.06 (m, 1H, CH*H*), 1.98–1.88 (m, 1H, CH*H*), 1.29 (t, 3H, $J = 7.1$ Hz, CH_2CH_3).

6.3.2. Ethyl 2-(p-tolyl)-1,2-thiazinane-1,1-dioxide-6-carboxylate (**3e**)

Yellow solid; yield 74%; ^1H NMR (600 MHz, $CDCl_3$) δ 7.24–7.18 (m, 2H, ArH), 7.17–7.13 (m, 2H, ArH), 4.41–4.17 (m, 2H, CH_2O), 4.03 (dd, 1H, $J = 10.1$, 4.1 Hz, $COCHSO_2$), 3.99–3.87 (m, 1H, CH*H*), 3.75–3.59 (m, 1H, CH*H*), 2.67–2.53 (m, 1H, CH*H*), 2.53–2.40 (m, 1H, CH*H*), 2.33 (s, 3H, CH_3), 2.16–2.01 (m, 1H, CH*H*), 2.00–1.86 (m, 1H, CH*H*), 1.29 (t, 3H, $J = 7.1$ Hz, CH_2CH_3).

6.3.3. Ethyl 2-(4-fluorophenyl)-1,2-thiazinane-1,1-dioxide-6-carboxylate (**3f**)

Yellow solid; yield 77%; ^1H NMR (600 MHz, $CDCl_3$) δ 7.35–7.27 (m, 2H, ArH), 7.08–6.99 (m, 2H, ArH), 4.35–4.17 (m, 2H, CH_2O), 4.04 (dd, 1H, $J = 9.5$, 4.2 Hz, $COCHSO_2$), 3.94–3.86 (m, 1H, CH*H*), 3.71–3.62 (m, 1H, CH*H*), 2.62–2.54 (m, 1H, CH*H*), 2.54–2.47 (m, 1H, CH*H*), 2.20–2.04 (m, 1H, CH*H*), 1.98–1.83 (m, 1H, CH*H*).

6.4. General methods for preparation of amide **6a–f**

Ethyl ester **3** (3 mmol) was treated with KOH (672 mg, 12 mmol) in a mixed solvent of methanol (5 mL) and water (5 mL) for 3 h. After most of the solvent was evaporated, the solution was acidified to pH 1 with 1 M HCl and extracted with EtOAc (3 × 20 mL). The organic extracts were combined and washed with brine (2 × 5 mL). Evaporation of the solvent gave the corresponding acid, which was used directly in the next step.

EDC·HCl (1.2 g, 6.25 mmol) was added to a suspension of the carboxylic acid and the amine [15] (**5**, 705 mg, 2.5 mmol) in THF (25 mL) at 0 °C followed by DMAP (30 mg, 0.25 mmol). The reaction mixture was warmed to room temperature and stirred overnight. After diluted with EtOAc (150 mL), the whole mixture was washed with 1 M HCl (3 × 10 mL), 5% $NaHCO_3$ (3 × 10 mL), and brine (3 × 10 mL), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography to give corresponding amides **6a–f**.

Table 2
Effects of **22d** and **22e** on cell proliferation (nM).

Cmpd	BaF3/TPR-Met	MKN45
22d	19.5 ± 8.8	39.7 ± 9.1
22e	36.3 ± 1.2	57.7 ± 6.6
BMS777607	188.4 ± 9.3	285.8 ± 22.7

The IC_{50} values are shown as the means ± SD (nM) from two separate experiments.

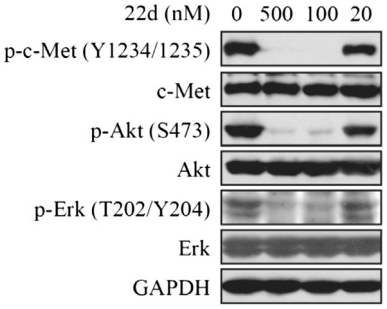


Fig. 4. 22d suppresses c-Met phosphorylation and downstreams signaling in MKN45 cells.

*6.4.1. 3-Chloro-4-(2-fluoro-4-(2-(N-phenylsulfamoyl)acetamido) phenoxy)picolinamide (**6a**)*

Gray solid; yield 55%; ^{1}H NMR (DMSO-d_6, 600 MHz) δ 10.74 (s, 1H, NH), 10.13 (s, 1H, NH), 8.34 (d, 1H, J = 5.5 Hz, ArH), 8.08 (s, 1H, NH), 7.82 (dd, 1H, J = 12.8, 2.3 Hz, ArH), 7.78 (s, 1H, NH), 7.45–7.34 (m, 4H, ArH), 7.30 (s, 1H, NH), 7.29 (d, 1H, J = 7.4 Hz, ArH), 7.15–7.12 (m, 1H, ArH), 6.83 (d, 1H, J = 5.0 Hz), 4.18 (s, 1H, $COCH_2SO_2$); ^{13}C NMR (DMSO-d_6, 150 MHz) δ 167.1, 162.9, 161.0, 160.5, 154.8, 152.7, 149.4, 138.2, 135.9, 129.8, 124.8. 124.4, 121.2, 119.7, 116.9, 116.7, 111.3, 108.8, 58.0.

*6.4.2. 3-Chloro-4-(2-fluoro-4-(2-(N-(p-tolyl)sulfamoyl)acetamido) phenoxy)picolinamide (**6b**)*

White solid; yield 57%; ^{1}H NMR (DMSO-d_6, 600 MHz) δ 10.71 (s, 1H, NH), 9.95 (s, 1H, NH), 8.33 (d, 1H, J = 6.1 Hz, ArH), 8.07 (s, 1H, NH), 7.83 (dd, 1H, J = 12.8, 1.9 Hz, ArH), 7.78 (s, 1H, NH), 7.44 (t-like, 1H, J = 9.0, 8.7 Hz, ArH), 7.38 (d, 1H, J = 8.7 Hz, ArH), 7.17 (m, 4H, ArH), 6.83 (d, 1H, J = 5.0 Hz), 4.11 (s, 1H, $COCH_2SO_2$), 2.26 (s, 1H, CH_3); ^{13}C NMR (DMSO-d_6, 150 MHz) δ 167.1, 161.1, 160.5, 154.8, 154.3, 152.7, 149.4, 138.4, 135.9, 135.5, 134.3, 130.1, 124.4, 121.9, 116.9, 116.7, 111.3, 108.8, 57.7, 20.9.

*6.4.3. 3-Chloro-4-(2-fluoro-4-(2-(N-(4-fluorophenyl)sulfamoyl) acetamido)phenoxy)picolinamide (**6c**)*

White solid; yield 48%; ^{1}H NMR (DMSO-d_6, 600 MHz) δ 10.73 (s, 1H, NH), 10.11 (s, 1H, NH), 8.33 (d, 1H, J = 5.5 Hz, ArH), 8.08 (s, 1H, NH), 7.83 (dd, 1H, J = 12.8, 1.9 Hz, ArH), 7.78 (s, 1H, NH), 7.45–7.36 (m, 2H, ArH), 7.33–7.31 (m, 2H, ArH), 7.23–7.19 (m, 2H, ArH), 6.83 (d, 1H, J = 5.5 Hz), 4.13 (s, 1H, $COCH_2SO_2$); ^{13}C NMR (DMSO-d_6, 150 MHz) δ 167.1, 161.1, 160.5, 159.1, 154.8, 149.4, 138.3, 135.9, 134.3, 124.4, 116.9, 116.7, 116.5, 116.4, 111.3, 108.8, 57.8.

*6.4.4. N-(4-((2-carbamoyl-3-chloropyridin-4-yl)oxy)-3-fluorophenyl)-2-phenyl-1,2-thiazinane-6-carboxamide 1,1-dioxide (**6d**)*

White solid; yield 43%; ^{1}H NMR (600 MHz, Acetone-d_6) δ 9.73 (s, 1H, NH), 8.34 (d, J = 5.5 Hz, 1H, NH), 7.94 (dt, 1H, J = 8.5, 1.0 Hz, ArH), 7.72 (dt, 1H, J = 8.3, 1.0 Hz, ArH), 7.58–7.53 (m, 1H, ArH), 7.49 (dt, 1H, J = 8.9, 1.7 Hz, ArH), 7.47–7.36 (m, 5H, ArH), 6.99 (s, 1H, NH), 6.91 (d, 1H, J = 5.5 Hz, ArH), 4.30 (dd, 1H, J = 10.9, 3.7 Hz, $COCHSO_2$), 4.06–3.94 (m, 1H, CH*H*), 3.82–3.71 (m, 1H, CH*H*), 2.77–2.62 (m, 1H, CH*H*), 2.54–2.42 (m, 1H, CH*H*), 2.17–2.05 (m, 2H, CH_2); ^{13}C NMR (150 MHz, Acetone-d_6) δ 162.9, 162.0, 153.7, 152.6, 148.9, 142.3, 142.2, 129.9, 129.8, 127.9, 127.8, 127.7, 127.6, 124.5, 117.2, 112.2, 100.8, 66.0, 61.3, 60.5, 54.1, 36.2, 28.1, 24.0, 23.8, 14.4.

*6.4.5. N-(4-((2-carbamoyl-3-chloropyridin-4-yl)oxy)-3-fluorophenyl)-2-(p-tolyl)-1,2-thiazinane-6-carboxamide 1,1-dioxide (**6e**)*

White solid; yield 55%; ^{1}H NMR (600 MHz, Acetone-d_6) δ 9.73 (s, 1H, NH), 8.33 (d, 1H, J = 5.6 Hz, ArH), 7.94 (dt, 2H, J = 8.4, 0.9 Hz, ArH), 7.72 (dt, 2H, J = 8.4, 1.0 Hz, ArH), 7.55 (ddd, 1H, J = 8.2, 6.9, 0.9 Hz, ArH), 7.51–7.47 (m, 1H, ArH), 7.43 (ddd, 1H, J = 8.4, 6.9, 1.0 Hz, ArH), 7.37 (t, 1H, J = 8.8 Hz, ArH), 7.30–7.26 (m, 2H, ArH), 7.24–7.18 (m, 2H, ArH), 6.99 (s, 1H, NH), 6.91 (dd, 1H, J = 5.5, 1.1 Hz, ArH), 4.28 (dd, 1H, J = 10.9, 3.7 Hz, $COCHSO_2$), 4.03–3.95 (m, 1H, CH*H*), 3.70 (m, 1H, CH*H*), 2.73–2.62 (m, 1H, CH*H*), 2.53–2.44 (m, 1H, CH*H*), 2.33 (s, 3H, CH_3), 2.12–2.06 (m, 2H, CH_2); ^{13}C NMR (150 MHz, Acetone-d_6) δ 163.0, 162.9, 155.3, 153.7, 152.6, 148.9, 138.2, 137.1, 129.9, 124.5, 117.0, 116.5, 112.2, 65.9, 65.9, 54.3, 36.1, 28.2, 23.7, 14.4.

*6.4.6. N-(4-((2-carbamoyl-3-chloropyridin-4-yl)oxy)-3-fluorophenyl)-2-(4-fluorophenyl)-1,2-thiazinane-6-carboxamide 1,1-dioxide (**6f**)*

White solid; yield 49%; ^{1}H NMR (600 MHz, Acetone-d_6) δ 9.73 (s, 1H, NH), 8.34 (d, 1H, J = 5.5 Hz, ArH), 7.98–7.89 (m, 1H, ArH), 7.65 (s, 1H, ArH), 7.53–7.47 (m, 1H, ArH), 7.47–7.43 (m, 2H, ArH), 7.37 (t, 1H, J = 8.9 Hz, ArH), 7.22–7.15 (m, 2H, ArH), 6.94 (s, 1H, NH), 6.91 (dd, 1H, J = 5.5, 1.1 Hz, ArH), 4.32 (dd, 1H, J = 10.6, 3.7 Hz, $COCHSO_2$), 4.02–3.96 (m, 1H, CH*H*), 3.77–3.72 (m, 1H, CH*H*), 2.73–2.61 (m, 1H, CH*H*), 2.54–2.43 (m, 1H, CH*H*), 2.17–2.07 (m, 2H, CH_2); ^{13}C NMR (150 MHz, Acetone-d_6) δ 162.2, 161.2, 151.8, 148.1, 138.8, 137.0, 129.6, 129.5, 127.0, 126.8, 123.7, 116.3, 111.4, 65.1, 59.7, 53.4, 27.4, 23.1, 20.1.

*6.5. General methods for preparation of compounds **7a**–**f***

To amide **6** (0.2 mmol) in ethyl acetate (2 mL), acetonitrile (2 mL), and water (1 mL) at 0 °C was added iodobenzene diacetate (82 mg, 0.26 mmol). After stirring at room temperature for 2 h, saturated $NaHCO_3$ (3 mL) was added, followed by 30 mL of ethyl acetate. The mixture was filtered, and the filtrate was washed with brine (3 × 5 mL), dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography on silica gel to give compounds **7a**–**f**.

*6.5.1. N-(4-((2-amino-3-chloropyridin-4-yl)oxy)-3-fluorophenyl)-2-(N-phenylsulfamoyl)acetamide (**7a**)*

White solid; yield 67%; ^{1}H NMR (600 MHz, Methanol-d_4) δ 7.73 (dd, 1H, J = 12.6, 2.5 Hz, ArH), 7.69 (d, 1H, J = 5.9 Hz, ArH), 7.39–7.23 (m, 5H, ArH), 7.22–7.07 (m, 2H, ArH), 5.96 (dd, 1H, J = 5.9, 0.9 Hz, ArH); ^{13}C NMR (150 MHz, Methanol-d_4) δ 162.5, 162.1, 156.0, 154.4, 147.6, 147.5, 138.5, 138.4, 130.3, 126.2, 124.4, 122.9, 117.4, 110.2, 110.1, 102.1; MS (ESI pos ion) m/z: calcd for $C_{19}H_{16}ClFN_4O_4S$, 450.1; found, 450.9 (M+H).

*6.5.2. N-(4-((2-amino-3-chloropyridin-4-yl)oxy)-3-fluorophenyl)-2-(N-(p-tolyl)sulfamoyl)acetamide (**7b**)*

White solid; yield 71%; ^{1}H NMR (600 MHz, Acetone-d_6) δ 9.84 (s, 1H, NH), 8.76 (s, 1H, NH), 7.85 (d, 1H, J = 12.8 Hz, ArH), 7.80 (d, 1H, J = 5.8 Hz, ArH), 7.39 (d, 2H, J = 8.8 Hz, ArH), 7.34 (d, 2H, J = 8.23 Hz, ArH), 7.29 (t, 1H, J = 8.8 Hz, ArH), 7.19 (d, 3H, J = 8.0 Hz, ArH), 6.03 (d, 1H, J = 5.5 Hz, ArH), 5.88 (s, 1H, NH), 5.87 (s, 1H, NH), 4.12 (s, 2H, $COCH_2SO_2$), 2.31 (s, 3H, CH_3); ^{13}C NMR (150 MHz, Acetone-d_6) δ 161.7, 161.1, 158.4, 155.5, 153.8, 148.1, 135.9, 135.8, 130.6, 124.3,

123.4, 116.8, 116.7, 109.4, 109.3, 101.8, 57.3, 20.8; MS (ESI pos ion) *m/z*: calcd for $C_{20}H_{18}ClFN_4O_4S$, 464.1; found, 465.1 (M+H).

*6.5.3. N-(4-((2-amino-3-chloropyridin-4-yl)oxy)-3-fluorophenyl)-2-(N-(4-fluorophenyl)sulfamoyl)acetamide (**7c**)*

White solid; yield 73%; ^{1}H NMR (600 MHz, Methanol-d_4) δ 7.75 (dd, 1H, *J* = 12.6, 2.5 Hz, ArH), 7.69 (d, 1H, *J* = 5.9 Hz, ArH), 7.41–7.34 (m, 2H, ArH), 7.31–7.24 (m, 1H, ArH), 7.18 (t, 1H, *J* = 8.8 Hz, ArH), 7.09–7.02 (m, 2H, ArH), 5.96 (dd, 1H, *J* = 5.9, 1.0 Hz, ArH); ^{13}C NMR (150 MHz, Methanol-d_4) δ 162.7, 162.5, 158.7, 156.0, 154.4, 147.4, 138.5, 134.7, 125.9, 125.8, 124.5, 117.4, 116.9, 116.8, 110.2, 102.1; MS (ESI pos ion) *m/z*: calcd for $C_{19}H_{15}ClF_2N_4O_4S$, 468.0; found, 469.0 (M+H).

*6.5.4. N-(4-((2-amino-3-chloropyridin-4-yl)oxy)-3-fluorophenyl)-2-phenyl-1,2-thiazinane-6-carboxamide 1,1-dioxide (**7d**)*

White solid; yield 72%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.09 (s, 1H, NH), 7.87–7.54 (m, 2H, ArH), 7.33–7.22 (m, 5H, ArH), 7.20 (s, 1H, NH), 7.16–7.11 (m, 1H, ArH), 7.03 (t, 1H, *J* = 8.6 Hz, ArH), 5.94 (dd, 1H, *J* = 6.0, 1.0 Hz, ArH), 5.48 (s, 2H, NH_2), 4.09 (dd, 1H, *J* = 9.8, 4.0 Hz, $COCHSO_2$), 3.96–3.85 (m, 1H, CH*H*), 3.75–3.65 (m, 1H, CH*H*), 2.70–2.59 (m, 1H, CH*H*), 2.59–2.50 (m, 1H, CH*H*), 2.12–2.01 (m, 1H, CH*H*), 2.00–1.86 (m, 1H, CH*H*); ^{13}C NMR (150 MHz, $CDCl_3$) δ 162.0, 161.7, 155.1, 154.6, 153.0, 142.0, 129.5, 128.0, 127.3, 123.3, 116.5, 116.4, 109.8, 109.6, 103.2, 101.8, 64.7, 53.8, 27.4, 23.4; MS (ESI pos ion) *m/z*: calcd for $C_{22}H_{20}ClFN_4O_4S$, 490.1; found, 490.9 (M+H).

*6.5.5. N-(4-((2-amino-3-chloropyridin-4-yl)oxy)-3-fluorophenyl)-2-(p-tolyl)-1,2-thiazinane-6-carboxamide 1,1-dioxide (**7e**)*

White solid; yield 67%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.14 (s, 1H, NH), 7.72 (d, 1H, *J* = 6.3 Hz, ArH), 7.70 (dd, 2H, *J* = 12.0, 2.5 Hz, ArH), 7.24–7.19 (m, 4H, ArH), 7.17 (d, 2H, *J* = 8.3 Hz, ArH), 7.09 (t, 1H, *J* = 8.6 Hz, ArH), 6.01 (dd, 1H, *J* = 6.3, 1.0 Hz, ArH), 5.54 (s, 2H, NH_2), 4.16–4.10 (m, 1H, $COCHSO_2$), 3.97–3.88 (m, 1H, CH*H*), 3.78–3.67 (m, 1H, CH*H*), 2.75–2.65 (m, 1H, CH*H*), 2.65–2.55 (m, 1H, CH*H*), 2.33 (s, 3H, CH_3), 2.13–2.06 (m, 1H, CH*H*), 2.03–1.94 (m, 1H, CH*H*); ^{13}C NMR (150 MHz, $CDCl_3$) δ 161.6, 161.3, 155.8, 154.8, 153.1, 144.1, 138.3, 137.6, 137.1, 136.5, 130.1, 127.1, 123.3, 116.5, 116.4, 112.7, 109.8, 109.7, 102.9, 101.9, 64.5, 53.8, 27.3, 23.4, 21.1; MS (ESI pos ion) *m/z*: calcd for $C_{23}H_{22}ClFN_4O_4S$, 504.1; found, 504.9 (M+H).

*6.5.6. N-(4-((2-amino-3-chloropyridin-4-yl)oxy)-3-fluorophenyl)-2-(4-fluorophenyl)-1,2-thiazinane-6-carboxamide 1,1-dioxide (**7f**)*

White solid; yield 77%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.12 (s, 1H, NH), 7.73 (d, 1H, *J* = 6.0 Hz, ArH), 7.70 (dd, 1H, *J* = 11.9, 2.5 Hz, ArH), 7.34–7.29 (m, 2H, ArH), 7.21–7.17 (m, 1H, ArH), 7.09 (t, 1H, *J* = 8.6 Hz, ArH), 7.07–7.03 (m, 2H, ArH), 6.00 (dd, 1H, *J* = 6.0, 1.0 Hz, ArH), 5.41 (s, 2H, NH_2), 4.15 (dd, 1H, *J* = 9.6, 4.0 Hz, $COCHSO_2$), 3.94–3.86 (m, 1H, CH*H*), 3.74–3.68 (m, 1H, CH*H*), 2.75–2.65 (m, 1H, CH*H*), 2.65–2.56 (m, 1H, CH*H*), 2.20–2.08 (m, 1H, CH*H*), 2.02–1.90 (m, 1H, CH*H*); ^{13}C NMR (150 MHz, $CDCl_3$) δ 162.8, 161.3, 161.2, 161.0, 156.0, 154.8, 153.1, 144.8, 136.3, 135.9, 129.2, 123.3, 116.4, 116.3, 116.2, 116.1, 109.6, 102.8, 101.9, 64.5, 60.5, 53.9, 27.3, 23.3, 14.2; MS (ESI pos ion) *m/z*: calcd for $C_{23}H_{22}ClF_2N_4O_4S$, 508.1; found, 508.9 (M+H).

*6.6. General methods for preparation of compounds **8a–c***

Triethylamine (14 mL) was added to a solution of the aromatic amine (**2**, 50 mmol) in dry DCM (100 mL) at 0 °C. The mixture was stirred at room temperature for another 5 h after the addition of 2-chloroacetyl chloride (5.65 mL) at 0 °C. Ethyl acetate (150 mL) was added; the whole organic layer was washed with 1 M HCl (3 × 30 mL), saturated $NaHCO_3$ (2 × 20 mL), and brine (2 × 20 mL). The organic solvent was dried over Na_2SO_4 and then concentrated in vacuo. The crude product was purified by recrystallization from ethyl acetate and hexane.

*6.6.1. 2-Chloro-N-phenylacetamide (**8a**)*

Gray solid; yield 89%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.30–8.22 (m, 1H, ArH), 7.57–7.50 (m, 2H, ArH), 7.36 (dd, 2H, *J* = 8.5, 7.4 Hz, ArH), 7.21–7.14 (m, 1H, ArH), 4.18 (s, 2H, CH_2).

*6.6.2. 2-Chloro-N-(p-tolyl)acetamide (**8b**)*

Gray solid; yield 93%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.22 (s, 1H, NH), 7.43–7.40 (m, 1H, ArH), 7.17–7.14 (m, 1H, ArH), 4.17 (s, 1H, CH_2), 2.33 (s, 3H, CH_3).

*6.6.3. 2-Chloro-N-(4-fluorophenyl)acetamide (**8c**)*

Gray solid; yield 95%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.23 (s, 1H, NH), 7.53–7.49 (m, 2H, ArH), 7.07–7.03 (m, 2H, ArH), 4.19 (s, 1H, CH_2).

*6.7. General methods for preparation of amide **10a–c***

Sulfonyl chloride **9** (0.6 mmol) was diluted with dry THF (2 mL) and added to a solution of amine **5** (141 mg, 0.5 mmol) and DIPEA (174 μL, 1 mmol) in dry THF (10 mL). The mixture was stirred for another 1 h before concentrated in vacuo. The residue was re-dissolved in ethyl acetate (50 mL) and washed with brine (3 × 10 mL). After dried over Na_2SO_4 and concentrated in vacuo, the residue was purified by column chromatography to give corresponding amide **10a–c**.

*6.7.1. 3-Chloro-4-(2-fluoro-4-(2-oxo-2-(phenylamino) ethylsulfonamido)phenoxy)picolinamide (**10a**)*

Yellow solid; yield 65%; ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.49 (s, 1H, NH), 10.36 (s, 1H, NH), 8.34 (d, 1H, *J* = 5.6 Hz, ArH), 8.06 (d, 1H, *J* = 2.3 Hz, ArH), 7.76 (s, 1H, NH), 7.58–7.54 (m, 2H, ArH), 7.42 (t, 1H, *J* = 9.0 Hz, ArH), 7.36–7.29 (m, 3H, ArH), 7.19 (dd, 1H, *J* = 8.5, 2.5 Hz, ArH), 7.10 (t, 1H, *J* = 7.3 Hz, ArH), 6.79 (d, 1H, *J* = 5.6 Hz, ArH), 4.30 (s, 2H, CH_2); ^{13}C NMR (150 MHz, DMSO-d_6) δ 167.6, 166.5, 160.0, 159.8, 154.2, 154.0, 152.4, 148.7, 138.3, 137.3, 128.9, 124.0, 119.2, 117.2, 116.4, 110.6, 109.1, 109.0, 57.7.

*6.7.2. 3-Chloro-4-(2-fluoro-4-(2-oxo-2-(p-tolylamino) ethylsulfonamido)phenoxy)picolinamide (**10b**)*

Yellow solid; yield 59%; ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.47 (s, 1H, NH), 10.28 (s, 1H, NH), 8.33 (d, *J* = 5.6 Hz, 1H, ArH), 8.07 (s, 1H, NH), 7.76 (s, 1H, NH), 7.47–7.39 (m, 3H, ArH), 7.32 (dd, 1H, *J* = 12.2, 2.5 Hz, ArH), 7.21–7.16 (m, 1H, ArH), 7.13 (d, *J* = 8.3 Hz, 2H, ArH), 6.79 (d, 1H, *J* = 5.6 Hz, ArH), 4.27 (s, 2H, SO_2CH_2CO), 2.25 (s, 3H, CH_3); ^{13}C NMR (150 MHz, DMSO-d_6) δ 166.6, 159.9, 159.6, 154.2, 154.0, 152.4, 149.4, 148.7, 137.3, 135.9, 133.1, 129.3, 124.0, 120.4, 119.3, 117.2, 116.4, 110.7, 109.1, 109.0, 105.9, 57.6, 20.5.

*6.7.3. 3-Chloro-4-(2-fluoro-4-(2-((4-fluorophenyl)amino)-2-oxoethylsulfonamido)phenoxy)picolinamide (**10c**)*

Yellow solid; yield 61%; ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.50 (s, 1H, NH), 10.44 (s, 1H, NH), 8.34 (d, 1H, *J* = 5.6 Hz, ArH), 8.06 (s, 1H, NH), 7.78–7.74 (m, 1H, ArH), 7.61–7.56 (m, 2H, ArH), 7.42 (t, 1H, *J* = 9.0 Hz, ArH), 7.31 (dd, 1H, *J* = 12.2, 2.5 Hz, ArH), 7.21–7.15 (m, 3H, ArH), 6.79 (d, 1H, *J* = 5.5 Hz, ArH), 4.28 (s, 2H, SO_2CH_2CO); ^{13}C NMR (150 MHz, DMSO-d_6) δ 166.5, 166.4, 159.9, 159.8, 159.2, 157.6, 157.3, 154.2, 154.0, 152.4, 148.7, 135.7, 134.7, 124.0, 121.3, 121.1, 117.2, 116.4, 115.6, 115.4, 110.6, 109.1, 108.9, 57.6.

*6.8. General methods for preparation of cyclic sulfonamide **10d–f***

Similar to the preparation method of **3d–f**.

*6.8.1. 2-(4-((2-Carbamoyl-3-chloropyridin-4-yl)oxy)-3-fluorophenyl)-N-phenyl-1,2-thiazinane-6-carboxamide 1,1-dioxide (**10d**)*

From **10a**; white solid; yield 52%; ^{1}H NMR (600 MHz, Acetone-d_6) δ 9.39 (s, 1H, NH), 8.38 (d, 1H, J = 5.3 Hz, ArH), 7.69–7.65 (m, 2H, ArH), 7.48 (dd, 1H, J = 11.8, 2.5 Hz, ArH), 7.44 (t, 1H, J = 8.8 Hz, ArH), 7.40–7.37 (m, 1H, ArH), 7.35–7.31 (m, 2H, ArH), 7.13–7.09 (m, 1H, ArH), 6.95 (s, 1H, NH), 6.89 (dd, 1H, J = 5.4, 1.1 Hz, ArH), 4.39 (dd, 1H, J = 10.3, 3.9 Hz, CH), 4.09–4.02 (m, 1H, CH*H*), 3.92–3.86 (m, 1H, CH*H*), 2.73–2.62 (m, 1H, CH*H*), 2.54–2.46 (m, 1H, CH*H*), 2.23–2.13 (m, 1H, CH*H*), 2.13–2.07 (m, 1H, CH*H*); ^{13}C NMR (150 MHz, Acetone-d_6) δ 162.2, 161.6, 154.9, 153.3, 152.7, 148.9, 140.9, 139.9, 139.4, 129.6, 125.0, 124.7, 124.5, 123.8, 120.4, 120.3, 116.8, 116.6, 112.6, 66.0, 54.1, 28.3, 23.4.

*6.8.2. 2-(4-((2-Carbamoyl-3-chloropyridin-4-yl)oxy)-3-fluorophenyl)-N-(p-tolyl)-1,2-thiazinane-6-carboxamide 1,1-dioxide (**10e**)*

From **10b**; white solid; yield 59%; ^{1}H NMR (600 MHz, Acetone-d_6) δ 9.29 (s, 1H, NH), 8.37 (d, 1H, J = 5.4 Hz, ArH), 7.65 (s, 1H, NH), 7.55–7.52 (m, 2H, ArH), 7.47 (dd, 1H, J = 11.8, 2.6 Hz, ArH), 7.43 (t, 1H, J = 8.8 Hz, ArH), 7.39–7.36 (m, 1H, ArH), 7.16–7.12 (m, 2H, ArH), 6.96 (s, 1H, NH), 6.89 (dd, 1H, J = 5.5, 1.1 Hz, ArH), 4.36 (dd, 1H, J = 10.2, 3.8 Hz, CH), 4.08–4.00 (m, 1H, CH*H*), 3.92–3.85 (m, 1H, CH*H*), 2.72–2.63 (m, 1H, CH*H*), 2.52–2.46 (m, 1H, CH*H*), 2.28 (s, 3H, CH_3), 2.20–2.13 (m, 1H, CH*H*), 2.12–2.06 (m, 1H, CH*H*); ^{13}C NMR (150 MHz, Acetone-d_6) δ 161.2, 160.8, 152.5, 152.0, 148.2, 140.2, 139.2, 136.1, 133.6, 129.2, 123.8, 123.1, 119.7, 119.6, 115.9, 111.8, 104.3, 100.0, 65.2, 53.3, 27.5, 22.6, 20.0.

*6.8.3. 2-(4-((2-Carbamoyl-3-chloropyridin-4-yl)oxy)-3-fluorophenyl)-N-(4-fluorophenyl)-1,2-thiazinane-6-carboxamide 1,1-dioxide (**10f**)*

From **10c**; white solid; yield 54%; ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.40 (s, 1H, NH), 8.39 (d, 1H, J = 5.5 Hz, ArH), 8.06–8.04 (m, 1H, ArH), 7.95 (s, 1H, NH), 7.76 (s, 1H, NH), 7.64–7.60 (m, 2H, ArH), 7.56 (dd, 1H, J = 11.8, 2.6 Hz, ArH), 7.47 (t, 1H, J = 9.0 Hz, ArH), 7.35 (ddd, 1H, J = 8.8, 2.6, 1.2 Hz, ArH), 7.26–7.15 (m, 2H, ArH), 6.87 (dd, 1H, J = 5.5, 0.9 Hz, ArH), 4.33 (dd, 1H, J = 10.7, 3.8 Hz, CH), 3.99–3.91 (m, 1H, CH*H*), 3.83–3.76 (m, 1H, CH*H*), 2.55–2.47 (m, 1H, CH*H*), 2.40–2.33 (m, 1H, CH*H*), 2.01–1.93 (m, 2H, CH*H*); ^{13}C NMR (150 MHz, DMSO-d_6) δ 167.0, 162.8, 161.9, 160.1, 159.7, 158.1, 154.0, 152.4, 149.4, 140.1, 139.0, 135.3, 124.3, 123.6, 121.8, 121.7, 117.3, 116.2, 116.1, 115.9, 111.7, 65.3, 56.3, 53.6, 36.3, 31.3, 30.1, 27.8, 22.6.

*6.9. General method for preparation of **11a–f***

Similar to the preparation of **7a–f**.

*6.9.1. 2-(N-(4-((2-amino-3-chloropyridin-4-yl)oxy)-3-fluorophenyl)sulfamoyl)-N-phenylacetamide (**11a**)*

From **10a**; white solid; yield 72%; ^{1}H NMR (600 MHz, Acetone-d_6) δ 9.58 (s, 1H, NH), 9.19 (s, 1H, NH), 7.79 (d, J = 5.7 Hz, 1H, ArH), 7.64–7.60 (m, 2H, ArH), 7.45 (dd, 1H, J = 12.0, 2.5 Hz, ArH), 7.37–7.29 (m, 4H, ArH), 7.12 (tt, 1H, J = 7.4, 1.1 Hz, ArH), 6.02 (dd, 1H, J = 5.8, 1.0 Hz, ArH), 5.86 (s, 2H, NH_2), 4.25 (s, 2H, SO_2CH_2CO); ^{13}C NMR (150 MHz, Acetone-d_6) δ 161.0, 160.9, 158.4, 155.7, 154.0, 148.3, 148.1, 139.3, 139.0, 138.9, 137.5, 137.3, 129.7, 125.1, 124.5, 120.3, 119.2, 119.1, 111.5, 111.3, 101.9, 57.8; MS (ESI pos ion) m/z: calcd for $C_{19}H_{16}ClFN_4O_4S$, 450.1; found, 450.9 (M+H).

*6.9.2. 2-(N-(4-((2-amino-3-chloropyridin-4-yl)oxy)-3-fluorophenyl)sulfamoyl)-N-(p-tolyl)acetamide (**11b**)*

From **10b**; white solid; yield 62%; ^{1}H NMR (600 MHz, Acetone-d_6) δ 9.54 (s, 1H, NH), 7.78 (d, 1H, J = 5.7 Hz, ArH), 7.50 (dd, 2H, J = 8.6, 2.0 Hz, ArH), 7.44 (dd, 1H, J = 12.1, 2.5 Hz, ArH), 7.36–7.32 (m, 1H, ArH), 7.30 (t, 1H, J = 8.6 Hz, ArH), 7.14 (d, 2H, J = 8.3 Hz, ArH), 6.02 (dd, 1H, J = 5.7, 1.0 Hz, ArH), 5.87 (s, 2H, NH_2), 4.23 (s, 2H, SO_2CH_2CO), 2.28 (s, 3H, CH_3); ^{13}C NMR (150 MHz, Acetone-d_6) δ 160.9, 160.8, 158.3, 155.6, 154.0, 148.0, 147.7, 138.9, 138.8, 137.4, 137.3, 136.8, 134.5, 130.0, 124.5, 120.3, 120.2, 119.1, 111.4, 111.3, 101.8, 57.6, 20.8; MS (ESI pos ion) m/z: calcd for $C_{20}H_{18}ClFN_4O_4S$, 464.1; found, 465.1 (M+H).

*6.9.3. 2-(N-(4-((2-amino-3-chloropyridin-4-yl)oxy)-3-fluorophenyl)sulfamoyl)-N-(4-fluorophenyl)acetamide (**11c**)*

From **10c**; white solid; yield 68%; ^{1}H NMR (600 MHz, Acetone-d_6) δ 9.62 (s, 1H, NH), 9.04 (s, 1H, NH), 7.79 (d, 1H, J = 5.5 Hz, ArH), 7.68–7.62 (m, 2H, ArH), 7.44 (dd, 1H, J = 12.0, 2.4 Hz, ArH), 7.36–7.29 (m, 2H, ArH), 7.14–7.08 (m, 2H, ArH), 6.02 (dd, 1H, J = 5.6, 0.9 Hz, ArH), 5.85 (s, 2H, NH_2), 4.24 (s, 2H, CH_2); ^{13}C NMR (150 MHz, Acetone-d_6) δ 160.9, 160.8, 158.2, 155.5, 153.9, 147.9, 147.7, 138.8, 138.7, 137.3, 137.2, 135.5, 124.4, 122.2, 122.1, 122.0, 119.0, 118.9, 116.1, 115.9, 111.3, 111.1, 102.1, 101.7, 57.6; MS (ESI pos ion) m/z: calcd for $C_{19}H_{15}ClF_2N_4O_4S$, 468.0; found, 469.0 (M+H).

*6.9.4. 2-(4-((2-Amino-3-chloropyridin-4-yl)oxy)-3-fluorophenyl)-N-phenyl-1,2-thiazinane-6-carboxamide 1,1-dioxide (**11d**)*

From **10d**; white solid; yield 66%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.79 (s, 1H, NH), 7.75 (d, 1H, J = 6.0 Hz, ArH), 7.55–7.47 (m, 2H, ArH), 7.31 (t, 2H, J = 7.9 Hz, ArH), 7.25 (dd, 1H, J = 11.6 Hz, ArH), 7.20–7.10 (m, 3H, ArH), 6.01 (d, 1H, J = 5.9 Hz, ArH), 5.47 (s, 2H, NH_2), 4.15 (dd, 1H, J = 9.2, 4.0 Hz, CH), 3.97–3.86 (m, 1H, CH*H*), 3.85–3.71 (m, 1H, CH*H*), 2.76–2.67 (m, 1H, CH*H*), 2.67–2.58 (m, 1H, CH*H*), 2.23–2.13 (m, 1H, CH*H*), 2.02–1.91 (m, 1H, CH*H*); ^{13}C NMR (150 MHz, $CDCl_3$) δ 160.7, 160.5, 156.3, 154.5, 152.9, 145.1, 140.5, 138.4, 138.3, 137.2, 129.1, 125.2, 123.6, 123.5, 123.1, 120.3, 116.6, 116.5, 103.3, 102.3, 100.0, 64.7, 53.7, 29.8, 27.4, 23.2, 22.8; MS (ESI pos ion) m/z: calcd for $C_{22}H_{20}ClFN_4O_4S$, 490.1; found, 490.9 (M+H).

*6.9.5. 2-(4-((2-Amino-3-chloropyridin-4-yl)oxy)-3-fluorophenyl)-N-(p-tolyl)-1,2-thiazinane-6-carboxamide 1,1-dioxide (**11e**)*

From **10e**; white solid; yield 58%; ^{1}H NMR (600 MHz, Acetone-d_6) δ 9.28 (s, 1H, NH), 7.82 (d, 1H, J = 5.6 Hz, ArH), 7.58–7.48 (m, 2H, ArH), 7.45–7.37 (m, 1H, ArH), 7.32 (d, 2H, J = 5.6 Hz, ArH), 7.13 (d, 2H, J = 8.2 Hz, ArH), 6.04 (d, 2H, J = 5.8 Hz, ArH), 5.91 (d, 1H, J = 8.7 Hz, ArH), 4.34 (dd, 1H, J = 10.3, 3.8 Hz, CH), 4.10–3.97 (m, 1H, CH*H*), 3.92–3.80 (m, 1H, CH*H*), 2.72–2.60 (m, 1H, CH*H*), 2.53–2.43 (m, 1H, CH*H*), 2.28 (s, 3H, CH_3), 2.18–2.12 (m, 1H, CH*H*), 2.12–2.06 (m, 1H, CH*H*); MS (ESI pos ion) m/z: calcd for $C_{23}H_{22}ClFN_4O_4S$, 504.1; found, 504.9 (M+H).

*6.9.6. 2-(4-((2-Amino-3-chloropyridin-4-yl)oxy)-3-fluorophenyl)-N-(4-fluorophenyl)-1,2-thiazinane-6-carboxamide 1,1-dioxide (**11f**)*

From **10f**; white solid; yield 68%; ^{1}H NMR (600 MHz, Acetone-d_6) δ 9.46 (s, 1H, NH), 7.82 (d, 1H, J = 5.7 Hz, ArH), 7.71–7.66 (m, 2H, ArH), 7.45–7.40 (m, 1H, ArH), 7.34–7.29 (m, 2H, ArH), 7.13–7.08 (m, 2H, ArH), 6.04 (dd, 1H, J = 5.7, 0.9 Hz, ArH), 5.90 (s, 2H, NH_2), 4.35 (dd, 1H, J = 10.4, 3.8 Hz, CH), 4.07–4.00 (m, 1H, CH*H*), 3.88–3.83 (m, 1H, CH*H*), 2.71–2.63 (m, 1H, CH*H*), 2.53–2.45 (m, 1H, CH*H*), 2.19–2.12 (m, 1H, CH*H*), 2.08–2.06 (m, 1H, CH*H*); ^{13}C NMR (150 MHz, Acetone-d_6) δ 162.2, 160.8, 158.5, 155.1, 148.2, 140.9, 140.8, 140.3, 140.2, 135.7, 124.4, 123.5, 122.4, 122.3, 122.2, 116.7, 116.5, 116.2, 116.1, 102.3, 100.8, 66.0, 54.2, 28.3, 23.5; MS (ESI pos ion) m/z: calcd for $C_{23}H_{22}ClFN_4O_4S$, 504.1; found, 504.9 (M+H).

*6.10. Preparation of 1-(4-fluorophenyl)piperidin-2-one (**14**)*

1-Fluoro-4-iodobenzene (2.22 g, 10 mmol) and piperidin-2-one (1.2 g, 12 mmol) were added to 30 mL of dry DMF, followed by the

addition of K_3PO_4 (6.36 g, 30 mmol) and CuI (190 mg, 0.1 mmol). The mixture solution was heated to 100 °C for 12 h, before filtered through celite. After washed with ethyl acetate (3 × 10 mL), the combined organic phase was concentrated and the residue was purified by column go give 1.73 g (90%) of compound **14** as yellow solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.20 (dd, 2H, J = 8.5, 5.0 Hz, ArH), 7.06 (t, 2H, J = 8.4 Hz, ArH), 3.60 (t, 2H, J = 5.4 Hz, NCH_2), 2.54 (t, 2H, J = 6.2 Hz, $COCH_2$), 2.01–1.84 (m, 4H, CH_2CH_2); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.2, 161.9, 160.2, 139.3, 128.0, 127.9, 115.9, 51.9, 32.8, 23.5, 21.5.

6.11. Preparation of isobutyl 1-(4-fluorophenyl)-2-oxopiperidine-3-carboxylate (**15**)

Piperidone (**14**, 386 mg, 2 mmol) was dissolved in 20 mL of dry THF and cooled to −78 °C. After the addition of ^{t}BuLi (1.4 mL, 1.6 M in THF, 2.2 mmol) and stirred at this temperature for 4 h, 400 μL (2 mmol) of isobutyl chlorofomate was added. 10 min later, the reaction was quenched by 2 mL of saturated NH_4Cl. The mixture was diluted with water (20 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column to give compound **15** (480 mg, 82%) as yellow wax. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.25–7.20 (m, 2H, ArH), 7.09–7.03 (m, 2H, ArH), 3.99 (dd, 1H, J = 10.6, 6.7 Hz, CH), 3.83 (d, 1H, J = 6.7 Hz, CH*H*), 3.70–3.61 (m, 1H, CH*H*), 3.58 (t, 1H, J = 6.9 Hz, CH), 2.32–2.24 (m, 1H, CH*H*), 2.23–2.16 (m, 1H, CH*H*), 2.12–2.04 (m, 1H, CH*H*), 2.02–1.87 (m, 2H, CH, CH*H*), 0.94 (d, 6H, J = 6.6 Hz, CH_3 × 2); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.0, 166.3, 162.1, 160.4, 138.8, 127.9, 127.9, 116.2, 116.0, 100.0, 71.5, 51.6, 49.6, 27.8, 25.3, 21.4, 19.1.

6.12. Preparation of 1-(4-fluorophenyl)-2-oxopiperidine-3-carboxylic acid (**16a**)

To a solution of **15** (217 mg, 0.74 mmol) in THF/MeOH/H_2O (1/1/1, 3 mL in total) at 0 °C was added LiOH monohydrate (94 mg, 2.2 mmol). The reaction mixture was warmed to room temperature and stirred for 5 h. The solution was acidified to pH 1 with 1 M HCl and extracted with EtOAc (3 × 20 mL). The organic extracts were combined and washed with brine (2 × 5 mL). Evaporation of the solvent gave the corresponding acid **16a** (152 mg, 87%) as white solid. ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.61 (s, 1H, OH), 7.33–7.28 (m, 1H, ArH), 7.25–7.19 (m, 1H, ArH), 3.69–3.55 (m, 2H, NCH_2), 3.43 (dd, 1H, J = 8.2, 6.5 Hz, CH), 2.16–2.10 (m, 1H, CH*H*), 2.08–2.02 (m, 1H, CH*H*), 1.98–1.91 (m, 1H, CH*H*), 1.91–1.83 (m, 1H, CH*H*).

6.13. Preparation of 3-bromo-1-(4-fluorophenyl)-2-oxopiperidine-3-carboxylic acid (**16b**)

To a solution of acid **16a** (220 mg, 0.93 mmol) in Et_2O (5 mL) was added liquid Br_2 (48 μL, 0.93 mmol) at 0 °C. The reaction mixture was stirred for 2 h, before concentrated in vacuo. The residue was purified by column, giving compound **16b** (265 mg, 91%) as white solid. ^{1}H NMR (600 MHz, Acetone-d_6) δ 13.03 (s, 1H, OH), 7.44–7.40 (m, 2H, ArH), 7.25–7.20 (m, 2H, ArH), 4.04 (td, 1H, J = 12.1, 4.6 Hz, NC*H*H), 3.82 (ddt, 1H, J = 13.0, 6.3, 2.4 Hz, NC*H*H), 2.77–2.69 (m, 1H, CH*H*), 2.62–2.56 (m, 1H, CH*H*), 2.53–2.43 (m, 1H, CH*H*), 2.19–2.12 (m, 1H, CH*H*); ^{13}C NMR (150 MHz, Acetone-d_6) δ 166.4, 162.5, 160.9, 140.6, 140.4, 129.0, 128.9, 116.2, 52.1, 32.3, 20.4.

6.14. Preparation of **17a** and **17b**

The procedure is very similar to the preparation of **6**.

6.14.1. 3-Chloro-4-(2-fluoro-4-(1-(4-fluorophenyl)-2-oxopiperidine-3-carboxamido)phenoxy)picolinamide (**17a**)

From **16a**; white solid; yield 76%; ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.56 (s, 1H, NH), 8.33 (d, 1H, J = 5.5 Hz, ArH), 8.07 (s, 1H, NH), 7.91 (dd, 1H, J = 12.9, 2.4 Hz, ArH), 7.77 (s, 1H, NH), 7.44 (dd, 1H, J = 8.9, 2.4 Hz, ArH), 7.41 (t, 1H, J = 8.8 Hz, ArH), 7.36–7.32 (m, 2H, ArH), 7.26–7.20 (m, 2H, ArH), 6.84 (dd, 1H, J = 5.5, 1.1 Hz, ArH), 3.76–3.68 (m, 1H, CH), 3.65–3.57 (m, 2H, CH_2), 2.21–2.13 (m, 2H, CH_2), 2.12–2.04 (m, 1H, CH*H*), 1.96–1.87 (m, 1H, CH*H*); ^{13}C NMR (150 MHz, DMSO-d_6) δ 169.3, 166.5, 160.9, 160.0, 159.3, 154.2, 153.8, 152.2, 148.7, 139.4, 138.5, 138.4, 134.8, 134.7, 128.3, 128.2, 123.7, 116.3, 115.9, 115.6, 115.4, 110.6, 107.9, 107.8, 54.9, 51.2, 50.5, 48.6, 24.8, 21.2; MS (ESI pos ion) m/z: calcd for $C_{24}H_{19}ClF_2N_4O_4$, 500.1; found, 501.1 (M+H).

6.14.2. 3-Chloro-4-(4-(3-chloro-1-(4-fluorophenyl)-2-oxopiperidine-3-carboxamido)-2-fluorophenoxy)picolinamide (**17b**)

From **16b**; white solid; yield 68%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.11 (s, 1H, NH), 8.24 (d, 1H, J = 5.5 Hz, ArH), 7.80 (dd, 1H, J = 11.9, 2.5 Hz, ArH), 7.54 (d, 1H, J = 3.9 Hz, ArH), 7.33–7.22 (m, 3H, ArH), 7.18–7.11 (m, 3H, NH), 6.68 (dd, 1H, J = 5.5, 1.1 Hz, ArH), 6.15 (d, 1H, J = 3.4 Hz, ArH), 3.85–3.78 (m, 1H, CH*H*), 3.73–3.68 (m, 1H, CH*H*), 2.96–2.87 (m, 1H, CH*H*), 2.65–2.56 (m, 1H, CH*H*), 2.45–2.34 (m, 1H, CH*H*), 2.17–2.07 (m, 1H, CH*H*); ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.8, 166.0, 164.9, 162.6, 161.8, 160.9, 154.7, 153.0, 148.3, 147.0, 137.9, 136.9, 136.8, 136.7, 127.9, 127.8, 123.4, 121.2, 116.7, 116.6, 116.5, 111.7, 109.8, 109.6, 64.4, 52.6, 33.8, 19.4; MS (ESI pos ion) m/z: calcd for $C_{24}H_{18}Cl_2F_2N_4O_4$, 534.1; found, 535.1 (M+H), 537.1 (M+H+2).

6.15. Preparation of **18a** and **18b**

The procedure is very similar to the preparation of **11**.

6.15.1. N-(4-((2-amino-3-chloropyridin-4-yl)oxy)-3-fluorophenyl)-1-(4-fluorophenyl)-2-oxopiperidine-3-carboxamide (**18a**)

From **17a**; white solid; yield 72%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.00 (s, 1H, NH), 7.71 (dd, 1H, J = 12.6, 2.5 Hz, ArH), 7.24–7.18 (m, 3H, ArH), 7.17–7.10 (m, 3H, ArH), 7.02 (dt, 1H, J = 9.0, 1.8 Hz, ArH), 6.62 (t, 1H, J = 8.9 Hz, ArH), 5.01 (s, 2H, NH_2), 3.65 (dq, 2H, J = 7.2, 4.3, 3.4 Hz, NCH_2), 3.54 (t, J = 6.3 Hz, 1H, CH), 2.59–2.49 (m, 1H, CH*H*), 2.21–2.15 (m, 1H, CH*H*), 2.10–2.05 (m, 1H, CH*H*), 2.04–1.98 (m, 1H, CH*H*); ^{13}C NMR (150 MHz, $CDCl_3$) 169.4, 165.7, 162.5, 160.9, 155.6, 154.7, 151.1, 146.5, 139.9, 138.5, 134.5, 134.4, 128.3, 128.2, 123.3, 116.9, 116.8, 116.7, 116.6, 116.5, 115.3, 115.2, 109.4, 109.2, 108.9, 52.8, 47.6, 47.5, 29.8, 22.9, 21.8; MS (ESI pos ion) m/z: calcd for $C_{23}H_{19}ClF_2N_4O_3$, 472.1; found, 473.1 (M+H).

6.15.2. N-(4-((2-amino-3-chloropyridin-4-yl)oxy)-3-fluorophenyl)-3-chloro-1-(4-fluorophenyl)-2-oxopiperidine-3-carboxamide (**18b**)

From **17b**; white solid; yield 76%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.02 (s, 1H, NH), 7.77 (d, 1H, J = 5.8 Hz, ArH), 7.74 (dd, 1H, J = 12.0, 2.5 Hz, ArH), 7.26–7.23 (m, 2H, ArH), 7.23–7.20 (m, 1H, ArH), 7.16–7.11 (m, 3H, ArH), 5.99 (dd, 1H, J = 5.8, 1.0 Hz, ArH), 5.04 (s, 2H, NH_2), 3.84–3.74 (m, 1H, CH*H*), 3.74–3.66 (m, 1H, CH*H*), 2.94–2.82 (m, 1H, CH*H*), 2.63–2.57 (m, 1H, CH*H*), 2.43–2.34 (m, 1H, CH*H*), 2.14–2.09 (m, 1H, CH*H*); ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.9, 164.8, 162.6, 161.0, 160.5, 156.6, 155.0, 153.3, 148.6, 147.8, 146.7, 137.9, 136.2, 127.8, 123.4, 116.7, 116.6, 116.2, 109.6, 109.4, 102.6, 102.1, 91.8, 64.2, 52.7, 33.8, 19.5; MS (ESI pos ion) m/z: calcd for $C_{23}H_{18}Cl_2F_2N_4O_3$, 506.1; found, 507.1 (M+H), 509.1 (M+H+2).

6.16. Preparation of fragments **19a–b** and **20a–c**

Following the known procedure [15,18,19].

6.17. Preparation of N-(4-((2-aminopyrimidin-4-yl)oxy)-3-fluorophenyl)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide (**21a**)

To the suspension of carboxylic acid **19a** (27 mg, 0.11 mmol) in dry toluene (5 mL) was added sulfuryl dichloride (0.5 mL). The mixture was stirred for 3 h before concentrated in vacuo. The residue was redissolved in 5 mL of dry toluene and concentrated again. The resulting yellow solid was then dissolved in 5 mL of dry THF and the solution was cooled to 0 °C. Compound **20a** (30 mg, 0.1 mmol) and DIPEA (50.6 μL, 0.29 mmol) was added to the mixture, respectively. After stirred at 0 °C for 15 min and at room temperature for 1 h, the reaction mixture was diluted with water (10 mL) and then extracted with EtOAc (3 × 20 mL). The combined organic layer was dried over Na_2SO_4 and concentrated in vacuo, giving a yellow solid (38 mg, 67%), which was directly dissolved in TFA (1 mL). The reaction mixture was heated to reflux for 6 h before concentrated in vacuo. The residue was purified by column, giving compound **21a** (24 mg, 77%) as pale yellow solid. ^{1}H NMR (600 MHz, Acetone-d_6) δ 8.70–8.60 (m, 1H, ArH), 8.35 (d, 1H, J = 7.0 Hz, ArH), 8.10 (dd, 1H, J = 12.7, 2.3 Hz, ArH), 8.06 (dd, 1H, J = 6.6, 2.2 Hz, ArH), 7.67–7.63 (m, 2H, ArH), 7.48–7.45 (m, 1H, ArH), 7.42–7.38 (m, 2H, ArH), 7.36 (t, 1H, J = 8.6 Hz, ArH); ^{13}C NMR (150 MHz, Acetone-d_6) δ 172.2, 163.2, 162.6, 159.3, 155.4, 153.8, 150.2, 150.1, 146.0, 144.6, 139.1, 135.1, 130.2, 130.0, 121.8, 117.1, 116.9, 108.9, 107.8, 107.7, 99.2, 99.1; MS (ESI pos ion) m/z: calcd for $C_{22}H_{15}F_2N_5O_3$, 435.1; found, 436.0 (M+H).

6.18. General procedure for the preparation of **21b**, **21c**, **23**, **25** and **22c**

Similar to the preparation of **21a**, but omitting the second step (treatment with TFA).

6.18.1. N-(4-((7H-pyrrolo[2,3-d]pyrimidin-4-yl)oxy)-3-fluorophenyl)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide (**21b**)

From **19a** and **20b**; white solid; yield 34%; ^{1}H NMR (600 MHz, DMSO-d_6) δ 11.83 (s, 1H, NH), 11.62 (s, 1H, NH), 8.14 (dd, 1H, J = 7.2, 2.3 Hz, ArH), 7.84 (s, 1H, ArH), 7.66 (dd, 1H, J = 6.5, 2.3 Hz, ArH), 7.51 (dd, 1H, J = 12.6, 2.5 Hz, ArH), 7.18–7.13 (m, 2H, ArH), 7.05 (t, 1H, J = 3.0 Hz, ArH), 7.01–6.92 (m, 4H, ArH), 6.27 (t, 1H, J = 6.9 Hz, ArH), 6.14 (dd, 1H, J = 3.6, 1.7 Hz, ArH); ^{13}C NMR (150 MHz, DMSO-d_6) δ 163.2, 162.1, 161.6, 161.4, 155.1, 154.1, 153.5, 150.5, 145.5, 144.6, 137.4, 137.3, 136.8, 135.8, 135.7, 129.9, 129.8, 126.1, 125.2, 120.7, 116.7, 116.6, 116.5, 107.5, 104.6, 100.0, 98.4; MS (ESI pos ion) m/z: calcd for $C_{24}H_{15}F_2N_5O_3$, 459.1; found, 460.0 (M+H), 482.1 (M+Na).

6.18.2. N-(4-((6,7-dimethoxyquinolin-4-yl)oxy)-3-fluorophenyl)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide (**21c**)

From **19a** and **20c**; white solid; yield 78%; ^{1}H NMR (600 MHz, DMSO-d_6) δ 11.98 (s, 1H, NH), 8.52 (d, 1H, J = 5.4 Hz, ArH), 8.50 (d, 1H, J = 3.0 Hz, ArH), 8.47 (d, 1H, J = 3.0 Hz, ArH), 8.05 (dd, 1H, J = 12.7, 2.5 Hz, ArH), 7.66–7.61 (m, 2H, ArH), 7.58–7.54 (m, 2H, ArH), 7.50–7.41 (m, 4H, ArH), 3.96 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3); ^{13}C NMR (150 MHz, DMSO-d_6) δ 162.9, 160.5, 159.8, 154.3, 153.0, 149.7, 148.2, 144.2, 142.0, 136.2, 135.6, 129.6, 129.4, 128.2, 128.0, 125.5, 124.3, 121.0, 116.2, 116.0, 114.6, 112.2, 108.9, 108.7, 106.9, 102.3, 99.0, 55.8; MS (ESI pos ion) m/z: calcd for $C_{29}H_{21}F_2N_3O_5$, 529.1; found, 530.0 (M+H).

6.18.3. N-(3-fluoro-4-((2-((4-methoxybenzyl)amino)pyrimidin-4-yl)oxy)phenyl)-1-(4-fluorophenyl)-4-iodo-2-oxo-1,2-dihydropyridine-3-carboxamide (**23**)

From **19b** and **20a**; yellow solid; yield 56%. Used directly for the next step without further structure characterization.

6.18.4. N-(4-((7H-pyrrolo[2,3-d]pyrimidin-4-yl)oxy)-3-fluorophenyl)-1-(4-fluorophenyl)-4-iodo-2-oxo-1,2-dihydropyridine-3-carboxamide (**25**)

From **19b** and **29b**; white solid; yield 46%; Used directly for the next step without further structure characterization.

6.18.5. N-(4-((6,7-dimethoxyquinolin-4-yl)oxy)-3-fluorophenyl)-1-(4-fluorophenyl)-4-iodo-2-oxo-1,2-dihydropyridine-3-carboxamide (**22c**)

From **19b** and **20c**; white solid; yield 76%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 11.61 (s, 1H, NH), 8.43 (d, 1H, J = 5.5 Hz, ArH), 7.89 (dd, 1H, J = 12.1, 2.6 Hz, ArH), 7.57–7.44 (m, 2H, ArH), 7.39–6.97 (m, 8H, ArH), 6.40 (d, 1H, J = 5.5 Hz, ArH), 3.99 (s, 3H, OCH_3), 3.98 (s, 3H, OCH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ 162.1, 161.3, 160.5, 157.3, 156.3, 155.1, 154.0, 153.4, 150.3, 137.8, 135.4, 134.9, 133.0, 128.4, 128.3, 128.2, 125.3, 123.6, 121.9, 120.4, 120.0, 117.1, 117.0, 116.8, 116.5, 115.7, 100.0, 99.7, 56.6, 56.4; MS (ESI pos ion) m/z: calcd for $C_{29}H_{20}F_2IN_3O_5$, 655.0; found, 655.8 (M+H).

6.19. 4-Ethoxy-N-(3-fluoro-4-((2-((4-methoxybenzyl)amino)pyrimidin-4-yl)oxy)phenyl)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide (**24**)

Sodium hydride (7 mg, 0.16 mmol, 60% dispersion in mineral oil) was added slowly to a solution of ethanol (1 mL) and THF (1 mL) under argon and the resulting mixture was stirred at rt for 5 min. After re-cooled to 0 °C, compound **23** (76 mg, 0.11 mmol) was added to the mixture. The resulting solution was kept stirring at 0 °C for 10 min, and then warmed to rt and stirred for 1 h. The reaction mixture was concentrated in vacuo. The resulting crude solid was suspended in ethyl acetate, washed with saturated aqueous sodium bicarbonate solution, and water. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by column to give the compound **24** (48 mg, 72%) as white solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.09 (s, 1H, NH), 7.86 (d, 1H, J = 12.3 Hz, ArH), 7.48 (dd, 1H, J = 7.9, 2.0 Hz, ArH), 7.33 (ddt, 2H, J = 6.5, 4.4, 2.0 Hz, ArH), 7.28–7.18 (m, 4H, ArH), 7.16–6.98 (m, 2H, ArH), 6.79 (d, 2H, J = 7.9 Hz, ArH), 6.33 (dd, 1H, J = 7.9, 2.0 Hz, ArH), 6.13 (dd, 1H, J = 5.7, 1.9 Hz, ArH), 5.52 (dd, 1H, J = 4.5, 2.2 Hz, ArH), 4.32 (q, 2H, J = 7.1 Hz, OCH_2), 4.28 (s, 1H, NH), 4.03–4.01 (m, 1H, NC*H*H), 3.87–3.77 (m, 1H, NCH*H*), 3.76 (s, 3H, OCH_3), 1.55 (t, 3H, J = 7.0 Hz, CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.9, 163.7, 163.5, 162.2, 161.9, 161.7, 158.8, 153.4, 140.5, 128.9, 128.7, 123.7, 116.9, 116.7, 113.9, 109.1, 106.6, 103.4, 100.0, 98.5, 97.4, 66.4, 55.4, 33.3, 14.8; MS (ESI pos ion) m/z: calcd for $C_{32}H_{27}F_2N_5O_5$, 599.2; found, 600.1 (M+H).

6.20. Preparation of N-(4-((7H-pyrrolo[2,3-d]pyrimidin-4-yl)oxy)-3-fluorophenyl)-4-ethoxy-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide (**22b**)

Similar to the preparation of **24** but using **25** as starting material. White solid; yield 46%; ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.31 (s, 1H, NH), 10.56 (s, 1H, NH), 8.30 (s, 1H, ArH), 7.97–7.79 (m, 2H, ArH), 7.63–7.27 (m, 7H, ArH), 6.60 (d, 1H, J = 3.5 Hz, ArH), 6.53 (d, 1H, J = 7.9 Hz, ArH), 4.26 (q, 2H, J = 6.9 Hz, OCH_2CH$_3$), 1.31 (t, 3H, J = 7.0 Hz, OCH$_2$$CH_3$); ^{13}C NMR (150 MHz, DMSO-d_6) δ 165.0, 162.9, 161.5, 161.1, 160.5, 153.9, 150.5, 141.3, 136.9, 129.7, 129.6, 125.0, 116.5,

116.3, 111.9, 104.5, 98.3, 96.5, 65.6, 31.2, 15.2; MS (ESI pos ion) *m*/*z*: calcd for $C_{26}H_{19}F_2N_5O_4$, 503.1; found, 503.9 (M+H), 526.1 (M+Na).

6.21. Preparation of N-(4-((6,7-dimethoxyquinolin-4-yl)oxy)-3-fluorophenyl)-4-ethoxy-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide (**22d**)

Similar to the preparation of **24** but using **22c** as starting material. White solid; yield 71%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.66 (s, 1H, NH), 8.48 (d, 1H, J = 5.3 Hz, ArH), 7.97 (dd, 1H, J = 12.6, 2.4 Hz, ArH), 7.59 (s, 1H, ArH), 7.53 (d, 1H, J = 7.8 Hz, ArH), 7.42 (s, 1H, ArH), 7.39–7.33 (m, 3H, ArH), 7.26–7.22 (m, 2H, ArH), 7.16 (t, 1H, J = 8.7 Hz, ArH), 6.42 (dd, 1H, J = 5.2, 0.8 Hz, ArH), 6.38 (d, 1H, J = 7.9 Hz, ArH), 4.37 (q, 2H, J = 7.0 Hz, OCH_2CH_3), 4.06 (s, 3H, OCH_3), 4.05 (s, 3H, OCH_3), 1.59 (t, 3H, J = 7.0 Hz, OCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 164.0, 163.8, 162.1, 160.4, 155.7, 152.9, 149.6, 149.0, 146.9, 140.6, 137.8, 137.7, 136.0, 128.8, 128.7, 123.5, 117.0, 116.8, 116.6, 115.7, 107.9, 106.5, 102.4, 99.7, 97.5, 66.5, 56.3, 14.8; MS (ESI pos ion) *m*/*z*: calcd for $C_{31}H_{25}F_2N_3O_6$, 573.2; found, 574.1 (M+H).

6.22. Preparation of N-(4-((6,7-dimethoxyquinolin-4-yl)oxy)-3-fluorophenyl)-1-(4-fluorophenyl)-4-methoxy-2-oxo-1,2-dihydropyridine-3-carboxamide (**22e**)

Similar to the preparation of **24** but using **22c** as starting material; ethanol was replaced with methanol. White solid; yield 71%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.75 (s, 1H, NH), 8.49 (d, 1H, J = 5.3 Hz, ArH), 8.40 (dd, 1H, J = 12.6, 2.4 Hz, ArH), 7.59 (s, 1H, ArH), 7.57 (d, 1H, J = 7.8 Hz, ArH), 7.42 (s, 1H, ArH), 7.39–7.33 (m, 3H, ArH), 7.29–7.27 (m, 1H, ArH), 7.26–7.23 (m, 1H, ArH), 7.16 (t, 1H, J = 8.7 Hz, ArH), 6.44–6.41 (m, 2H, ArH), 4.13 (s, 3H, OCH_3), 4.06 (s, 3H, OCH_3), 4.05 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 163.7, 162.1, 160.4, 155.7, 153.2, 152.9, 149.6, 149.1, 146.9, 140.9, 137.8, 137.7, 136.5, 135.9, 128.8, 128.7, 123.5, 117.1, 116.8, 116.5, 115.7, 107.9, 106.3, 102.4, 99.6, 96.8, 57.5, 56.31, 56.26; MS (ESI pos ion) *m*/*z*: calcd for $C_{30}H_{23}F_2N_3O_6$, 559.2; found, 559.8 (M+H).

6.23. Preparation of N-(4-((2-aminopyrimidin-4-yl)oxy)-3-fluorophenyl)-4-ethoxy-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide (**22a**)

Compound **24** (40 mg, 0.07 mmol) was dissolved in TFA and heated to reflux for 6 h. The solvent was removed before the residue was purified by column, giving title compound (23 mg, 77%) as pale yellow solid. ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.57 (s, 1H, NH), 8.26 (d, 1H, J = 6.3 Hz, ArH), 7.87–7.80 (m, 4H, ArH + NH_2), 7.47–7.43 (m, 2H, ArH), 7.40 (dd, 1H, J = 8.9, 2.4 Hz, ArH), 7.39–7.31 (m, 3H, ArH), 4.25 (q, 2H, J = 7.0 Hz, OCH_2), 1.29 (t, 3H, J = 7.0 Hz, CH_3); ^{13}C NMR (150 MHz, DMSO-d_6) δ 170.2, 164.5, 162.7, 160.7, 160.0, 154.1, 152.5, 140.9, 138.7, 138.6, 136.4, 129.2, 129.1, 124.2, 116.0, 115.9, 115.4, 111.5, 97.1, 96.1, 65.1, 14.7; MS (ESI pos ion) *m*/*z*: calcd for $C_{24}H_{19}F_2N_5O_4$, 479.1; found, 480.1 (M+H).

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejmech.2014.04.056.

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