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Article

Discovery of Novel c-Met Inhibitors Bearing a 3-Carboxyl Piperidin-2-one Scaffold

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Abstract: A series of compounds containing a novel 3-carboxypiperidin-2-one scaffold based on the lead structure BMS-777607 were designed, synthesized and evaluated for their c-Met kinase inhibition and cytotoxicity against MKN45 cancer cell lines. The results indicated that five compounds exhibited significant inhibitory effect on c-Met with IC_{50} values of 8.6−81 nM and four compounds showed potent inhibitory activity against MKN45 cell proliferation, with IC_{50}s ranging from 0.57−16 μM.

Keywords: c-Met; synthesis; kinase inhibitor; 3-carboxypiperidin-2-one

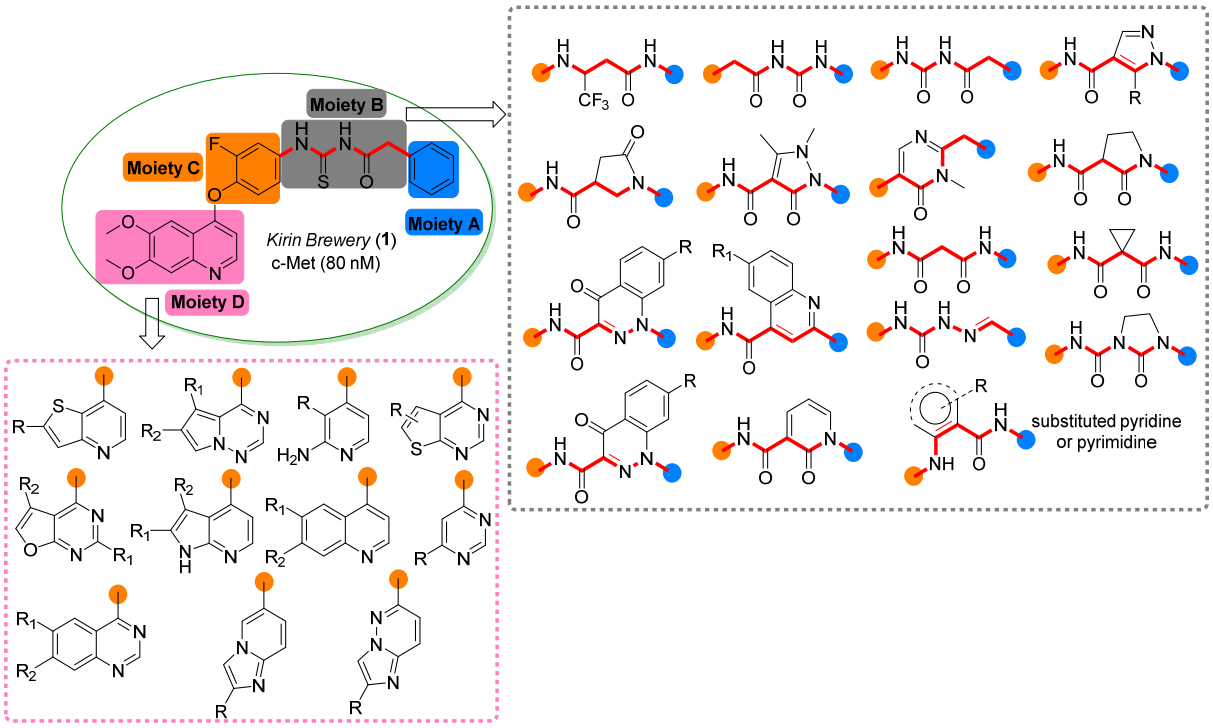
1. Introduction

c-Met kinase is a transmembrane receptor tyrosine kinase (RTK). Upon binding of its endogenous ligand hepatocyte growth factor (HGF, also known as scatter factor, SF), c-Met receptor undergoes dimerization and in turn triggers signal transducers to mediate a variety of cellular responses such as cell growth, invasion, migration and survival [1,2]. The normal c-Met/HGF pathway plays an important role in embryogenesis and wound healing, but aberrant forms of this pathway (for example, as a result of overexpression of c-Met and HGF) have frequently been observed in a variety of human solid tumors and hematologic malignancies. Importantly, both increased levels of c-Met and HGF have

been associated with poor clinical outcomes [3–5]. Therefore, c-Met has been pursued as an attractive anticancer drug target for the past two decades [6,7]. Several approaches to inhibition of the HGF/c-Met pathway in cancer cells have been reported, such as antagonistic ligands to c-Met, antibodies against HGF or c-Met, and small molecule c-Met inhibitors [8–10].

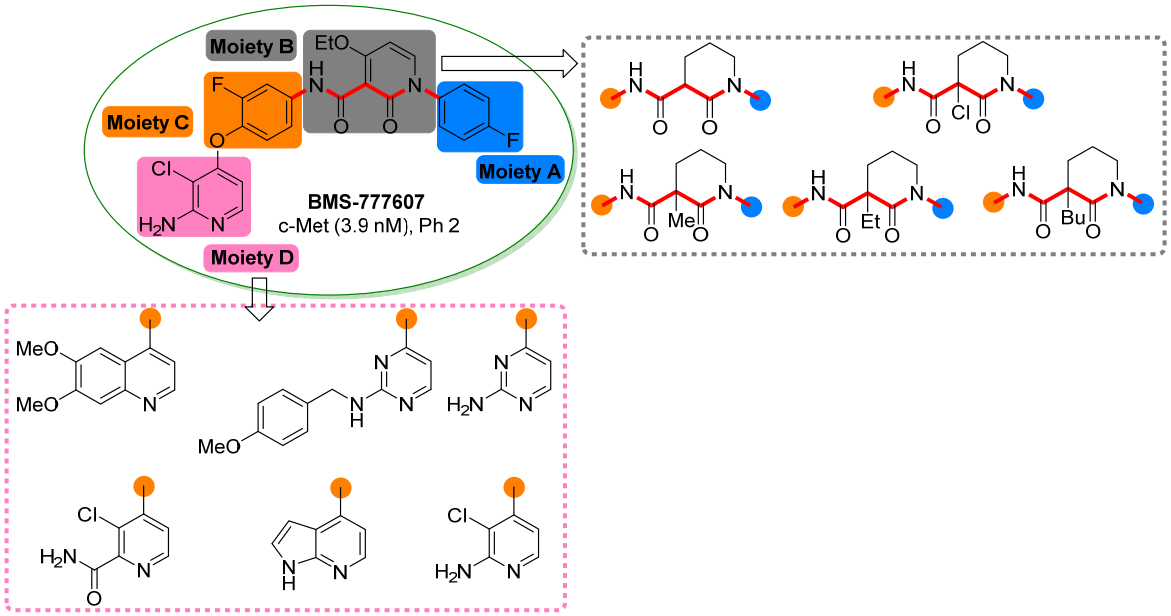
During the development of small molecular c-Met kinase inhibitors, a compound disclosed by Kirin Brewery Company in 2003 [11] could be regarded as a milestone (Figure 1). Structurally, this compound (**1**) is composed of four moieties: a phenyl group (moiety A), a bridge moiety B, an ortho-fluoro phenol and a 6,7-dimethoxyquinoline. Initiated by this discovery, numerous c-Met kinase inhibitors bearing diverse chemical scaffolds have been reported. Generally, structural optimization based on compound **1** mainly focused on moiety D and B. Replacement of the 6,7-dimethoxy-quinoline moiety by various *N*-containing heterocycles, such as substituted quinoline [12], thienopyridine [13–15], pyrrolopyridine [16], aminopyridine [17], thienopyrimidine [18], furopyrimidine [18], imidazopyridine [19] or imidazopyridazine [19], has been investigated. The bridge moiety B connecting moiety A and C was designed as linear [20–22] or cyclic [14,15,23–26], bearing at least one amide bond with 5-atoms in the main chain [22,24] (i.e., six chemical bonds distance between moiety A and C, Figure 1). However, there are little changes to moiety A and C, except for phenyl ring or substituted phenyl ring modifications to the former.

Figure 1. Representative scaffolds used for the structural optimization of c-Met inhibitors.



A good example for these inhibitors is BMS-777067, which is now in phase 2 trial because of its excellent *in vivo* efficacy and favorable pharmacokinetic and preclinical safety profiles [17]. Taking BMS-777607 as leading compound, the design and synthesis of new derivatives with novel structures are under study in our laboratory. Preliminary investigation indicated that 3-carboxypiperidin-2-one is a promising scaffold for the design of new c-Met inhibitors. Herein we would like to report our efforts in this respect (Figure 2).

Figure 2. Scaffolds used for the structural optimization based on BMS-777607 in this paper.

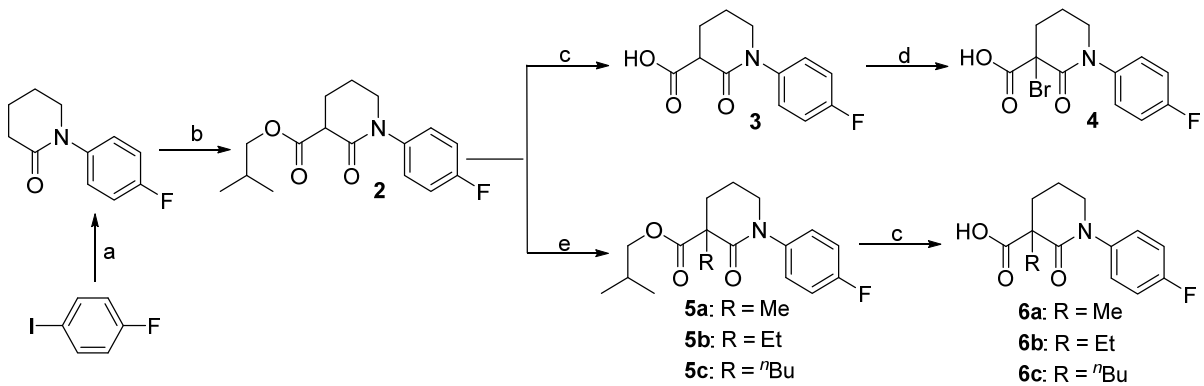


2. Results and Discussion

2.1. Chemistry

As shown in Scheme 1, saponification of isobutyl ester **2** with lithium hydroxide gave the piperidinone 3-carboxylic acid **3**, which could be further brominated giving compound **4** in 92% yield. On the other hand, deprotonation of compound **2** with sodium hydride, followed by treatment with an alkyl halide (MeI, EtBr, or *n*-BuBr) led to the corresponding α-substituted piperidinones. Saponification of these esters **5a**–**c** gave the corresponding carboxylic acids smoothly. In this way, we had five carboxylic acids (compounds **3**, **4**, **6a**–**c**) in hand, which would be used in next coupling step.

Scheme 1. Synthesis of the piperidinone 3-carboxylic acids **3**, **4** and **6a**–**c**.

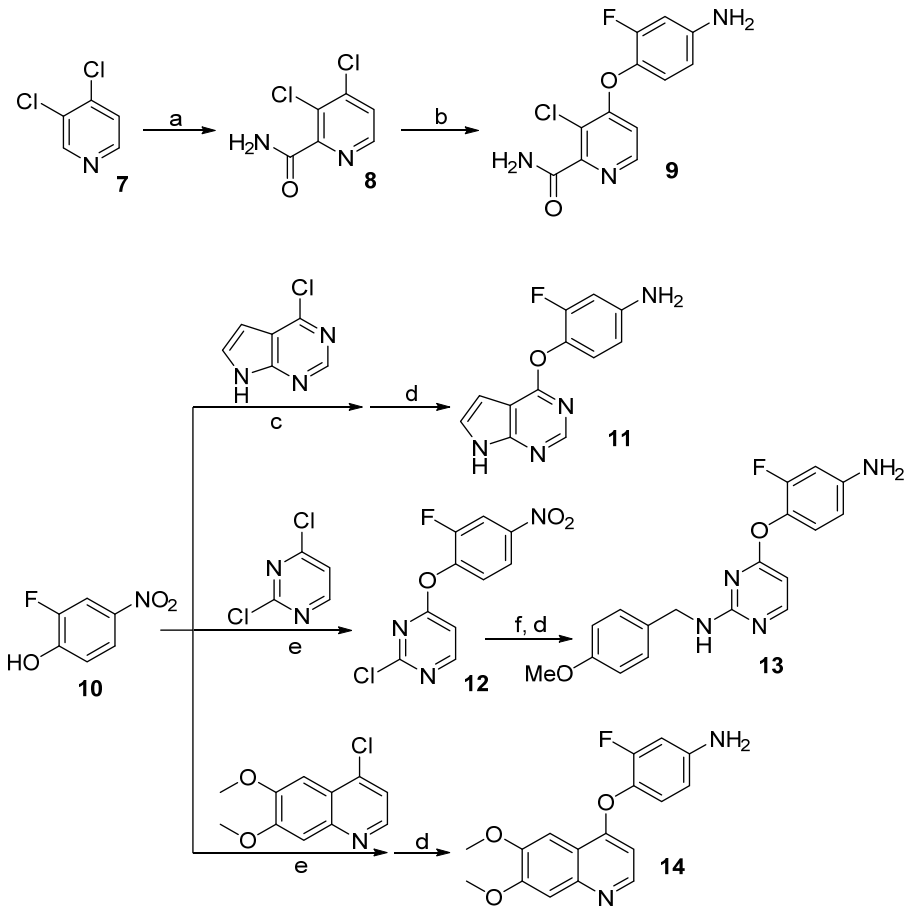


Reagents and conditions: (**a**) piperidin-2-one, CuI, K_3PO_4, DMF, 90%; (**b**) t-BuLi, isobutyl chloroformate, 82%; (**c**) LiOH, THF/MeOH/H_2O, 87% for **3**, 88% for **6a**, 79% for **6b**, 84% for **6c**; (**d**) Br_2/Et_2O, 92%; (**e**) NaH/MeI, 87% for **5a**; NaH/EtBr, 76% for **5b**; NaH/*n*-BuBr, 83% for **5c**.

Deprotonation of 3,4-dichloropyridine (**7**) with lithium 2,2,6,6-tetramethylpiperidide (TMPLi) followed by treated with trimethylsilyl isothiocyanate and acidic workup, gave 3,4-dichloropicolinamide

(**8**) in 40% yield (Scheme 2). This pyridyl chloride was coupled with 4-amino-2-fluorophenol in the presence of potassium *tert*-butoxide to afford the aromatic amine **9** in 72% yield. Similarly, coupling of phenol (**10**) with 4-chloro-7*H*-pyrrolo[2,3-*d*]pyrimidine and 4-chloro-6,7-dimethoxyquinoline followed by conversion of the nitryl to an amino group gave amines **11** and **14**, respectively. For the preparation of substituted pyrimidine **13**, the amino group was introduced to the C-2 position before zinc-mediated reduction. Thus we had four aromatic amines (compounds **9**, **11**, **13** and **14**) in hand, which were subjected to the next step directly.

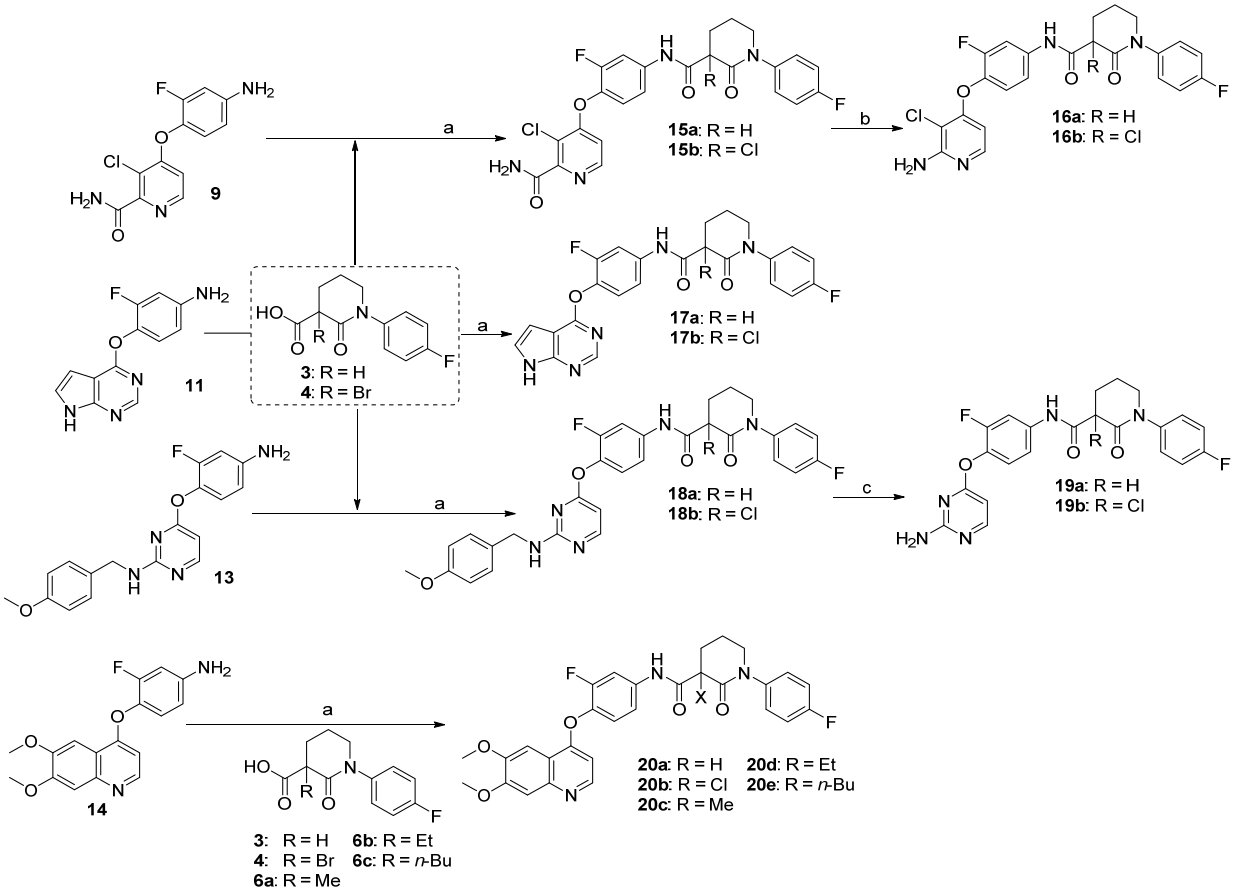
Scheme 2. Synthesis of aromatic amines **9**, **11**, **13** and **14**.



Reagents and conditions: (**a**) TMPLi, trimethylsilyl isothiocyanate, −78 °C, 40%; (**b**) *t*-BuOK, 4-amino-2-fluorophenol, 72%; (**c**) PhBr, 130 °C, 85%; (**d**) Zn, NH_4Cl, 88% for **11**, 69% for **13**; 91% for **14**; (**e**) K_2CO_3, DMF; (**f**) 4-methoxybenzylamine, K_2CO_3, 68%.

Coupling of aromatic amines **9**, **11**, **13** or **14** with the 3-carboxypiperidin-2-one **3** in the presence of 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride (EDC-HCl) and *N*,*N*-dimethyl-4-amino pyridine (DMAP) gave the corresponding amides **15a**, **17a**, **18a** or **20a**, respectively (Scheme 3). When bromide **4** was used as the carboxylic acid component, halo-exchanged products **15b**, **17b**, **18b**, **20b** were observed (confirmed by NMR and MS). The aminopyridine-containing products **16a**–**b** were achieved after Hoffman degradation and the aminopyrimidine derivates **19a**–**b** were generated after treatment of **18a**–**b** with trifluoroacetic acid (TFA).

Scheme 3. Synthesis of the newly designed c-Met inhibitors **15**–**20**.

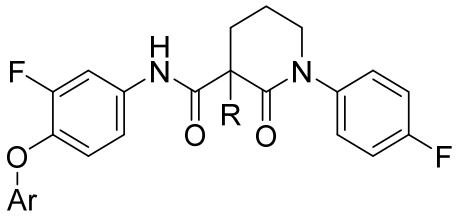


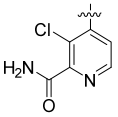
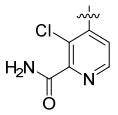
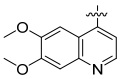
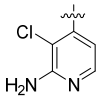
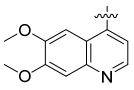
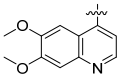
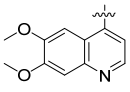
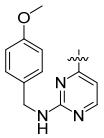
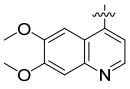
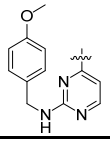
Reagents and conditions: (**a**) EDC-HCl, DMAP, 76% for **15a**, 68% for **15b**, 31% for **17a**, 42% for **17b**, 69% for **18a**, 57% for **18b**, 61% for **20a**, 54% for **20b**, 68% for **20c**, 58% for **20d**, 64% for **20e**; (**b**) $PhI(OAc)_2$, 72% for **16a**, 76% for **16b**; (**c**) TFA, 71% for **19a**, 58% for **19b**.

2.2. Evaluation of Biological Activity

As illustrated in Table 1, all of the compounds bearing a 3-carboxypiperidin-2-one scaffold exhibit potent c-Met kinase inhibition activity. However, compounds lacking an α-substituent group (**15a**, **17a**, **18a**, **19a**, **20a**) only showed much less potent anti-c-Met kinase activity. When the α-proton was substituted by chlorine, the activity generally increased (*cf.* **15b** *vs.* **15a**, **16b** *vs.* **16a**, **20b** *vs.* **20a**). When alkyl groups (Me, Et, or *n*-Bu) were introduced to this position, the inhibitory effects were greatly enhanced (**20c**, **20d** and **20e** *vs.* **20a**). Among these three derivatives, the smallest methyl group was the most favorable among the compounds exerting inhibitory activity against c-Met kinase activity and c-Met-driven cell proliferation. Generally, 6,7-dimethoxyquinoline -containing analogues showed more potency than the pyrropyridine, pyrimidine, or aminopyrimidine counterparts (**20b** *vs.* **15b**, **16b**, **17b**, **18b**, **19b**) according to the biological activity results. The most potent analogue **20b** exhibited significant potency against c-Met kinase and c-Met-driven MKN45 cell proliferation, with IC_{50} values of 8.6 nM and 0.57 μM, respectively. Other three analogues **20c**–**e** with alkyl substitution in the piperidone moiety are also promising, showing inhibitory activity against c-Met enzymatic activities with the IC_{50}s of 11.2~64.0 nM and inhibiting MKN45 cell proliferation with IC_{50}s of 0.65~16.0 μM, individually.

Table 1. SAR of the compounds bearing a 3-carboxypiperidin-2-one scaffold.



Cmpd	Ar	R	c-Met IC_{50} (nM)	MKN45 [a] IC_{50} (μM)	Compd	Ar	R	c-Met IC_{50} (nM)	MKN45 [a] IC_{50} (μM)
15a		H	63.9%@10 μM	NT [b]	**19a**		H	59.1%@10 μM 27.5%@1 μM	NT
15b		Cl	90.2%@10 μM 38.7%@1 μM	NT	**19b**		Cl	52.5%@10 μM 28.3%@1 μM	NT
16a		H	427.0 ± 6.1	NT	**20a**		H	38.4%@10 μM	NT
16b		Cl	81.0 ± 7.6	NT	**20b**		Cl	8.6 ± 1.6	0.57 ± 0.04
17a		H	70.7%@10 μM 41.9%@1 μM	NT	**20c**		Me	11.2 ± 4.1	0.65 ± 0.13
17b		Cl	15.4%@10 μM	NT	**20d**		Et	19.1 ± 4.5	2.95 ± 0.12
18a		H	28.4%@10 μM	NT	**20e**		^{n}Bu	64.0 ± 10.8	16.0 ± 0.8
18b		Cl	10%@10 μM	NT	BMS-777607	—	—	3.7 ± 1.3	0.29 ± 0.02

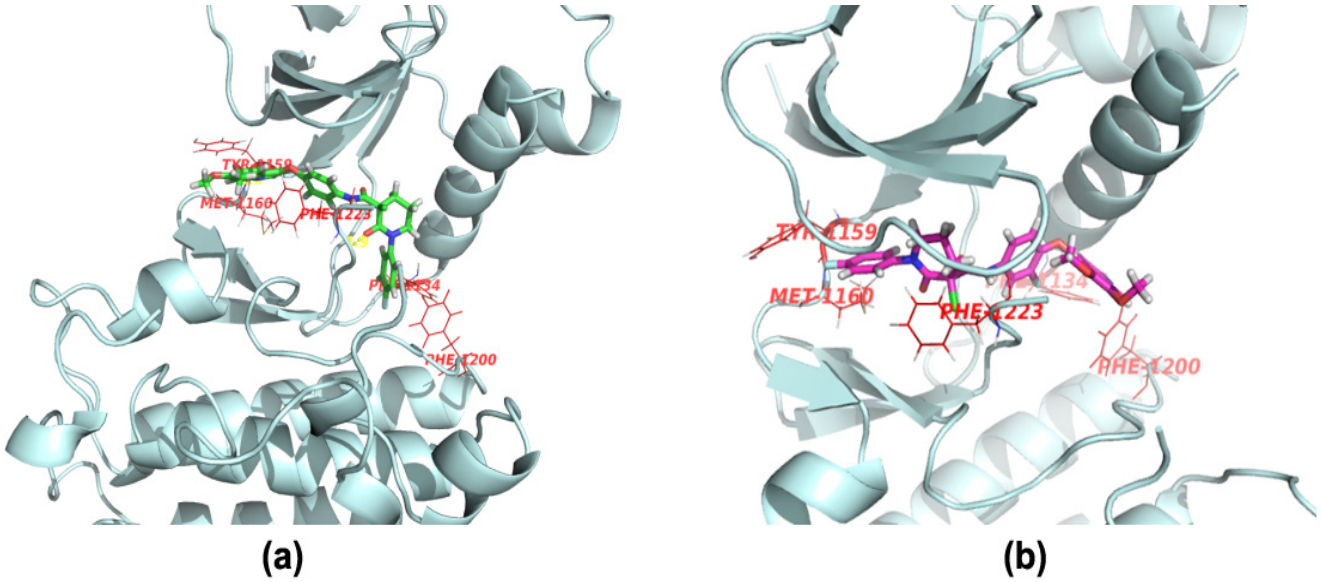
[a]: MKN45, human gastric cancer cell line that expresses elevated levels of constitutively active c-Met; [b]: NT, Not tested.

2.3. Molecular Modeling

To further elucidate the binding mode of compounds, docking analysis was performed. In our study, the co-crystal structure of BMS-777607 with c-Met kinase (PDB ID:3F82) was selected as the docking model. The inhibitor was docked using the GLIDE docking algorithm [27] in the XP (extra precision) mode. A binding model for (*R*)-**20b** in the ATP binding site is presented in Figure 3a. The resulting model successfully identifies key hydrogen bond interaction and hydrophobic interactions between the ligands and residues of the protein's ATP binding pocket. The carbonyl oxygen of the

3-carboxypiperidin-2-one and the nitrogen atom of the quinoline ring in **20b** formed hydrogen bonding interactions with Asp1222 and Met1160, respectively. π-π Interactions were formed between the phenyl ring (moiety C) and Phe1223. In addition, hydrophobic interactions were formed between the phenyl ring (moiety A) in **20b** and Phe1134, Phe1200. A binding model for (*S*)-**20b** in the ATP binding site is presented in Figure 3b. However, this compound failed to dock into the binding pocket, as the orientation of the ligand in the binding model was opposite to that of BMS-777607. Therefore, we postulate that the requisite chirality for these compound may be the *R*-configuration. We are now seeking an efficient route to access the enantiomers, and the optical pure compounds will be synthesized and evaluated in the due course.

Figure 3. Binding poses of compounds (*R*)-**20b** and (*S*)-**20b** with c-Met.



3. Experimental

3.1. General Information

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 performed under a positive pressure of argon. Flash column chromatography was performed on silica gel (200–300 mesh, Qingdao Haiyang Chemical Co., Ltd, Qingdao, China). Analytical thin layer chromatography (TLC) was performed on glass plates pre-coated with a 0.25 mm thickness of silica gel. ^{1}H-NMR and ^{13}C-NMR spectra were taken on a Jeol JNM-ECP 600 spectrometer (Jeol Ltd., Tokyo, Japan) at room temperature. Chemical shifts of the ^{1}H-NMR spectra are expressed in ppm relative to the solvent residual signal 7.26 in $CDCl_3$ or to tetramethylsilane (δ = 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 (δ = 0.00) unless otherwise noted. Electrospray (ESI) mass spectra were recorded on a Global Q-TOF mass spectrometer (Waters, Wilford, MA, USA).

3.2. Synthesis

Isobutyl 1-(4-fluorophenyl)-2-oxopiperidine-3-carboxylate (**2**). 1-Fluoro-4-iodobenzene (2.22 g, 10 mmol) and piperidin-2-one (1.2 g, 12 mmol) were added to dry DMF (30 mL), followed by the addition of K_3PO_4 (6.36 g, 30 mmol) and CuI (190 mg, 0.1 mmol). The mixture was heated to 100 °C for 12 h before filtering through Celite. After washing with ethyl acetate (3 × 10 mL), the combined organic phase was concentrated and the residue was purified by column chromatography to give 1-(4-fluorophenyl)piperidin-2-one (1.73 g, 90%) as a yellow solid. This *N*-arylpiperidin-2-one (386 mg, 2 mmol) was dissolved in dry THF (20 mL) and cooled to −78 °C. After the addition of *tert*-BuLi (1.4 mL, 1.6 M in THF, 2.2 mmol) and stirring at this temperature for 4 h, isobutyl chlorofomate (400 μL, 2 mmol) was added. Ten min later, the reaction was quenched by addition of saturated aq. NH_4Cl (2 mL). 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 chromatography to give compound **2** (480 mg, 82%) as a 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, 1 H, *J* = 6.7 Hz, CHH), 3.70–3.61 (m, 1H, CHH), 3.58 (t, 1 H, *J* = 6.9 Hz, CH), 2.32–2.24 (m, 1H, CHH), 2.23–2.16 (m, 1H, CHH), 2.12–2.04 (m, 1H, CHH), 2.02–1.87 (m, 2H, CH, CHH), 0.94 (d, 6 H, *J* = 6.6 Hz, CH_3); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 171.0, 166.3, 162.1, 160.4, 138.8, 127.9, 116.2, 100.0, 71.5, 51.6, 49.6, 27.8, 25.3, 21.4, 19.1; HR-MS (ESI) Calcd for $C_{16}H_{21}FNO_3$ $[M + H]^+$ 294.1506, Found 294.1518.

1-(4-Fluorophenyl)-2-oxopiperidine-3-carboxylic acid (**3**). To a solution of **2** (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 mol/L 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 **3** (152 mg, 87%) as a white solid. ^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.33–7.28 (m, 1H, ArH), 7.25–7.19 (m, 1H, ArH), 3.69–3.55 (m, 2H, NCH2), 3.43 (dd, 1H, *J* = 8.2, 6.5 Hz, CH), 2.16–2.10 (m, 1 H, CHH), 2.08–2.02 (m, 1H, CHH), 1.98–1.91 (m, 1H, CHH), 1.91–1.83 (m, 1H, CHH); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 174.3, 170.2, 161.3, 159.6, 138.7, 127.9, 115.6, 51.8, 50.3, 27.5, 21.6; HR-MS (ESI) Calcd for $C_{12}H_{13}FNO_3$ 238.0880 $[M + H]^+$, found 238.0910.

3-Bromo-1-(4-fluorophenyl)-2-oxopiperidine-3-carboxylic acid (**4**). To a solution of acid **3** (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 chromatography, giving compound **4** (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, NCHH), 3.82 (ddt, 1H, *J* = 13.0, 6.3, 2.4 Hz, NCHH), 2.77–2.69 (m, 1H, CH*H*), 2.62–2.56 (m, 1H, CH*H*), 2.53–2.43 (m, 1H, CHH), 2.19–2.12 (m, 1H, CHH); ^{13}C-NMR (150 MHz, acetone-d_6) δ 166.4, 162.5, 160.9, 140.6, 140.6, 129.0, 129.0, 116.2, 52.1, 32.3, 20.4.

3.2.1. General Procedure for the Synthesis of Isobutyl 1-(4-Fluorophenyl)-3-alkyl-2-oxopiperidine-3-carboxylates **5a**–**c**

To a solution of compound **2** (586 mg, 2 mmol) in dry THF (10 mL) at 0 °C was added NaH (72 mg, 80% suspension in mineral oil, 2.4 mmol) in portions. Thirty min later, alkyl halide (MeI, EtBr, or *n*-BuBr, 2.6 mmol) was added slowly and the reaction mixture was stirred at this temperature for another 5 h. When TLC showed all the starting material consumed, the reaction mixture was quenched with 0.5 mol/L HCl, 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. The residue was purified by column chromatography to give the desired compound as pale yellow oil.

Isobutyl 1-(4-fluorophenyl)-3-methyl-2-oxopiperidine-3-carboxylate (**5a**). 87% yield; ^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.25–7.19 (m, 1 H, ArH), 7.12–7.01 (m, 1H, ArH), 4.06–3.88 (m, 2H, OCH_2), 3.78–3.58 (m, 1H, CH*H*), 2.47–2.31 (m, 1H, CH*H*), 2.10–1.94 (m, 3H, CH_2, CH), 1.94–1.84 (m, 1H, CH*H*), 1.57 (d, 3H, *J* = 2.4 Hz, CH_3), 0.97 (d, 3H, *J* = 2.0 HzCH_3), 0.96 (d, 3H, *J* = 2.1 Hz, CH_3); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 173.8, 170.1, 161.9, 160.2, 139.3, 127.8, 116.0, 115.9, 71.5, 51.9, 51.3, 33.6, 27.8, 22.9, 20.4, 19.2; HR-MS (ESI) Calcd for $C_{17}H_{23}FNO_3$ 308.1662 $[M + H]^+$, found 308.1599.

Isobutyl 3-ethyl-1-(4-fluorophenyl)-2-oxopiperidine-3-carboxylate (**5b**). 76% yield; ^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.24–7.18 (m, 2H, ArH), 7.08–7.03 (m, 2H, ArH), 4.01–3.90 (m, 2H, OCH_2), 3.72–3.65 (m, 1 H, CHH), 3.63–3.56 (m, 1H, CHH), 2.31–2.24 (m, 1H, CHH), 2.16–2.09 (m, 1H, CHH), 2.10–2.04 (m, 1H, CHH), 2.02–1.91 (m, 4H, CH_2), 0.98 (t, 3H, *J* = 7.4 Hz, CH_3), 0.96 (d, 6H, *J* = 2.1 Hz, 2 × CH_3); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 173.6, 170.0, 161.8, 160.2, 139.3, 127.8, 116.0, 71.5, 51.9, 51.3, 33.6, 30.1, 27.8, 22.9, 20.4, 19.8; HR-MS (ESI) Calcd for $C_{18}H_{25}FNO_3$ 322.1819 $[M + H]^+$, found 322.1830.

Isobutyl 3-butyl-1-(4-fluorophenyl)-2-oxopiperidine-3-carboxylate (**5c**). 83% yield; ^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.23–7.18 (m, 2H, ArH), 7.08–7.02 (m, 2H, ArH), 4.00–3.89 (m, 2H, OCH_2), 3.72–3.66 (m, 1H, CHH), 3.61–3.56 (m, 1H, CHH), 2.32–2.26 (m, 1H, CHH), 2.10–1.86 (m, 6H), 1.46–1.38 (m, 1H, CHH), 1.37–1.29 (m, 2H, CH_2), 1.30–1.21 (m, 1H, CHH), 0.96 (d, 6H, *J* = 2.1 Hz, 2 × CH_3), 0.90 (t, 3H, *J* = 7.2 Hz, CH_3); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 173.5, 169.4, 161.8, 160.2, 139.4, 127.8, 115.9, 71.5, 54.9, 51.6, 35.7, 30.1, 27.0, 23.2, 20.7, 19.2, 14.1; HR-MS (ESI) Calcd for $C_{20}H_{29}FNO_3$ 350.2132, $[M + H]^+$, found 350.2122.

3.2.2. 1-(4-Fluorophenyl)-3-alkyl-2-oxopiperidine-3-carboxylic Acids **6a**–**c** were Prepared by a Procedure Similar to that of Compound **3**.

3-Methyl-1-(4-fluorophenyl)-2-oxopiperidine-3-carboxylic acid (**6a**). White solid; 88% yield; ^{1}H-NMR (600 MHz, DMSO-d_6) δ 12.59 (s, 1 H, OH), 7.31–7.25 (m, 2H, ArH), 7.24–7.17 (m, 2H, ArH), 3.65 (dt, 1H, *J* = 12.1, 6.1 Hz, NCHH), 3.59 (dt, 1H, *J* = 11.9, 5.8 Hz, NC*H*H), 2.25–2.18 (m, 1H, CHH), 1.95–1.87 (m, 2H, CH_2), 1.87–1.80 (m, 1H, CHH), 1.37 (s, 3H, CH_3); ^{13}C-NMR (150 MHz, DMSO-d_6) δ 174.9, 169.7, 160.9, 159.3, 139.8, 128.2, 115.6, 51.2, 50.4, 32.8, 22.6, 19.8; HR-MS (ESI) Calcd for $C_{13}H_{15}FNO_3$ 252.1036, $[M + H]^+$, found 252.1040.

3-Ethyl-1-(4-fluorophenyl)-2-oxopiperidine-3-carboxylic acid (**6b**). white solid; 79% yield; ^{1}H-NMR (600 MHz, DMSO-d_6) δ 12.79 (s, 1 H, OH), 7.26–7.23 (m, 2H, ArH), 7.16–7.12 (m, 2H, ArH), 3.92 (dt, J = 12.7, 6.5 Hz, 1H, NCHH), 3.74 (dt, J = 12.6, 6.4 Hz, 1H, NCHH), 2.56–2.50 (m, 1H, CHH), 2.20 (q, J = 6.7 Hz, 1H, CHH), 2.05–2.01 (m, 1H, CHH), 2.01–1.91 (m, 2H, CHH), 1.84 (dt, J = 12.3, 7.0 Hz, 1 H, CHH), 0.71 (t, J = 6.6 Hz, 3H, CH_3); ^{13}C-NMR (150 MHz, DMSO-d_6) δ 174.8, 169.8, 161.2, 159.6, 139.5, 128.4, 115.8, 51.7, 50.9, 33.6, 29.7, 22.6, 18.8; HR-MS (ESI) Calcd for $C_{14}H_{17}FNO_3$ 266.1193, $[M + H]^+$, found 266.1201.

3-Butyl-1-(4-fluorophenyl)-2-oxopiperidine-3-carboxylic acid (**6c**). White solid; 84% yield; ^{1}H-NMR (600 MHz, DMSO-d_6) δ 12.66 (s, 1H, OH), 7.25–7.20 (m, 2H, ArH), 7.14 (dd, 2H, J = 8.6, 7.0 Hz, ArH), 3.96–3.87 (m, 1H, CHH), 3.78–3.72 (m, 1H, CHH), 2.49–2.42 (m, 1H, CHH), 2.22 (dt, J = 19.0, 7.5 Hz, 2H, CH_2), 2.03–1.91 (m, 3H, CHH, CH_2), 1.38–1.21 (m, 4H, CH_2CH_2), 0.88 (t, 3 H, J = 6.4 Hz, CH_3); ^{13}C-NMR (150 MHz, DMSO-d_6) δ 174.7, 169.5, 161.6, 160.0, 139.6, 127.9, 115.6, 54.6, 51.3, 35.4, 30.3, 23.2, 20.7, 14.2; HR-MS (ESI) Calcd for $C_{16}H_{21}FNO_3$ 294.1506, $[M + H]^+$, found 294.1496.

3,4-Dichloropicolinamide (**8**). To a solution of 2,2,6,6-tetramethylpiperidine (1.56 g, 11 mmol) in dry ether (20 mL) at 0 °C was added *n*-BuLi (4.4 mL, 2.5 M in THF, 11 mmol) slowly. The reaction mixture was stirred at this temperature for 30 min before cooled to −78 °C. A solution of 3,4-dichloropyridine (1.48 g, 10 mmol) in dry ether (5 mL) was injected via syringe to the above reaction mixture and stirred for 2 h before trimethylsilyl isothiocyanate (15 mmol) was added. After warmed to room temperature, the reaction was quenched by the addition of HOAc (2 mL) and water (10 mL), and then let to stir overnight. The suspension was filtered and washed with cold water, giving the title compound as a gray solid (686 mg, 40%). ^{1}H-NMR (DMSO-d_6, 600 MHz) δ 8.50 (d, 1H, J = 5.2 Hz, ArH), 8.12 (br s, 1H, $CONH_2$), 7.83 (d, 1H, J = 5.2 Hz, ArH), 7.82 (br s, 1H, $CONH_2$).

4-(4-Amino-2-fluorophenoxy)-3-chloropicolinamide (**9**). To a solution of 4-amino-2-fluorophenol (465 mg, 3.65 mmol) in DMF (10 mL) was added potassium *tert*-butoxide (440 mg, 3.95 mmol). Thirty min later, 3,4-dichloropicolinamide (**8**) was added and the solution was heated to 50 °C. When TLC showed all the starting materials consumed, the reaction mixture was diluted with EtOAc (50 mL), washed with saturated $NaHCO_3$, brine, and dried over Na_2SO_4. After concentration, the residue was purified by column chromatography giving the title compound as a pale yellow solid (580 mg, 79%). ^{1}H-NMR (DMSO-d_6, 600 MHz) δ 8.29 (d, 1 H, J = 5.6 Hz, ArH), 7.00 (t, 1H, J = 8.8 Hz, ArH), 6.79 (d, 1H, J = 5.6 Hz, ArH), 6.63–6.55 (m, 2H, ArH); ^{13}C-NMR (DMSO-d_6, 150 MHz) δ 166.6, 160.8, 154.1, 153.9, 149.0, 148.7, 128.5, 123.7, 115.9, 110.1, 110.0, 101.3.

4-((7H-Pyrrolo[2,3-d]pyrimidin-4-yl)oxy)-3-fluoroaniline (**11**). The solution of 4-chloro-*7H*-pyrrolo-[2,3-d]pyrimidine (1.0 g, 6.5 mmol) and 2-fluoro-4-nitrophenol (1.5 g, 9.5 mmol) in bromobenzene (5 mL) was heated at 130 °C for 4 h in a sealed tube. After that, the reaction mixture was cooled to room temperature, diluted with Et_2O (5 mL) and filtered. Recrystallization in MeOH gave 4-(2-fluoro-4-nitrophenoxy)-7*H*-pyrrolo[2,3-*d*]pyrimidine as a yellow solid (1.6 g, 85%), which was used for the next step directly. To a solution of this nitro compound in THF (5 mL) and MeOH (5 mL) was added zinc powder (130 mg, 2 mmol) and NH_4Cl (270 mg, 5 mmol). The reaction mixture was stirred at room temperature for 5 h before filtered through a Celite pad. The filtrate was diluted with EtOAc, washed

with water, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography giving compound **11** (115 mg, 69%) as a brown solid. ^{1}H-NMR (600 MHz, DMSO-d_6) δ 12.19 (s, 1H, NH), 8.28 (s, 1H, CH), 7.44 (t, 1H, *J* = 3.1 Hz, ArH), 7.00 (t, 1H, *J* = 8.9 Hz, ArH), 6.48 (dd, 1H, *J* = 13.0, 2.6 Hz, ArH), 6.45 (dd, 1H, *J* = 3.4, 1.5 Hz, CH), 6.42–6.39 (m, 1H, CH), 5.35 (s, 2H, NH_2).

2-Chloro-4-(2-fluoro-4-nitrophenoxy)pyrimidine (**12**). 2-Fluoro-4-nitrophenol (314 mg, 2 mmol), K_2CO_3 (304 mg, 2.2 mmoo) and 2,4-dichloropyrimidine (300 mg, 2 mmol) were dissolved in DMF (20 mL) and heated at 100 °C for 2 h. the reaction mixture was concentrated, diluted with EtOAc (100 mL), washed with water, brine, and concentrated *in vacuo*. The residue was purified by column chromatography giving compound **12** (324 mg, 65%) as a white solid. ^{1}H-NMR (600 MHz, DMSO-d_6) δ 8.78 (d, *J* = 5.7 Hz, 1H, ArH), 8.44 (dd, 1H *J* = 10.2, 2.7 Hz, ArH), 8.25 (ddd, 1H, *J* = 9.0, 2.7, 1.3 Hz, ArH), 7.82 (dd, 1H, *J* = 9.0, 7.7 Hz, ArH), 7.49 (d, 1H, *J* = 5.7 Hz, ArH).

4-(4-Amino-2-fluorophenoxy)-N-(4-methoxybenzyl)pyrimidin-2-amine (**13**). To the solution of compound **12** (239 mg 1mmol) and 4-methoxybenzylamine (192 mg, 1.4 mmol) in DMF (8 mL) was added K_2CO_3 (152 mg, 1.1 mmol). The reaction mixture was heated at 100 °C for 1 h before concentrated in vacuo. After diluted with EtOAc, the solution was washed with water and brine, and then concentrated. The residue was purified by column chromatography giving a yellow solid (231 mg, 68%), which was treated by zinc powder and NH_4Cl as described for the preparation of compound **11**. After workup and purification, compound **13** was obtained as a brown solid (115 mg, 69%). ^{1}H-NMR (600 MHz, $CDCl_3$) δ 8.06 (br s, 1H, ArH), 7.12 (br s, 2H, ArH), 6.92 (t, 1H, *J* = 8.6 Hz, ArH), 6.80 (d, 2H, *J* = 8.2 Hz, ArH), 6.47 (dd, 1H, *J* = 11.8, 2.7 Hz, ArH), 6.45–6.39 (m, 1H, ArH), 6.15 (d, 1H, *J* = 5.8 Hz, ArH), 4.36 (br s, 2H, NH_2), 3.92 (br s, 2H, CH_2), 3.78 (s, 3H, CH_3).

4-((6,7-Dimethoxyquinolin-4-yl)oxy)-3-fluoroaniline (**14**). The procedure used was similar to that used for the synthesis of compound **11**. Compound **14** was obtained as a brown solid in 76% yield. ^{1}H-NMR (600 MHz, $CDCl_3$) δ 8.47 (d, 1H, *J* = 5.1 Hz, ArH), 7.58 (s, 1H, ArH), 7.40 (s, 1H, ArH), 7.02 (t, 1H, *J* = 8.6 Hz, ArH), 6.55 (dd, 1H, *J* = 12.0, 2.7 Hz, ArH), 6.49 (dd, 1H, *J* = 8.9, 2.6 Hz, ArH), 6.40 (d, 1H, *J* = 5.0 Hz, ArH), 4.05 (s, 3H, OCH_3), 4.03 (s, 3H, OCH_3), 3.84 (br s, 2H, NH_2).

3.2.3. General Procedure for the Preparation of **15a**–**b**, **17a**–**b**, **18a**–**b** and **20a**–**b**

EDC-HCl (1.2 g, 6.25 mmol) was added to a suspension of the carboxylic acid (2.5 mol of **3**, **4**, or **6a**–**c**) and the amine (2.5 mmol of **9**, **11**, **13** or **14**) 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 amide.

3-Chloro-4-(2-fluoro-4-(1-(4-fluorophenyl)-2-oxopiperidine-3-carboxamido)phenoxy)picolinamide (**15a**, from **9** and **3**): 76% yield; ^{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, CHH), 1.96–1.87 (m, 1H, CHH); ^{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 $[M + H]^+$; HR-MS (ESI) Calcd for $C_{24}H_{20}ClF_2N_4O_4$ 501.1141 $[M + H]^+$, found 501.1160.

3-Chloro-4-(4-(3-chloro-1-(4-fluorophenyl)-2-oxopiperidine-3-carboxamido)-2-fluorophenoxy)-picolinamide (**15b**, from **9** and **4**) 68% yield; ^{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, CHH), 3.73–3.68 (m, 1H, CHH), 2.96–2.87 (m, 1H, CHH), 2.65–2.56 (m, 1H, CHH), 2.45–2.34 (m, 1H, CHH), 2.17–2.07 (m, 1H, CHH); ^{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, 136.8, 136.8, 136.8, 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 $[M + H]^+$; HR-MS (ESI) Calcd for $C_{24}H_{19}Cl_2F_2N_4O_4$ 535.0752 $[M + H]^+$, found 535.0764.

N-(4-((7H-pyrrolo[2,3-d]pyrimidin-4-yl)oxy)-3-fluorophenyl)-1-(4-fluorophenyl)-2-oxopiperidine-3-carboxamide (**17a**, from **11** and **3**): 31% yield, ^{1}H-NMR (600 MHz, $CDCl_3$) δ 11.02 (s, 1H, NH), 10.19 (s, 1H, NH), 8.87 (s, 1H, ArH), 8.54 (s, 1H, ArH), 8.13–7.93 (m, 1H, ArH), 7.81 (d, 1H, *J* = 11.6 Hz, ArH), 7.42 (s, 1H, ArH), 7.31–7.20 (m, 2H, ArH), 7.16–7.03 (m, 2H, ArH), 6.92 (s, 1H, ArH), 3.74–3.59 (m, 2H, NCH_2), 3.59–3.47 (m, 1H, CH), 2.63–2.51 (m, 1H, CHH), 2.26–2.16 (m, 1 H, CH*H*), 2.15–2.07 (m, 1 H, CHH), 2.08–1.98 (m, 1 H, CHH); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 169.5, 168.3, 162.5, 160.9, 156.2, 155.9, 154.6, 152.4, 151.1, 139.8, 138.5, 134.5, 134.2, 128.2, 128.1, 126.2, 123.0, 116.9, 116.8, 116.7, 116.6, 115.8, 115.6, 109.4, 109.2, 100.3, 53.1, 47.8, 47.7, 29.7, 22.8, 21.6; MS (ESI pos ion) *m/z*: calcd for $C_{24}H_{19}F_2N_5O_3$ 463.1, found 464.2 $[M + H]^+$; HR-MS (ESI) Calcd for $C_{24}H_{20}F_2N_5O_3$ 464.1534 $[M + H]^+$, found 464.1547.

N-(4-((7H-pyrrolo[2,3-d]pyrimidin-4-yl)oxy)-3-fluorophenyl)-3-chloro-1-(4-fluorophenyl)-2-oxo-piperidine-3-carboxamide (**17b**, from **11** and **4**): 42% yield; ^{1}H-NMR (600 MHz, $CDCl_3$) δ 8.25 (s, 1H, ArH), 7.89 (dd, *J* = 12.5, 2.5 Hz, 1H, ArH), 7.50 (d, *J* = 3.6 Hz, 1H, ArH), 7.48 (dd, *J* = 2.5, 1.3 Hz, 1H, ArH), 7.46–7.42 (m, 3H, ArH), 7.38 (t, *J* = 8.7 Hz, 1H, ArH), 7.25–7.19 (m, 2H, ArH), 6.64 (d, *J* = 3.6 Hz, 1H, ArH), 3.98–3.88 (m, 1H. CHH), 3.84–3.78 (m, 1H. CHH), 2.96 (ddd, *J* = 14.8, 11.6, 3.2 Hz, 1H. CHH), 2.59–2.52 (m, 1H. CHH), 2.40–2.31 (m, 1H. CHH), 2.21–2.11 (m, 1H. CHH); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 169.7, 168.5, 162.7, 160.9, 156.3, 155.9, 154.7, 152.4, 151.3, 139.8, 138.6, 134.7, 134.5, 128.4, 128.3, 126.4, 123.6, 117.0, 116.8, 116.7, 116.6, 115.9, 115.7, 109.6, 109.4, 100.6, 64.5, 53.5, 47.9, 47.7, 29.9, 22.8, 21.8; MS (ESI pos ion) *m/z*: calcd for $C_{24}H_{18}ClF_2N_5O_3$ 497.1, found 498.0 $[M + H]^+$; HR-MS (ESI) Calcd for $C_{24}H_{19}ClF_2N_5O_3$ 498.1145 $[M + H]^+$, found 498.1155.

N-(3-fluoro-4-((2-((4-methoxybenzyl)amino)pyrimidin-4-yl)oxy)phenyl)-1-(4-fluorophenyl)-2-oxo-piperidine-3-carboxamide (**18a**, from **13** and **3**): 69% yield, ^{1}H-NMR (600 MHz, $CDCl_3$) δ 10.19 (s, 1H, NH), 8.06 (s, 1H, ArH), 7.75 (d, 1H, *J* = 12.2 Hz, ArH), 7.24–7.18 (m, 3H, ArH), 7.11 (t, 2H,

J = 8.3 Hz, ArH), 7.06 (t, 1H, *J* = 8.4 Hz, ArH), 7.00 (d, 1H, *J* = 8.6 Hz, ArH), 6.78 (s, 2H, ArH), 6.23 (s, 1H, ArH), 4.24 (s, 2H, CH_2), 3.76 (s, 3H, OCH_3), 3.71–3.62 (m, 2H, NCH_2), 3.62–3.57 (m, 1H, CH), 2.58–2.48 (m, 1H, CHH), 2.25–2.14 (m, 1H, CHH), 2.13–2.05 (m, 1H, CHH), 2.05–1.97 (m, 1H, CHH); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 169.3, 166.0, 162.4, 160.8, 159.0, 156.7, 154.8, 138.4, 129.3, 128.2, 128.1, 123.7, 116.6, 116.5, 115.3, 114.0, 55.4, 52.7, 47.7, 22.9, 21.7; MS (ESI pos ion) *m/z*: calcd for $C_{30}H_{27}F_2N_5O_4$ 559.2, found 560.2 $[M + H]^+$; HR-MS (ESI) Calcd for $C_{30}H_{28}F_2N_5O_4$ 560.2109 $[M + H]^+$, found 560.2125.

3-Chloro-N-(3-fluoro-4-((2-((4-methoxybenzyl)amino)pyrimidin-4-yl)oxy)phenyl)-1-(4-fluorophenyl)-2-oxopiperidine-3-carboxamide (**18b**, from **13** and **4**):57% yield; ^{1}H-NMR (600 MHz, $CDCl_3$) δ 9.96 (s, 1H, NH), 8.12 (s, 1H, ArH), 7.69 (dd, *J* = 11.8, 2.5 Hz, 1H, ArH), 7.25–7.22 (m, 2H, ArH), 7.19 (dd, 1H, *J* = 8.9, 2.4 Hz, ArH), 7.15–7.08 (m, 4H, ArH), 6.80 (d, 2H, *J* = 8.0 Hz, ArH), 6.18 (d, 1H, *J* = 5.7 Hz, ArH), 4.32 (s, 2H, CH_2), 3.81–3.75 (m, 1H, CHH), 3.77 (s, 3H, OCH_3), 3.69 (dt, 1H, *J* = 12.4, 4.9 Hz, CHH), 2.90 (ddd, 1H, *J* = 14.6, 11.3, 3.0 Hz, CHH), 2.63–2.54 (m, 1H, CHH), 2.41–2.31 (m, 1H, CHH), 2.15–2.06 (m, 1H, CHH); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 166.9, 164.6, 162.6, 162.1, 160.9, 159.5, 158.9, 157.7, 155.3, 153.70, 138.0, 136.4, 136.3, 135.8, 135.8, 130.9, 129.1, 127.9, 127.8, 124.2, 116.7, 116.5, 115.7, 113.9, 64.4, 55.4, 55.3, 52.7, 45.0, 33.9, 19.5; MS (ESI pos ion) m/z: calcd for $C_{30}H_{26}ClF_2N_5O_4$ 593.2, found 594.2 $[M + H]^+$; HR-MS (ESI) Calcd for $C_{30}H_{27}ClF_2N_5O_4$ 594.1720 $[M + H]^+$, found 594.1733.

N-(4-((6,7-dimethoxyquinolin-4-yl)oxy)-3-fluorophenyl)-1-(4-fluorophenyl)-2-oxopiperidine-3-carboxamide (**20a**, from **14** and **3**): 61% yield; ^{1}H-NMR (600 MHz, $CDCl_3$) δ 10.30 (s, 1H, NH), 8.51 (s, 1 H, ArH), 7.84 (dd, 1H, *J* = 12.1, 2.5 Hz, ArH), 7.69 (s, 1H, ArH), 7.59 (s, 1H, ArH), 7.29–7.26 (m, 1H, ArH), 7.25–7.21 (m, 2H, ArH), 7.18 (t, 1H, *J* = 8.6 Hz, ArH), 7.12 (t, 2H, *J* = 8.5 Hz, ArH), 6.49 (d, 1H, *J* = 5.5 Hz, ArH), 4.08 (s, 3H, OCH_3), 4.06 (s, 3H, OCH_3), 3.75–3.60 (m, 2H, CHH), 3.58–3.49 (m, 1H, CH), 2.60–2.47 (m, 1H, CHH), 2.29–2.19 (m, 1H, CHH), 2.14–1.97 (m, 2H, CH_2); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 169.3, 166.4, 154.6, 150.6, 145.7, 138.4, 128.1, 123.5, 116.6, 116.5, 116.2, 99.7, 56.7, 56.4, 52.7, 47.8, 29.8, 23.0, 22.8, 21.7; MS (ESI pos ion) *m/z*: calcd for $C_{29}H_{25}F_2N_3O_5$ 533.2, found 534.2 $[M + H]^+$; HR-MS (ESI) Calcd for $C_{29}H_{26}F_2N_3O_5$ 534.1841 $[M + H]^+$, found 534.1850.

3-Chloro-N-(4-((6,7-dimethoxyquinolin-4-yl)oxy)-3-fluorophenyl)-1-(4-fluorophenyl)-2-oxopiperidine-3-carboxamide (**20b**, from **14** and **4**): 54% yield; ^{1}H-NMR (600 MHz, $CDCl_3$) δ 10.05 (s, 1H, NH), 8.48 (d, 1H, *J* = 5.4 Hz, ArH), 7.79 (dd, 1H, *J* = 12.0, 2.5 Hz, ArH), 7.57 (s, 1H, ArH), 7.44 (s, 1H, ArH), 7.29–7.23 (m, 4H, ArH), 7.20 (t, 1H, *J* = 8.6 Hz, ArH), 7.13 (t, 2H, *J* = 8.4 Hz, ArH), 6.39 (d, 1H, *J* = 5.3 Hz, ArH), 4.05 (s, 3H, OCH_3), 4.04 (s, 3H, OCH_3), 3.80 (ddd, 1H, *J* = 14.5, 10.3, 4.7 Hz, CH*H*), 3.74–3.66 (m, 1H, CHH), 2.97–2.83 (m, 1H, CHH), 2.67–2.56 (m, 1H, CHH), 2.45–2.34 (m, 1H, CHH), 2.15–2.07 (m, 1H, CHH); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 166.9, 164.8, 162.6, 161.0, 160.2, 155.3, 153.6, 153.1, 149.8, 148.6, 146.7, 137.9, 137.7, 137.6, 136.3, 136.2, 127.9, 127.8, 123.8, 116.6, 116.5, 116.4, 115.6, 113.0, 109.8, 109.7, 109.6, 109.6, 107.8, 107.74, 99.5, 99.5, 64.3, 56.3, 56.2, 52.7, 33.8, 29.8, 19.5; MS (ESI pos ion) *m/z*: calcd for $C_{29}H_{24}ClF_2N_3O_5$ 567.1, found 568.1 $[M + H]^+$; HR-MS (ESI) Calcd for $C_{29}H_{25}ClF_2N_3O_5$ 568.1451 $[M + H]^+$, found 568.1461.

N-(4-((6,7-dimethoxyquinolin-4-yl)oxy)-3-fluorophenyl)-1-(4-fluorophenyl)-3-methyl-2-oxopiperidine-3-carboxamide (**20c**, from **14** and **6a**): 68% yield; ^{1}H-NMR (600 MHz, $CDCl_3$) δ 10.01 (s, 1H, NH), 8.47 (d, 1H, *J* = 5.3 Hz, ArH), 7.82 (dd, 1H, *J* = 12.2, 2.5 Hz, ArH), 7.58 (s, 1H, ArH), 7.42 (s, 1H, ArH), 7.25–7.20 (m, 3H, ArH), 7.19 (t, 1H, *J* = 8.5 Hz, ArH), 7.15–7.11 (m, 2H, ArH), 6.38 (d, 1H, *J* = 5.1 Hz, ArH), 4.06 (s, 3H, OCH_3), 4.04 (s, 3H, OCH_3), 3.71–3.62 (m, 2H, NCH_2), 2.83–2.76 (m, 1H, CHH), 2.07–1.97 (m, 2H, CH_2), 1.87–1.81 (m, 1H, CHH), 1.71 (s, 3H, CH_3); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 173.7, 170.1, 162.4, 160.8, 160.2, 153.7, 153.0, 149.7, 148.9, 146.9, 138.7, 137.1, 128.2, 123.8, 116.6, 116.5, 116.0, 116.0, 115.6, 109.2, 107.9, 102.3, 99.5, 56.3, 56.2, 53.1, 50.5, 30.9, 27.7, 20.7, 14.3; MS (ESI pos ion) *m/z*: calcd for $C_{30}H_{27}F_2N_3O_5$ 547.2, found 548.2 $[M + H]^+$; HR-MS (ESI) Calcd for $C_{30}H_{28}F_2N_3O_5$ 548.1997 $[M + H]^+$, found 548.2012.

N-(4-((6,7-dimethoxyquinolin-4-yl)oxy)-3-fluorophenyl)-3-ethyl-1-(4-fluorophenyl)-2-oxopiperidine-3-carboxamide (**20d**, from **14** and **6b**): 58% yield; ^{1}H-NMR (600 MHz, $CDCl_3$) δ 9.99 (s, 1H, NH), 8.47 (d, 1H, *J* = 5.4 Hz, ArH), 7.82 (dd, 1H, *J* = 12.1, 2.4 Hz, ArH), 7.58 (s, 1H, ArH), 7.44 (s, 1H, ArH), 7.24–7.16 (m, 4H, ArH), 7.15–7.11 (m, 2H, ArH), 6.39 (d, 1H, *J* = 5.2 Hz, ArH), 4.06 (s, 3H, OCH_3), 4.05 (s, 3H, OCH_3), 3.71–3.59 (m, 2H, NCH_2), 2.81 (1H, ddd, *J* = 13.9, 6.4, 2.7 Hz, CHH), 2.22–2.14 (m, 1H, CHH), 2.12–1.93 (m, 4H, CH_2CH_3), 1.82–1.76 (m, 1H, CHH), 1.02 (t, 3H, *J* = 7.4 Hz, CH_2CH_3); ^{13}C-NMR(150 MHz, $CDCl_3$) δ 173.3, 169.0, 165.8, 162.5, 160.4, 155.3, 153.7, 153.1, 149.7, 148.7, 146.8, 138.8, 137.1, 137.1, 137.0, 136.9, 128.3, 115.7, 107.8, 102.3, 99.6, 56.3, 55.2, 53.1, 33.8, 27.0, 20.8; MS (ESI pos ion) *m/z*: calcd for $C_{31}H_{29}F_2N_3O_5$ 561.2, found 562.2 $[M + H]^+$; HR-MS (ESI) Calcd for $C_{31}H_{30}F_2N_3O_5$ 562.2154 $[M + H]^+$, found 562.2160.

N-(4-((6,7-dimethoxyquinolin-4-yl)oxy)-3-fluorophenyl)-3-butyl-1-(4-fluorophenyl)-2-oxopiperidine-3-carboxamide **(20e**, from **14** and **6c**): 64% yield; ^{1}H-NMR (600 MHz, $CDCl_3$) δ 9.98 (s, 1H, NH), 8.47 (d, 1H, *J* = 5.4 Hz, ArH), 7.82 (dd, 1H, *J* = 12.5, 2.6 Hz, ArH), 7.58 (s, 1H, ArH), 7.42 (s, 1H, ArH), 7.25–7.16 (m, 4H, ArH), 7.16–7.11 (m, 2H, ArH), 6.39 (d, 1H, *J* = 5.1 Hz, ArH), 4.06 (s, 3H, OCH_3), 4.05 (s, 3H, OCH_3), 3.71–3.59 (m, 2H, NCH_2), 2.82 (ddd, 1H, *J* = 14.0, 6.1, 2.7 Hz, CHH), 2.13–1.92 (m, 4H, 2 × CH_2), 1.84–1.77 (m, 1H, CHH), 1.42–1.28 (m, 4H, 2 × CH_2), 0.95–0.89 (m, 3H, CH_2CH_3); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 173.3, 169.1, 160.3, 153.0, 149.7, 148.9, 147.0, 138.8, 137.1, 128.3, 128.2, 123.8, 116.7, 116.5, 116.0, 115.7, 109.4, 108.0, 102.3, 99.6, 56.3, 56.3, 54.9, 53.1, 40.5, 27.5, 27.0, 23.0, 20.9, 14.1; MS (ESI pos ion) *m/z*: calcd for $C_{33}H_{33}F_2N_3O_5$ 589.2, found 590.2 $[M + H]^+$; HR-MS (ESI) Calcd for $C_{33}H_{34}F_2N_3O_5$ 590.2467 $[M + H]^+$, found 590.2478.

3.2.4. Preparation of **16a** and **16b**

To amide **15a** or **15b** (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 **16a**–**b**.

N-(4-((2-amino-3-chloropyridin-4-yl)oxy)-3-fluorophenyl)-1-(4-fluorophenyl)-2-oxopiperidine-3-carboxamide (**16a**). 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, CHH), 2.21–2.15 (m, 1H, CHH), 2.10–2.05 (m, 1H, CHH), 2.04–1.98 (m, 1H, CHH); ^{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, 128.2, 128.2, 123.3, 116.9, 116.8, 116.7, 116.6, 116.6, 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 $[M + H]^+$; HR-MS (ESI) Calcd for $C_{23}H_{20}ClF_2N_4O_3$ 473.1192 $[M + H]^+$, found 473.1214.

N-(4-((2-amino-3-chloropyridin-4-yl)oxy)-3-fluorophenyl)-3-chloro-1-(4-fluorophenyl)-2-oxo-piperidine-3-carboxamide (**16b**). 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 (br s, 2H, NH2), 3.84–3.74 (m, 1H, CHH), 3.74–3.66 (m, 1H, CHH), 2.94–2.82 (m, 1H, CHH), 2.63–2.57 (m, 1H, CHH), 2.43–2.34 (m, 1H, CHH), 2.14–2.09 (m, 1H, CHH); ^{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 $[M + H]^+$; HR-MS (ESI) Calcd for $C_{23}H_{19}Cl_2F_2N_4O_3$ 507.0802 $[M + H]^+$, found 507.0816.

3.2.5. Preparation of **19a** and **19b**

Compound **18a** or **18b** (40 mg, 0.07 mmol) was dissolved in TFA and heated to reflux for 6 h. The solvent was removed and the residue was purified by column chromatography, giving the title compound **19a** or **19b** as a pale yellow solid.

N-(4-((2-aminopyrimidin-4-yl)oxy)-3-fluorophenyl)-1-(4-fluorophenyl)-2-oxopiperidine-3-carboxamide (**19a**). 71% yield; ^{1}H-NMR (600 MHz, $CDCl_3$) δ 10.20 (s, 1 H, NH), 7.95 (s, 1H, ArH), 7.75 (d, 1H, *J* = 11.8 Hz, ArH), 7.21 (dd, 2H, *J* = 8.7, 4.8 Hz, ArH), 7.18 (d, 1H, *J* = 8.6 Hz, ArH), 7.13 (t, 2H, *J* = 8.2 Hz, ArH), 7.07 (t, 1H, *J* = 8.4 Hz, ArH), 6.49 (s, 1H, ArH), 5.77 (s, 1H, NH), 3.67 (q, 2H, *J* = 6.0 Hz, NCH_2), 3.57 (s, 1H, CH), 2.57–2.46 (m, 1H, CHH), 2.25–2.16 (m, 1H, CHH), 2.13–1.95 (m, 2H, CH_2); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 166.3, 162.5, 160.9, 154.4, 152.8, 138.4, 137.8, 134.1, 128.2, 128.1, 123.1, 116.7, 116.5, 115.6, 108.9, 108.7, 52.7, 47.7, 29.8, 23.0, 21.7; MS (ESI pos ion) *m/z*: calcd for $C_{22}H_{19}F_2N_5O_3$ 439.1, found 440.1 $[M + H]^+$; HR-MS (ESI) Calcd for $C_{22}H_{20}F_2N_5O_3$ 440.1534 $[M + H]^+$, found 440.1528.

N-(4-((2-aminopyrimidin-4-yl)oxy)-3-fluorophenyl)-3-chloro-1-(4-fluorophenyl)-2-oxopiperidine-3-carboxamide (**19b**). 87% yield; ^{1}H-NMR (600 MHz, $CDCl_3$) δ 10.04 (s, 1H, NH), 7.96 (d, 1H, *J* = 6.7 Hz, ArH), 7.72 (dd, 1H, *J* = 11.8, 2.5 Hz, ArH), 7.25–7.18 (m, 3H, ArH), 7.16–7.06 (m, 3H, ArH), 6.47 (d, 1H, *J* = 6.7 Hz, ArH), 3.79 (ddd, 1H, *J* = 12.4, 10.1, 4.7 Hz, CHH), 3.69 (dt, 1H, *J* = 11.3, 4.5 Hz, CHH), 2.88 (ddd, 1H, *J* = 14.9, 11.6, 3.1 Hz, CHH), 2.63–2.49 (m, 1H, CHH), 2.44–2.31 (m, 1H, CHH), 2.15–2.05 (m, 1H, CHH); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 171.2, 166.8, 164.9, 162.6, 161.0, 154.5, 152.8, 137.9, 137.9, 137.2, 137.1, 134.8, 134.7, 127.9, 127.9, 127.8, 123.3, 116.7, 116.6, 116.0,

109.3, 109.2, 109.1, 109.1, 100.0, 99.0, 64.4, 52.7, 33.8, 19.4; MS (ESI pos ion) *m/z*: calcd for $C_{22}H_{18}ClF_2N_5O_3$ 473.1, found 474.0 $[M + H]^+$; HR-MS (ESI) Calcd for $C_{22}H_{19}ClF_2N_5O_3$ 474.1145 $[M + H]^+$, found 474.1151.

3.3. Biology

3.3.1. c-Met Kinase Assay

The effects of indicated compound on the activities of c-Met kinases were determined using enzyme-linked immunosorbent assays (ELISAs) with purified recombinant proteins. Briefly, 20 μg/mL poly $(Glu,Tyr)_{4:1}$ (Sigma, St. Louis, MO, USA) was pre-coated in 96-well plates as a 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; 1 μL of various concentrations of indicated compound 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 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 3 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 as the color changed, and the plate was analyzed using a multi-well spectrophotometer (SpectraMAX 190, Molecular Devices, Sunnyvale, CA, USA) 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 in two separate experiments.

3.3.2. Cell Proliferation Assay

Cells were seeded in 96-well tissue culture plates. On the next day, the cells were exposed to various concentrations of compounds and further cultured for 72 h. Cell proliferation was then determined using sulforhodamine B (SRB, Sigma, St. Louis, MO, USA). The IC_{50} values were calculated by concentration-response curve fitting using the four-parameter method.

4. Conclusions

In summary, a series of compounds based upon the 3-carboxylpiperidin-2-one scaffold were designed, synthesized and evaluated for their c-Met kinase inhibition and cytotoxicity against MKN45 cancer cell lines. Five compounds (**16b**, **20b**–**e**) exhibited moderate to excellent activity against c-Met kinase, with IC_{50} values ranging from 8.6–81 nM. Moreover, four compounds (**20b**–**e**) showed potent inhibitory activity against MKN45 cell proliferation, with IC_{50}s ranging from 0.57–16 μM. Further structure-activity relationship studies are under way in our laboratory and will be reported in due course.

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Conflicts of Interest

The authors declare no conflict of interest.

References

1. Gherardi, E.; Birchmeier, W.; Birchmeier, C.; Vande Woude, G. Targeting MET in cancer: Rationale and progress. *Nat. Rev. Cancer* **2012**, *12*, 89–103.
2. Benvenuti, S.; Comoglio, P.M. The MET receptor tyrosine kinase in invasion and metastasis. *J. Cell. Physiol.* **2007**, *213*, 316–325.
3. Cappuzzo, F.; Marchetti, A.; Skokan, M.; Rossi, E.; Gajapathy, S.; Felicioni, L.; del Grammastro, M.; Sciarrotta, M.G.; Buttitta, F.; Incarbone, M.; *et al.* Increased MET gene copy number negatively affects survival of surgically resected non-small-cell lung cancer patients. *J. Clin. Oncol.* **2009**, *27*, 1667–1674.
4. Okuda, K.; Sasaki, H.; Yukiue, H.; Yano, M.; Fujii, Y. Met gene copy number predicts the prognosis for completely resected non-small cell lung cancer. *Cancer Sci.* **2008**, *99*, 2280–2285.
5. Toiyama, Y.; Miki, C.; Inoue, Y.; Okugawa, Y.; Tanaka, K.; Kusunoki, M. Serum hepatocyte growth factor as a prognostic marker for stage II or III colorectal cancer patients. *Int. J. Cancer* **2009**, *125*, 1657–1662.
6. Corso, S.; Comoglio, P.M.; Giordano, S. Cancer therapy: Can the challenge be MET? *Trends Mol. Med.* **2005**, *11*, 284–292.
7. Birchmeier, C.; Birchmeier, W.; Gherardi, E.; Vande Woude, G.F. Met, metastasis, motility and more. *Nat. Rev. Mol. Cell Biol.* **2003**, *4*, 915–925.
8. Christensen, J.; Burrows, J.; Salgia, R. c-Met as a target for human cancer and characterization of inhibitors for therapeutic intervention. *Cancer Lett*. **2005**, *225*, 1−26.
9. Abidoye, O.; Murukurthy, N.; Salgia, R. Review of clinic trials: Agents targeting c-Met. *Rev. Recent Clin. Trials* **2007**, *2*, 143−147.
10. Eder, J.P.; Vande Woude, G.F.; Boerner, S.A.; LoRusso, P.M. Novel therapeutic inhibitors of the c-Met signaling pathway in cancer. *Clin. Cancer Res.* **2009**, *15*, 2207−2214.
11. Fujiwara, Y.; Senga, T.; Nishitoba, T.; Osawa, T.; Miwa, A.; Nakamura, K. Quinoline Derivative and Quinazoline Derivative Inhibiting Self-phosphorylation of Hepatocytus Proliferator Receptor, and Medicinal Composition Containing the Same. WO03000660 A1, 3 January 2003.
12. Mannoin, M.; Raeppel, S.; Claridge, S.; Zhou, N.; Savedra, O.; Isakovic, L.; Zhan, L.; Gaudette, F.; Raeppel, F.; Déziel, R.; *et al*. *N*-(4-(6,7-Disubstituted-quinolin-4-yloxy)-3-fluorophenyl)-2-oxo-3-phenylimidazolidine-1-carboxamides: A novel series of dual c-Met/VEGFR2 receptor tyrosine kinase inhibitors. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 6552–6556.

13. Claridge, S.; Raeppel, F.; Granger, M.-C.; Bernstein, N.; Saavedra, O.; Zhan, L.; Llewellyn, D.; Wahhab, A.; Deziel, R.; Rahil, J.; *et al*. Discovery of a novel and potent series of thieno[3,2-*b*]pyridine-based inhibitors of c-Met and VEGFR2 tyrosine kinases. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 2793–2798.
14. Raeppel, S.; Claridge, S.; Saavedra, O.; Gaudette, F.; Zhan, L.; Mannion, M.; Zhou, N.; Raeppel, F.; Granger, M.-C.; Isakovic, L.; *et al*. *N*-(3-Fluoro-4-(2-arylthieno[3,2-*b*]pyridin-7-yloxy)phenyl)-2-oxo-3-phenylimidazolidine-1-carboxamides: A novel series of dual c-Met/VEGFR2 receptor tyrosine kinase inhibitors. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 1323–1328.
15. Raeppel, S.; Gaudette, F.; Mannion, M.; Claridge, S.; Saavedra, O.; Isakovic, L.; Déziel, R.; Beaulieu, N.; Beaulieu, C.; Dupont, I.; *et al*. Identification of a novel series of potent RON receptor tyrosine kinase inhibitors. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 2745–2749.
16. Kim, K.S.; Zhang, L.; Schmidt, R.; Cai, Z.-W.; Wei, D.; Williams, D.K.; Lombardo, L.J.; Trainor, G.L.; Xie, D.; Zhang, Y.; *et al*. Discovery of pyrrolopyridine−pyridone based inhibitors of Met kinase: Synthesis, X-ray crystallographic analysis, and biological activities *J. Med. Chem.* **2008**, *51*, 5330–5341.
17. Schroeder, G.M.; An, Y.; Cai, Z.W.; Chen, X.T.; Clark, C.; Cornelius, L.A.; Dai, J.; Gullo-Brown, J.; Gupta, A.; Henley, B.; *et al.* Discovery of *N*-(4-(2-amino-3-chloropyridin-4-yloxy)-3-fluorophenyl)-4-ethoxy-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide (BMS-777607), a selective and orally efficacious inhibitor of the Met kinase superfamily. *J. Med. Chem.* **2009**, *52*, 1251−1254.
18. Zhao, A.; Gao, X.; Wang, Y.; Ai, J.; Wang, Y.; Chen, Y.; Geng, M.; Zhang, A. Discovery of novel c-Met kinase inhibitors bearing a thieno[2,3-*d*]pyrimidine or furo[2,3-*d*]pyrimidine scaffold. *Bioorg. Med. Chem.* **2011**, *19*, 3906–3918.
19. Matsumoto, S.; Miyamoto, N.; Hirayama, T.; Oki, H.; Okada, K.; Tawada, M.; Iwata, H.; Nakamura, K.; Ymasaki, S.; Miki, H.; *et al*. Structure-based design, synthesis, and evaluation of imidazo[1,2-*b*]pyridazine and imidazo[1,2-*a*]pyridine derivatives as novel dual c-Met and VEGFR2 kinase inhibitors. *Bioorg. Med. Chem.* **2013**, *21*, 7686–7698.
20. Schroeder, G.M.; Chen, X.-T.; Williams, D.K.; Nirschl, D.S.; Cai, Z.-W.; Wei, D.; Tokarski, J.S.; An, Y.; Sack, J.; Chen, Z.; *et al.* Identification of pyrrolo[2,1-*f*][1,2,4]triazine-based inhibitors of Met kinase. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 1945–1951.
21. Gaudette, F.; Raeppel, S.; Nguyen, H.; Beaulieu, N.; Beaulieu, C.; Dupont, I.; Macleod, A.R.; Besterman, J.M.; Vaisburg, A. Identification of potent and selective VEGFR receptor tyrosine kinase inhibitors having new amide isostere headgroups. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 848–852.
22. Qi, B.; Mi, B.; Zhai, X.; Xu, Z.; Zhang, X.; Tian, Z.; Gong, P. Discovery and optimization of novel 4-phenoxy-6,7-disubstituted quinolones possessing semicarbazones as c-Met kinase inhibitors. *Bioorg. Med. Chem.* **2013**, *21*, 5246–5260.
23. Williams, D.K.; Chen, X.-T.; Tarby, C.; Kaltenbach, R.; Cai, Z.-W.; Tokarski, J.S.; An, Y.; Sack, J.S.; Wautlet, B.; Gullo-Brown, J.; *et al*. Design, synthesis and structure-activity relationships of novel biarylamine-based Met kinase inhibitors. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 2998–3002.

24. Li, S.; Zhao, Y.; Wang, K.; Gao, Y.; Han, J.; Cui, B.; Gong, P. Discovery of novel 4-(2-fluorophenoxy)quinoline derivatives bearing 4-oxo-1,4-dihydrocinnoline-3-carboxamide moiety as c-Met kinase inhibitors. *Bioorg. Med. Chem.* **2013**, *21*, 2843–2855.
25. Norman, M.H.; Liu, L.; Lee, M.; Xi, N.; Fellows, I.; D'Angelo, N.D.; Dominguez, C.; Rex, K.; Bellon, S.F.; Kim, T.-S.; *et al*. Structure-based design of novel class II c-Met inhibitors: 1. Identification of pyrazolone-based derivatives. *J. Med. Chem.* **2012**, *55*, 1858–1867.
26. D'Angelo, N.D.; Bellon, S.F.; Booker, S.K.; Cheng, Y.; Coxon, A.; Dominguez, C.; Fellows, I.; Hoffman, D.; Hungate, R.; Kaplan-Lefko, P.; *et al*. Design, synthesis, and biological evaluation of potent c-Met inhibitors. *J. Med. Chem.* **2008**, *51*, 5766–5779.
27. Friesner, R.A.; Murphy, R.B.; Repasky, M.P.; Frye, L.L.; Greenwood, J.R.; Halgren, T.A.; Sanschagrin, P.C.; Mainz, D.T. Extra precision glide: Docking and scoring incorporating a model of hydrophobic enclosure for protein−ligand complexes. *J. Med. Chem.* **2006**, *49*, 6177−6196.

Sample Availability: Samples of the compounds **15**–**20** are available from the authors.