Available online at www.sciencedirect.com
ScienceDirect
European Journal of Medicinal Chemistry 43 (2008) 1321–1329
EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY
http://www.elsevier.com/locate/ejmech

Short communication

Structure activity relationships of quinoline-containing c-Met inhibitors

Pei-Pei Kung*, Lee Funk, Jerry Meng, Gordon Alton, Ellen Padrique, Barbara Mroczkowski

Pfizer Global Research and Development, La Jolla Laboratories, 10770 Science Center Drive, San Diego, CA 92121, USA

Received 13 May 2007; received in revised form 26 July 2007; accepted 9 August 2007
Available online 11 September 2007

Abstract

A series of quinoline-containing c-Met inhibitors were prepared and studied. Chemistry was developed to introduce a pyridyl moiety onto the 2-aryl ring present in a lead molecule which mitigated the potential for quinone formation relative to the original compound. The study also assessed the importance of an acylthiourea moiety present in the lead structure for effective binding to the c-Met protein ATP site.

Keywords: c-Met; Quinoline

1. Introduction

c-Met signaling is implicated in a wide variety of human malignancies, including colon, gastric, bladder, breast, ovarian, pancreatic, kidney, liver, lung, and prostate cancers [1,2].

The MET oncogene was isolated from a human osteogenic sarcoma cell line [3] and analysis of the full-length Met proto-oncogenic coding sequence revealed structural features of a membrane spanning receptor tyrosine kinase (TK) [3]. Upon hepatocyte growth factor (HGF) and scattering factor (SF) binding, c-Met phosphorylation occurs on two tyrosine residues (Y1234 and Y1235) within the activation loop of the TK domain which regulates kinase activity [4,5]. Phosphorylation on two other tyrosine residues near the COOH terminus (Y1349 and Y1356) forms a multifunctional docking site that recruits intracellular adaptors leading to downstream signaling [4,5] and cell proliferation. Therefore, c-Met is an important target for inhibiting tumor metastasis and angiogenesis.

Literature reported c-Met inhibitors **1** and **2** (Table 1) exhibit very potent c-Met inhibition properties [6] but also contain several structural motifs that may be linked to toxicity, and/or chemical instability (e.g., the masked *para*-hydroxyaniline and thiourea moieties) [7,8]. We were intrigued by the reported inhibitory potency of **1** and **2** and sought to synthesize analogs of this class of compounds that lacked either or both structural concerns. Below, we detail the results of our efforts.

Initially, compound **3** was synthesized to examine whether a 2-amino-4-hydroxypyridine moiety could replace the masked *para*-hydroxyaniline present in structures **1** and **2**. Encouragingly, compound **3** displayed similar c-Met inhibitory properties as compared with the lead molecules (Table 1). We therefore retained the central 2-amino-4-hydroxypyridine moiety in our subsequent inhibitor designs in order to mitigate the risk of metabolically forming a reactive (and potentially toxic) quinone species [8a,8b].

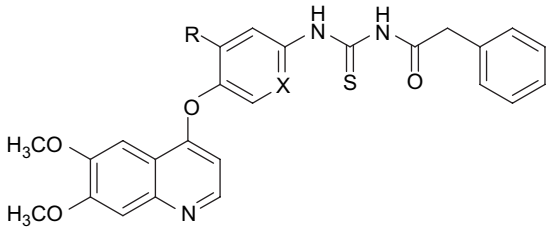
2. Chemistry

The syntheses of compounds **3** and **7–14** are depicted in Scheme 1. These compounds could be prepared in moderate to excellent yields by derivatization of amino-pyridine **6** which in turn, was prepared in two steps from the known [9a,9b,10] chloro-quinoline **4** [11]. The synthetic route used to convert **6**

* Corresponding author. Tel.: +1 858 526 4867; fax: +1 858 526 4447.
E-mail address: peipeikung@pfizer.com (P.-P. Kung).

0223-5234/$ - see front matter © 2007 Elsevier Masson SAS. All rights reserved.
doi:10.1016/j.ejmech.2007.08.011

Table 1



Compound no.	R	X	K_i (μM)
1	F	C	0.001
2	H	C	0.002
3	H	N	0.003

to compound **3** followed a literature procedure with minor modification [6]. Alternatively, compound **6** was coupled with various carboxylic acids or acyl chlorides (the former requiring the inclusion of a carbodiimide activating agent) to provide inhibitors **7**–**9**. The reaction of compound **6** with various commercially available isocyanates afforded the urea derivatives (compounds **10**–**14**).

In contrast, the synthesis of compound **16** from **6** was achieved through a three-step process including (i) formation of the isocyanate derivative of **6**, (ii) trapping with *tert*-butyl-1-piperazine-carboxylate (to form compound **15**), and (iii) removal of the Boc protecting group under acidic conditions (Scheme 2).

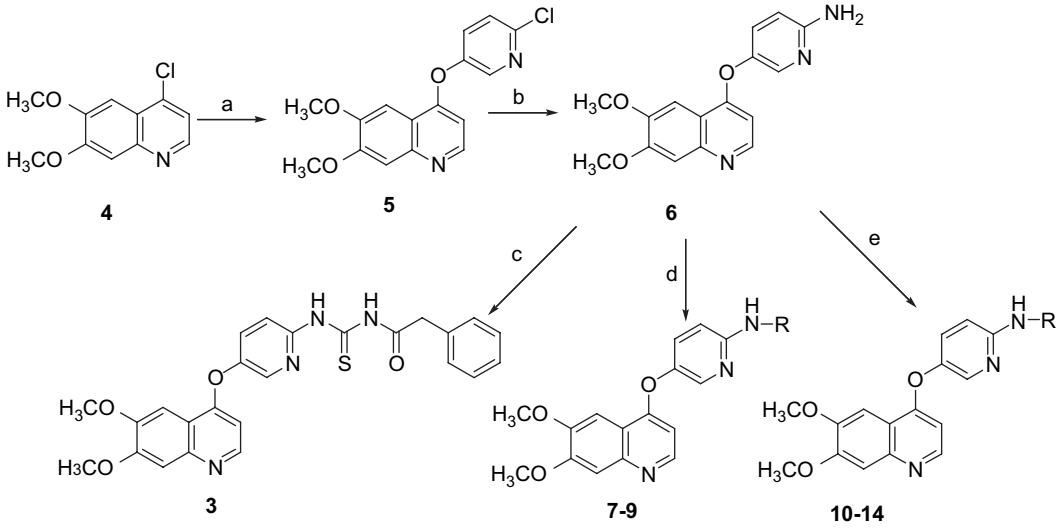
The syntheses of compounds **19** and **20** are depicted in Scheme 3. Compound **6** was treated with ethyl isocyanatoacetate to give compound **17** which was then hydrolyzed to afford **18**. Derivatization of **18** via HATU-mediated amide formation then provided compounds **19** and **20**. The synthesis of compounds **22** and **23** are depicted in Scheme 4 and involve the reaction of **6** with chloroacetylisocyanate (to give the intermediate **21**) followed by alkylation of the appropriate amines in the presence of diisopropylethylamine (50–80% yield in two steps).

3. Results and discussion

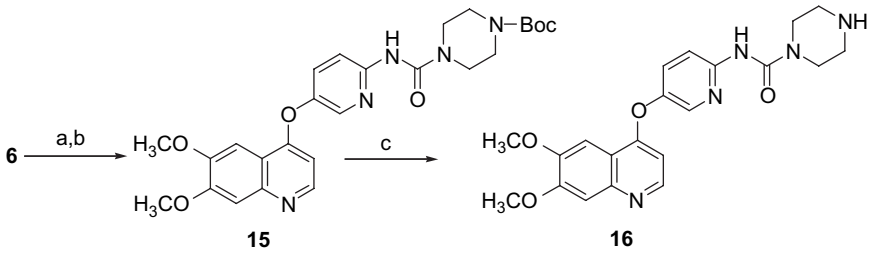
A key intermediate for our SAR exploration (compound **6**, Table 2) was screened in the c-Met inhibition assay to explore the importance of the acylthiourea portion of compound **3**. Compound **6** displayed drastically reduced inhibitory potency compared with **3** and was also significantly weaker than its acetylated analog (compound **7**, Table 2). Introducing a benzylic moiety improved the inhibitory potency 17-fold (compare compound **8** with compound **7**) suggesting the presence of a c-Met hydrophobic binding pocket in the vicinity of the inhibitor acyl group. A pyridyl moiety was also examined to replace the phenyl ring present in compound **8** but the new analog (**9**) lost significant inhibitory potency (Table 2).

In addition to the *N*-acyl derivatives depicted in Table 2, we also examined a series of urea-containing c-Met inhibitors (Table 3). The tertiary urea (compound **16**) did not significantly inhibit c-Met activity at the highest concentration examined (30 μM). In contrast, a secondary urea (compound **10**) displayed moderate c-Met inhibition properties. This result suggested the terminal urea NH might act as a hydrogen bond donor when interacting with the c-Met enzyme. Accordingly, we examined several other inhibitors which retained this structural feature in their design (compounds **11**, **12**, **19**, **20**, Table 3). All of these compounds displayed moderately potent c-Met inhibition activity but were significantly less active than inhibitors **1**–**3** (Table 1). We therefore introduced a second acyl group to our inhibitor design to more closely mimic the original lead structures. Compounds **22** and **23** improved c-Met inhibition potency several fold relative to other urea-containing compounds (e.g., compounds **19** and **20**, Table 3), indicating the importance of the second carbonyl group to the inhibitor design.

Encouraged by these results, we synthesized two additional acylurea inhibitors which incorporated terminal benzoyl substituents (compounds **13** and **14**, Table 3). Both molecules



Scheme 1. Reagents and conditions: (a) 2-chloro-5-hydroxypyridine, chlorobenzene, 140 °C, 12 h, 65%; (b) $LiN(TMS)_2$, $Pd_2(dba)_3$, 2-(dicyclohexylphosphino)-biphenyl, 80 °C, 12 h, HCl (aq), 2 h, Na_2CO_3, 59%; (c) ammonium thiocyanate, phenylacetylchloride, chlorobenzene, 105 °C, 3 h; 70 °C, 3 h, 23%; (d) acyl chlorides, DIEA, CH_2Cl_2, 23 °C, 12 h, 57% (**7**); 60% (**8**) or carboxylic acid, CDI, DIEA, CH_2Cl_2, 23 °C, 12 h, 34% (**9**); (e) isocyanates, CH_2Cl_2, 23 °C, 12 h, 30–95%.



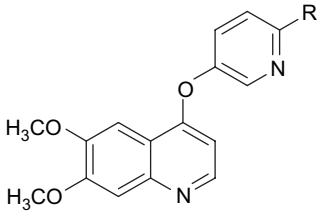
Scheme 2. Reagents and conditions: (a) triphosgene, CH_2Cl_2, DIEA, 40 °C; (b) *tert*-butyl-1-piperazine-carboxylate, CH_2Cl_2, 23 °C, 12 h, 6% (two steps); (c) HCl, 1,4-dioxane, 23 °C, 12 h, 17%.

exhibited improved c-Met inhibition properties relative to other compounds described in this work with K_i values <100 nM. However, the potency of these compounds was at least 10-fold weaker than that exhibited by compounds **1**–**3**, indicating the importance of the thiourea moiety and/or the terminal benzyl substituent present in these molecules for optimal c-Met recognition.

4. Conclusion

In summary, a variety of 5-[(6,7-dimethoxyquinolin-4-yl)oxy]pyridin-2-amine derivatives were explored as novel c-Met inhibitors. The acylthiourea moiety was shown to be important for the effective binding to the c-Met protein.

Table 2



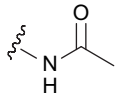
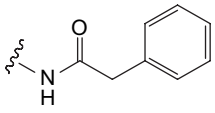
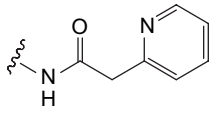
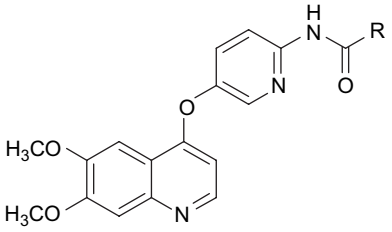
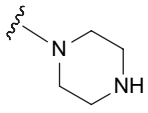
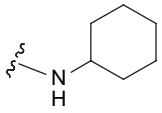
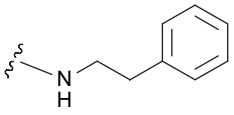
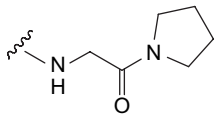
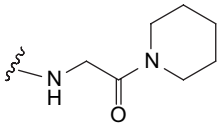
Compound no.	R	K_i (μM)
6		2% @ 1 μM
7		7
8		0.4
9		8

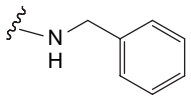
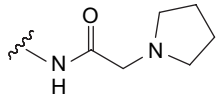
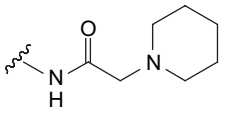
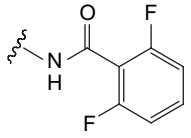
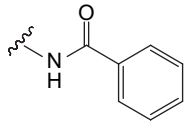
Table 3



Compound no.	R	K_i (μM)
16		>30
10		5
11		1
19		6.4
20		2.8

(*continued on next page*)

Table 3 (*continued*)

Compound no.	R	K_i (μM)
12		1
22		0.5
23		0.5
13		0.08
14		0.05

5. Experimental section

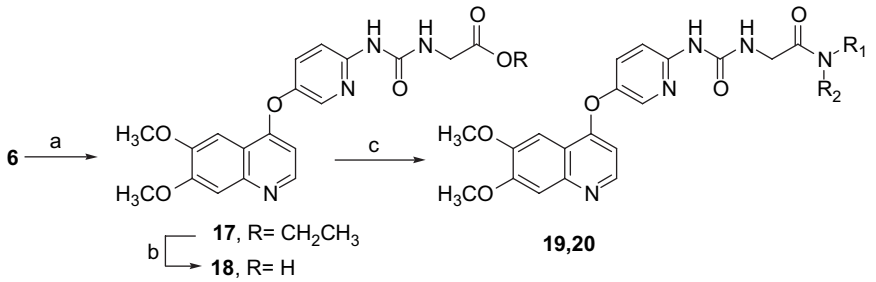
5.1. Chemistry

General methods: The structures of the compounds of the following examples were confirmed by one or more of the following: proton magnetic resonance spectroscopy, liquid chromatography–mass spectrometry, and elemental microanalysis. Proton magnetic resonance (^{1}H NMR) spectra were determined using either a Varian UNITY plus 300 or a Brucker 400. Chemical shifts are reported in parts per million (ppm, δ) downfield from an internal tetramethylsilane standard. Alternatively, ^{1}H NMR spectra were referenced to residual protic solvent signals as follows: $CHCl_3 = 7.26$ ppm; DMSO = 2.49 ppm, $CH_3OH = 3.40$ ppm. Peak multiplicities are designated as follows: s, singlet; d, doublet; dd, doublet of doublets; t, triplet; q, quartet; br, broad resonance; m, multiplet. Coupling constants are given in Hertz. Elemental microanalyses were performed by Atlantic Microlab Inc., Norcross, GA and gave results for the elements stated within −0.4% of the theoretical values. Flash column chromatography was performed using silica gel 60 (Merk Art 9385). Analytical thin layer chromatography (TLC) was performed using precoated sheets of Silica 60 F_{254} (Merk Art 5719). Melting points were determined on a MelTemp apparatus and are uncorrected. All commercial reagents were used as received from their perspective supplier.

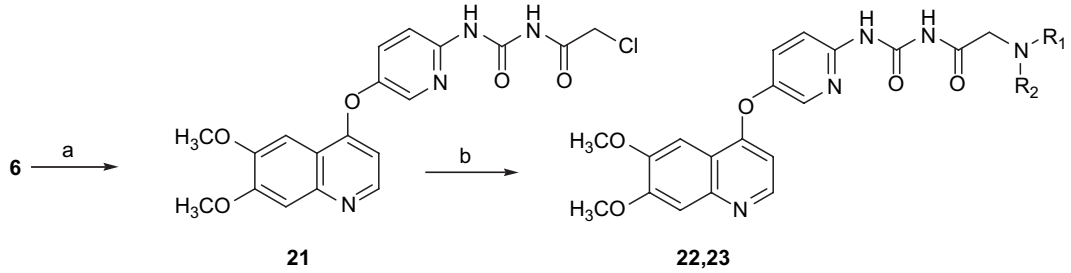
DMF refers to *N*,*N*-dimethylformamide. DMSO refers to dimethylsulfoxide. HMPA refers to hexamethylphosphorous triamide. Other abbreviations include: CH_3OH (methanol), DCM (dichloromethane), EtOH (ethanol), EtOAc (ethyl acetate), HCl (hydrochloric acid), AcOH (acetic acid), EDC [1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride], DCC (dicyclohexyl-carbodiimide).

5.1.1. *N-[({5-[(6,7-Dimethoxyquinolin-4-yl)oxy]pyridin-2-yl}amino)carbonothioyl]-2-phenylacetamide (**3**)*

Ammonium thiocyanate (40 mg, 0.52 mmol) was added to a stirred solution of phenylacetylchloride (0.07 mL, 0.47 mmol) in chlorobenzene (2 mL). The resulting solution was heated to 105 °C for 3 h. Compound **6** (153.7 mg, 0.52 mmol) was added and the resulting mixture was stirred at 70 °C for 3 h. Water (50 mL) was added to the reaction mixture to quench the reaction. EtOAc (2 × 50 mL) was added to extract the aqueous solution. The combined organic layers were dried, filtered and evaporated to get a brown yellow oil. The residue was purified by silica gel chromatography (eluting with 0 → 5% CH_3OH in EtOAc) to give compound **3** as a white foam (57.5 mg; 0.12 mmol; 23.3% yield); MS (APCI) $(M + H)^+$ 475. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 3.77 (s, 2H) 4.05 (s, 3H) 4.06 (s, 3H) 6.49 (d, $J = 5.3$ Hz, 1H) 7.27 (s, 1H) 7.33 (m, 2H) 7.40 (m, 3H) 7.51 (s, 1H) 7.57 (dd, $J = 9.0$, 2.9 Hz, 1H) 8.35 (d, $J = 2.8$ Hz, 1H) 8.53 (d, $J = 5.1$ Hz, 1H) 8.61 (s, 1H) 8.88 (d, $J = 9.1$ Hz, 1H) 12.92 (s, 1H).



Scheme 3. Reagents and conditions: (a) $OCNCH_2COOC_2H_5$, CH_2Cl_2, 23 °C, 94%; (b) NaOH, EtOH, 23 °C, 3 h, 94%; (c) amines (cyclopentylamine for **19** and cyclohexylamine for **20**), HATU, DIEA, DMF, 23 °C, 12 h, 27% (**19**), 18% (**20**).



Scheme 4. Reagents and conditions: (a) $OCN(CO)CH_2Cl$, CH_2Cl_2, 23 °C, 68%; (b) amines (pyrrolidine for **22** and piperidine for **23**), DIEA, DMF, 23 °C, 12 h, 50% (**22**), 81% (**23**).

Anal. Calcd for $C_{25}H_{22}N_4O_4S \cdot 0.2CHCl_3 \cdot 0.75H_2O$: C, 59.13; H, 4.67; N, 10.94. Found: C, 59.20; H, 4.42; N, 10.76.

*5.1.2. 5-[(6,7-Dimethoxyquinolin-4-yl)oxy]pyridin-2-amine (**6**)*

*5.1.2.1. Synthesis of 4-[(6-chloropyridin-3-yl)oxy]-6,7-dimethoxyquinoline (**5**).* 2-Chloro 5-hydroxypyridine (310 mg, 2.3 mmol) and triethylamine (5 mL, 28.7 mmol) were added sequentially to a stirred solution of **4** (354 mg, 1.58 mmol) in chlorobenzene (3 mL). The resulting solution was heated to 140 °C for 12 h. The reaction mixture was quenched with H_2O (100 mL) and EtOAc (2 × 100 mL) was added to extract the aqueous solution. The combined organic layers were dried over Na_2SO_4 then concentrated under vacuum. The residue was purified by flash chromatography (eluting with 0 → 10% CH_3OH in EtOAc) to give compound **5** as a light brown yellow oil (324.2 mg; 1.02 mmol; 64.8% yield); MS (APCI) $(M + H)^+$ 317. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 4.00 (s, 3H) 4.01 (s, 3H) 6.45 (d, $J = 5.3$ Hz, 1H) 7.44 (m, 4H) 8.32 (d, $J = 2.5$ Hz, 1H) 8.51 (d, $J = 5.1$ Hz, 1H).

Anal. Calcd for $C_{16}H_{13}ClN_2O_3$: C, 60.67; H, 4.14; N, 8.84. Found: C, 60.25; H, 4.05; N, 8.66.

*5.1.2.2. Synthesis of 5-[(6,7-dimethoxyquinolin-4-yl)oxy]pyridin-2-amine (**6**).* Lithium hexamethyldisilazide (1.5 mL, 1.5 mmol), tris(dibenzylideneacetone) dipalladium(0) chloroform adduct (54 mg, 0.052 mmol), and 2-(dicyclohexylphosphino) biphenyl (45 mg, 0.12 mmol) were added sequentially to a stirred solution of compound **5** (324.4 mg, 1.02 mmol) in THF (3 mL) under a nitrogen atmosphere. The reaction mixture was heated at 80 °C for 12 h and then 2 M HCl (17 mL) was added and the mixture was stirred for an additional 2 h. The reaction mixture was neutralized with Na_2CO_3 and then extracted with THF (2 × 100 mL). The combined organic layers were dried over Na_2SO_4 then concentrated under vacuum. The residue was purified by silica gel chromatography (eluting with 10 → 20% CH_3OH in EtOAc) to afford compound **6** as a light brown foam (177.4 mg; 0.60 mmol; 59% yield); MS (APCI) $(M + H)^+$ 298. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 3.94 (s, 6H) 6.07 (s, 2H) 6.41 (d, $J = 5.1$ Hz, 1H) 6.56 (d, $J = 9.1$ Hz, 1H) 7.34–7.41 (m, 2H) 7.51 (s, 1H) 8.45 (d, $J = 5.3$ Hz, 1H).

Anal. Calcd for $C_{16}H_{15}N_3O_3 \cdot 0.3EtOAc$: C, 63.81; H, 5.42; N, 12.98. Found: C, 64.14; H, 5.14; N, 12.71.

*5.1.3. N-{5-[(6,7-Dimethoxyquinolin-4-yl)oxy]-pyridin-2-yl}acetamide (**7**)*

Acetyl chloride (55 mg, 0.66 mmol) and diisopropylethylamine (0.3 mL, 1.65 mmol) were added to a solution of 5-[(6,7-dimethoxyquinolin-4-yl)oxy]pyridin-2-amine (compound **6**, 97 mg, 0.33 mmol) in DCM (10 mL). The mixture was stirred at room temperature for 16 h. The reaction was quenched with H_2O (10 mL) and EtOAc (2 × 20 mL). The mixture was then purified by silica gel chromatography (eluting with 100% EtOAc) to afford compound **7** (80 mg, 0.24 mmol, 72% yield) as a tan solid; MS (*m/z*) (APCI) $[M + H]^+$ 340.2. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 2.12 (s, 3H) 3.94 (d, $J = 4.0$ Hz, 6H) 6.51 (d, $J = 5.3$ Hz, 1H) 7.41 (s, 1H) 7.53 (s, 1H) 7.77 (dd, $J = 9.1$, 3.1 Hz, 1H) 8.22 (d, $J = 9.1$ Hz, 1H) 8.34 (d, $J = 2.8$ Hz, 1H) 8.48 (d, $J = 5.3$ Hz, 1H) 10.67 (s, 1H).

Anal. Calcd for $C_{18}H_{17}N_3O_4 \cdot 0.25HOAc$: C, 62.71; H, 5.12; N, 11.86. Found: C, 62.71; H, 5.27; N, 11.67.

*5.1.4. N-[5-(6,7-Dimethoxy-quinolin-4-yloxy)-pyridin-2-yl]-2-phenyl-acetamide (**8**)*

Diisopropylamine (0.4 mL, 2 mmol) and phenylacetylchloride (250 mg, 1.5 mmol) were added to a solution of 5-[(6,7-dimethoxyquinolin-4-yl)oxy]pyridin-2-amine (compound **6**, 150 mg, 0.5 mmol) in 5 mL of DCM. The mixture was stirred at room temperature for 12 h under inert atmosphere. Water (20 mL) was added to the reaction mixture to quench the reaction. EtOAc (2 × 50 mL) was added to extract the aqueous solution. The combined organic layers were dried (Na_2SO_4), filtered and evaporated to get a yellow oil. The residue was purified by silica gel chromatography (eluting with 80 → 90% EtOAc in hexanes) to afford *N*-[5-(6,7-dimethoxyquinolin-4-yloxy)-pyridin-2-yl]-2-phenyl-acetamide (108.4 mg; 0.26 mmol; 52% yield); MS (APCI) $(M + H)^+$ 416. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 3.75 (s, 2H) 3.93 (s, 3H) 3.95 (s, 3H) 6.51 (d, $J = 5.31$ Hz, 1H) 7.21–7.39 (m, 5H) 7.40 (s, 1H) 7.52 (s, 1H) 7.78 (dd, $J = 9.1$, 2.78 Hz, 1H) 8.21 (d, $J = 9.1$ Hz, 1H) 8.36 (d, $J = 2.8$ Hz, 1H) 8.47 (d, $J = 5.3$ Hz, 1H) 10.93 (s, 1H).

Anal. Calcd for $C_{24}H_{21}N_3O_4 \cdot 0.5EtOAc$: C, 69.39; H, 5.10; N, 10.11. Found: C, 68.92; H, 5.13; N, 9.32.

*5.1.5. N-{5-[(6,7-Dimethoxyquinolin-4-yl)-oxy]pyridin-2-yl}-2-pyridin-2-ylacetamide (**9**)*

Diisopropylethylamine (0.2 mL, 1 mmol) and 1,1′-carbonyldiimidazole (200 mg, 1.2 mmol) were added to a solution

of 2-pyridylacetic acid hydrochloride in 2 mL of dichloroethane. The mixture was stirred at room temperature for 30 min under inert atmosphere. A solution of 5-[(6,7-dimethoxyquinolin-4-yl)oxy]pyridin-2-amine (compound **6**, 150 mg, 0.5 mmol) in 2 mL of dichloroethane was added. The mixture was heated at 80 °C for 12 h then cooled to ambient temperature. Water (50 mL) was added to the reaction mixture to quench the reaction. EtOAc (2 × 50 mL) was added to extract the aqueous solution. The combined organic layers were dried (Na_2SO_4), filtered and evaporated to get a tan oil. The residue was purified by silica gel chromatography (eluting with 10% CH_3OH in DCM) to afford compound **9** a yellow solid (70 mg; 0.168 mmol; 33.6% yield); MS (APCI) $(M+H)^+$ 417. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 4.01 (s, 1H) 4.02 (s, 3H) 4.03 (s, 3H) 4.07 (s, 1H) 6.97 (d, $J = 6.3$ Hz, 1H) 7.42–7.50 (m, 1H) 7.53–7.59 (m, 2H) 7.74 (s, 1H) 7.91 (t, $J = 9.1$, 3.0 Hz, 1H) 7.96 (t, $J = 7.2$ Hz, 1H) 8.26 (d, $J = 9.1$ Hz, 1H) 8.48 (d, $J = 3.0$ Hz, 1H) 8.61 (d, $J = 4.3$ Hz, 1H) 8.75–8.84 (m, $J = 6.3$ Hz, 1H) 11.10 (s, 1H).

Anal. Calcd for $C_{23}H_{20}N_4O_4 \cdot 2.5CF_3COOH \cdot 0.5H_2O$: C, 47.33; H, 3.33; N, 7.89. Found: C, 47.14; H, 3.36; N, 8.07.

*5.1.6. N-{5-[(6,7-Dimethoxyquinolin-4-yl)-oxy]pyridin-2-yl}piperazine-1-carboxamide (**16**)*

*5.1.6.1. Synthesis of 4-[5-(6,7-dimethoxy-quinolin-4-yloxy)-pyridin-2-ylcarbamoyl]-piperazine-1-carboxylic acid tert-butyl ester (**15**).* DIEA (1 mL, 6 mmol) and triphosgene (200 mg, 0.6 mmol) were added sequentially to a solution of 5-[(6,7-dimethoxyquinolin-4-yl)oxy]pyridin-2-amine (compound **6**, 600 mg, 2 mmol) in 10 mL of DCM under inert atmosphere. After stirring at room temperature for 12 h and subsequently heating at 40°C for 6 h, precipitate formed in the reaction mixture. This precipitate was filtered off and the filtrate was concentrated to an oil residue. *tert*-Butyl-1-piperazine-carboxylate (200 mg, 1.1 mmol) was added to this oil residue (350 mg, 1 mmol) in 10 mL of DCM. The mixture was heated at room temperature for 12 h then water (50 mL) was added to the reaction mixture to quench the reaction. EtOAc (2 × 50 mL) was added to extract the aqueous solution. The combined organic layers were dried (Na_2SO_4), filtered and evaporated to get a tan oil. The residue was purified by silica gel chromatography (eluting 80 → 90% EtOAc in hexanes) to afford compound **15** as a yellow oil (60 mg; 0.12 mmol; 6% yield); MS (APCI) $(M+H)^+$ 510. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.45 (s, 9H) 3.34–3.42 (m, 2H) 3.47–3.53 (m, $J = 5.4$, 5.4 Hz, 2H) 4.01 (s, 3H) 4.01–4.03 (m, 3H) 6.39 (d, $J = 5.3$ Hz, 1H) 7.39 (s, 1H) 7.44 (s, 1H) 7.48–7.58 (m, 2H) 8.08–8.17 (m, 2H) 8.46 (d, $J = 5.1$ Hz, 1H).

*5.1.6.2. Synthesis of N-{5-[(6,7-dimethoxyquinolin-4-yl)oxy]-pyridin-2-yl}piperazine-1-carboxamide (**16**).* Hydrogen chloride (3 mL, 12 mmol, 4 M in dioxane) was added to a solution of *tert*-butyl 4-[({5-[(6,7-dimethoxyquinolin-4-yl)oxy]pyridin-2-yl}amino)carbonyl]piperazine-1-carboxylate (compound **15**, 60 mg, 0.12 mmol) at room temperature. The reaction mixture was stirred at room temperature for 12 h then was evaporated to a yellow solid to afford compound **16** (8 mg, 0.02 mmol, 17% yield); MS (*m/z*) (APCI) $[M+H]^+$ 410.2. ^1H NMR (400 MHz, MeOD) δ ppm 3.01–3.08 (m, 4H) 3.63–3.69 (m, 4H) 4.00 (s, 3H) 4.01 (s, 3H) 6.54 (d, $J = 5.3$ Hz, 1H) 7.35 (s, 1H) 7.62 (s, 1H) 7.66 (dd, $J = 9.1$, 3.0 Hz, 1H) 7.92 (d, $J = 9.1$ Hz, 1H) 8.22 (d, $J = 2.5$ Hz, 1H) 8.43 (d, $J = 5.3$ Hz, 1H).

*5.1.7. N-Cyclohexyl-N′-{5-[(6,7-dimethoxyquinolin-4-yl)oxy]pyridin-2-yl}urea (**10**)*

Cyclohexyl isocyanate (1 mL, 8 mmol) was added to a solution of 5-(6,7-dimethoxy-quinolin-4-yloxy)-pyridin-2-ylamine (compound **6**, 119 mg, 0.4 mmol) in 4 mL of DCM. The mixture was stirred at room temperature for 12 h.

The reaction mixture was partitioned between DCM (150 mL) and sat. $NaHCO_3$ solution (50 mL) and brine (50 mL). The organic layer was dried (Na_2SO_4) and concentrated by vacuum. The residue was purified by silica gel chromatography (eluting with 10% CH_3OH in DCM) to afford compound **10** (148 mg, 0.35 mmol, 88% yield) as a yellowish solid; MS (APCI) $(M+H)^+$ 423. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.18–1.45 (m, 3H) 1.58 (s, 2H) 1.71 (s, 2H) 1.85–2.22 (m, 3H) 3.82 (s, 1H) 4.05 (s, 6H) 6.43 (d, $J = 5.3$ Hz, 1H) 7.04 (d, $J = 9.1$ Hz, 1H) 7.42–7.50 (m, 2H) 7.54 (s, 1H) 8.12 (d, $J = 2.5$ Hz, 1H) 8.50 (d, $J = 5.1$ Hz, 1H) 8.91 (s, 1H) 8.95–9.07 (m, 1H).

Anal. Calcd for $C_{23}H_{26}N_4O_4 \cdot 0.28$hexane: C, 65.69; H, 6.70; N, 12.38. Found: C, 65.63; H, 6.92; N, 12.05.

*5.1.8. N-{5-[(6,7-Dimethoxyquinolin-4-yl)amino]pyridin-2-yl}-N′-(2-phenylethyl)urea (**11**)*

(2-Isocyanatoethyl) benzene (64 mg, 0.437 mmol) was added to a solution of 5-[(6,7-dimethoxyquinolin-4-yl)oxy]-pyridin-2-amine (compound **6**, 100 mg, 0.34 mmol) in DCM (2 mL). The mixture was then heated to 75 °C for 16 h and allowed to cool to ambient temperature. The mixture was concentrated to dryness and the crude product was purified by silica gel chromatography (eluting with 10% CH_3OH in DCM) to afford 85 mg of compound **11** as a white solid (57%); MS (APCI) $(M+H)^+$ 445. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 2.79 (t, $J = 7.1$ Hz, 2H) 3.43 (q, $J = 6.8$ Hz, 2H) 3.94 (d, $J = 2.3$ Hz, 6H) 6.47 (d, $J = 5.3$ Hz, 1H) 7.21 (t, $J = 7.1$ Hz, 1H) 7.25–7.34 (m, 4H) 7.40 (s, 1H) 7.52 (s, 1H) 7.57 (d, $J = 8.8$ Hz, 1H) 7.70 (dd, $J = 9.1$, 2.8 Hz, 1H) 7.88 (s, 1H) 8.14 (d, $J = 2.8$ Hz, 1H) 8.48 (d, $J = 5.1$ Hz, 1H) 9.36 (s, 1H).

Anal. Calcd for $C_{25}H_{24}N_4O_4 \cdot 0.25H_2O$: C, 66.88; H, 5.50; N, 12.48. Found: C, 67.27; H, 5.56; N, 12.01.

*5.1.9. 1-[5-(6,7-Dimethoxy-quinolin-4-yloxy)-pyridin-2-yl]-3-(2-oxo-2-pyrrolidin-1-yl-ethyl)urea (**19**)*

*5.1.9.1. Synthesis of ethyl N-[({5-[(6,7-dimethoxyquinolin-4-yl)oxy]pyridin-2-yl}amino)carbonyl]glycinate (**17**).* Ethyl isocyanatoacetate (0.12 mL, 1.1 mmol) was added to a reaction solution of 5-(6,7-dimethoxy-quinolin-4-yloxy)-pyridin-2-yl-amine (297.3 mg, 1 mmol.) in DCM (8 mL). The mixture

was stirred at room temperature for 12 h. The reaction mixture was partitioned between DCM (150 mL) and sat. $NaHCO_3$ solution (50 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated to an oil residue. The residue was purified by silica gel chromatography (eluting with eluting with 10% CH_3OH in DCM) to afford compound **17** (400 mg, 94% yield) as a yellowish solid; MS (APCI) $(M+H)^+$ 427. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.26–1.33 (m, 3H) 4.07 (d, $J=4.8$ Hz, 6H) 4.15–4.21 (m, 2H) 4.23 (d, $J=7.1$ Hz, 2H) 6.48 (d, $J=5.6$ Hz, 1H) 7.03 (d, $J=9.1$ Hz, 1H) 7.49 (dd, $J=8.8$, 2.8 Hz, 1H) 7.55 (s, 1H) 7.61 (s, 1H) 8.17 (d, $J=2.8$ Hz, 1H) 8.52 (d, $J=5.6$ Hz, 1H) 8.56 (s, 1H) 9.46 (s, 1H).

Anal. Calcd for $C_{21}H_{22}N_4O_6\cdot 0.26$hexane: C, 59.51; H, 5.70; N, 12.25. Found: C, 59.57; H, 5.47; N, 11.90.

*5.1.9.2. Synthesis of N-[({5-[(6,7-dimethoxyquinolin-4-yl)oxy]-pyridin-2-yl}amino)carbonyl]glycine (**18**).* Sodium hydroxide (2 M, 0.9 mL, 1.8 mmol) was added to a solution of ethyl *N*-[({5-[(6,7-dimethoxyquinolin-4-yl)oxy]pyridin-2-yl}amino) carbonyl]glycinate (compound **17**, 390 mg, 0.9 mmol) in EtOH (20 mL). The resulting mixture was stirred at room temperature for 3 h. The pH of the reaction mixture was adjusted to 4.0 by adding 4 M HCl and then it was extracted with EtOAc (2×100 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated by vacuum to afford compound **18** (510 mg, 94% yield) as a yellow solid; MS (APCI) $(M+H)^+$ 399. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 3.89 (d, $J=5.8$ Hz, 2H) 3.96–4.08 (m, 6H) 6.94 (d, $J=6.3$ Hz, 1H) 7.70–7.81 (m, 3H) 7.84 (dd, $J=9.1$, 3.0 Hz, 1H) 7.98 (s, 1H) 8.33 (d, $J=2.8$ Hz, 1H) 8.77 (d, $J=6.6$ Hz, 1H) 9.69 (s, 1H) 12.63 (s, 1H).

*5.1.9.3. Synthesis of 1-[5-(6,7-dimethoxy-quinolin-4-yloxy)-pyridin-2-yl]-3-(2-oxo-2-pyrrolidin-1-yl-ethyl)-urea (**19**).* Diisopropylethylamine (90 μL, 0.5 mmol) and HATU (95 mg, 0.25 mmol) were added to a solution of *N*-[({5-[(6,7-dimethoxyquinolin-4-yl)oxy]pyridin-2-yl}amino)carbonyl]glycine (compound **18**, 100 mg, 0.25 mmol). After stirring at room temperature for 30 min, cyclopentylamine (20 mg, 0.25 mmol) was added. The resulting mixture was stirred at room temperature for 12 h. The reaction mixture was partitioned between EtOAc (150 mL) and sat. $NaHCO_3$ (75 mL). The organic layer was dried (Na_2SO_4), filtered, and then concentrated by vacuum to give a yellow oil. To the oil residue was added MeOH (5 mL) and a precipitate formed. The precipitate was collected and washed well with more MeOH. The solid was dried under vacuum to give compound **19** as a white solid (30 mg, 27% yield); MS (APCI) $(M+H)^+$ 452. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 1.71–1.83 (m, 2H) 1.84–1.95 (m, 2H) 3.32–3.36 (m, 2H) 3.41 (t, $J=6.8$ Hz, 2H) 3.94 (d, $J=2.3$ Hz, 6H) 3.98 (d, $J=4.8$ Hz, 2H) 6.48 (d, $J=5.3$ Hz, 1H) 7.39 (s, 1H) 7.52 (s, 1H) 7.62–7.67 (m, 1H) 7.66–7.78 (m, 1H) 7.97 (s, 1H) 8.21 (d, $J=2.8$ Hz, 1H) 8.47 (d, $J=5.3$ Hz, 1H) 9.56 (s, 1H).

Anal. Calcd for $C_{23}H_{25}N_5O_5\cdot 0.36$MeOH: C, 60.60; H, 5.76; N, 15.13. Found: C, 60.34; H, 5.61; N, 15.09.

*5.1.10. N-Cyclohexyl-N′-{5-[(6,7-dimethoxyquinolin-4-yl)oxy]pyridin-2-yl}urea (**20**)*

Diisopropylethylamine (90 μL, 0.5 mmol) and HATU (95 mg, 0.25 mmol) were added to a solution of *N*-[({5-[(6,7-dimethoxyquinolin-4-yl)oxy]pyridin-2-yl}amino)carbonyl]glycine (compound **18**, 100 mg, 0.25 mmol). After stirring at room temperature for 30 min, cyclohexylamine (22 mg, 0.25 mmol) was added. The resulting mixture was stirred at room temperature for 12 h. The reaction mixture was partitioned between EtOAc (2×50 mL) and sat. $NaHCO_3$ (20 mL). The organic layer was dried (Na_2SO_4), filtered, and then concentrated by vacuum to give a yellow oil. The oil residue was purified by reverse phase chromatography (eluting with 50% acetonitrile in H_2O, containing 0.1% acetic acid) to afford compound **20** as white solid (20 mg, 18% yield); MS (APCI) $(M+H)^+$ 467. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 1.35–1.63 (m, 6H) 3.40–3.50 (m, 4H) 3.95 (d, $J=2.8$ Hz, 6H) 4.05 (d, $J=4.6$ Hz, 2H) 6.58 (s, 1H) 7.42 (s, 1H) 7.52–7.59 (m, 1H) 7.63–7.70 (m, 1H) 7.70–7.77 (m, 1H) 7.96 (d, $J=11.9$ Hz, 1H) 8.18–8.28 (m, 1H) 8.54 (d, $J=5.1$ Hz, 1H) 9.59 (s, 1H).

Anal. Calcd for $C_{24}H_{27}N_5O_5\cdot 1.42H_2O\cdot 0.26$HOAc: C, 58.12; H, 6.14; N, 13.82. Found: C, 58.01; H, 5.73; N, 13.70.

*5.1.11. N-Benzyl-N′-{5-[(6,7-dimethoxyquinolin-4-yl)oxy]pyridin-2-yl}urea (**12**)*

Isocyanatomethyl benzene (67 mg, 0.51 mmol) was added to a solution of 5-[(6,7-dimethoxyquinolin-4-yl)oxy]pyridin-2-amine (compound **6**, 100 mg, 0.34 mmol) in DCM (2 mL). The mixture was then heated to 75 °C for 16 h and allowed to cool to ambient temperature. The mixture was concentrated to dryness and the crude product was purified by silica gel chromatography (eluting with 3% CH_3OH in DCM) to afford compound **12** (137 mg, 95% yield) as a white solid; MS (*m*/*z*) (APCI) $[M+H]^+$ 431. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 3.94 (d, $J=2.8$ Hz, 6H) 4.41 (d, $J=6.1$ Hz, 2H) 6.49 (d, $J=5.3$ Hz, 1H) 7.22–7.29 (m, 1H) 7.30–7.37 (m, 4H) 7.40 (s, 1H) 7.52 (s, 1H) 7.62–7.67 (m, 1H) 7.69–7.75 (m, 1H) 8.15–8.25 (m, 2H) 8.47 (d, $J=5.3$ Hz, 1H) 9.43 (s, 1H).

Anal. Calcd for $C_{24}H_{22}N_4O_4\cdot 0.5H_2O$: C, 65.59; H, 5.28; N, 12.75. Found: C, 65.43; H, 5.32; N, 12.60.

*5.1.12. N-[({5-[(6,7-Dimethoxyquinolin-4-yl)oxy]pyridin-2-yl}amino)carbonyl]-2-pyrrolidin-1-ylacetamide (**22**)*

*5.1.12.1. Synthesis of 2-chloro-N-[({5-[(6,7-dimethoxyquinolin-4-yl)oxy]pyridin-2-yl}amino)carbonyl]acetamide (**21**).* Chloroacetylisocyanate (114 mg, 0.95 mmol) was added to a solution of 5-[(6,7-dimethoxyquinolin-4-yl)oxy]pyridin-2-amine (compound **6**, 300 mg, 1 mmol) in DCM (5 mL) under inert atmosphere. After stirring at room temperature for 12 h, a precipitate formed in the reaction mixture. This precipitate was collected and washed with DCM to afford compound **21** (270.5 mg, 0.65 mmol, 68.4% yield) as an off white solid; MS (APCI): $(M+H)^+$ 417. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 3.93 (s, 3H) 3.94 (s, 3H) 4.43 (s, 2H) 6.54 (d, $J=5.1$ Hz, 1H) 7.41 (s, 1H) 7.52 (s, 1H) 7.84 (dd, $J=9.1$,

2.8 Hz, 1H) 8.09 (d, $J = 9.1$ Hz, 1H) 8.37 (d, $J = 3.0$ Hz, 1H) 8.49 (d, $J = 5.1$ Hz, 1H).

*5.1.12.2. Synthesis of N-[({5-[(6,7-dimethoxyquinolin-4-yl)oxy]pyridin-2-yl}amino)carbonyl]-2-pyrrolidin-1-ylacetamide (**22**)*

Pyrrolidine (35 mg, 0.4 mmol) and DIEA (0.2 mL, 1 mmol) were added sequentially to a solution of 2-chloro-*N*-[({5-[(6,7-dimethoxyquinolin-4-yl)oxy]pyridin-2-yl}amino)carbonyl] acetamide (compound **21**, 80 mg, 0.19 mmol) in 3 mL of DMF. The mixture was heated at 60 °C for 12 h then cooled to ambient temperature. Water (50 mL) was added to the reaction mixture to quench the reaction. EtOAc (2 × 50 mL) was added to extract the aqueous solution. The combined organic layers were dried (Na_2SO_4), filtered and evaporated to get a tan oil. The residue was purified by silica gel chromatography (eluting 0 → 5% CH_3OH in EtOAc) to afford compound **22** as a white solid (43 mg; 0.09 mmol; 49.5% yield); MS (APCI) $(M + H)^+$ 452. ^1H NMR (400 MHz, MeOD) δ ppm 1.82–1.89 (m, 4H) 2.68 (t, $J = 5.6$ Hz, 4H) 3.39 (s, 2H) 3.97 (s, 3H) 3.98 (s, 3H) 6.53 (d, $J = 5.3$ Hz, 1H) 7.30 (s, 1H) 7.56 (s, 1H) 7.69 (dd, $J = 9.1$, 3.0 Hz, 1H) 8.15 (d, $J = 7.3$ Hz, 1H) 8.24 (d, $J = 2.5$ Hz, 1H) 8.40 (d, $J = 5.6$ Hz, 1H).

Anal. Calcd for $C_{23}H_{25}N_5O_5 \cdot 0.5H_2O$: C, 59.99; H, 5.69; N, 15.21. Found: C, 59.76; H, 5.44; N, 15.25.

*5.1.13. Compound **15** (PF-3187208, PK7292-086)*

*5.1.13.1. N-[({5-[(6,7-Dimethoxyquinolin-4-yl)oxy]pyridin-2-yl}amino)carbonyl]-2-piperidin-1-ylacetamide (**23**).* Piperidine (40 mg, 0.4 mmol) and DIEA (0.2 mL, 1 mmol) were added sequentially to a solution of 2-chloro-*N*-[({5-[(6,7-dimethoxyquinolin-4-yl)oxy]pyridin-2-yl}amino)carbonyl]acetamide (compound **21**, 80 mg, 0.19 mmol) in DMF (3 mL). The mixture was heated at 60 °C for 12 h then cooled to ambient temperature. Water (50 mL) was added to the reaction mixture to quench the reaction. EtOAc (2 × 50 mL) was added to extract the aqueous solution. The combined organic layers were dried (Na_2SO_4), filtered and evaporated to get a tan oil. The residue was purified by silica gel chromatography (eluting 85 → 90% EtOAc in hexane) to afford compound **23** as a white solid (72 mg; 0.16 mmol; 80.7% yield); MS (APCI) $(M + H)^+$ 466. ^1H NMR (400 MHz, MeOD) δ ppm 1.43 (d, $J = 3.8$ Hz, 2H) 1.57–1.65 (m, 4H) 2.44–2.53 (m, 4H) 3.12 (s, 2H) 3.93 (s, 3H) 3.94 (s, 3H) 6.47 (d, $J = 5.3$ Hz, 1H) 7.22 (s, 1H) 7.47 (s, 1H) 7.63 (dd, $J = 9.1$, 2.8 Hz, 1H) 8.08 (d, $J = 7.3$ Hz, 1H) 8.18 (d, $J = 2.8$ Hz, 1H) 8.35 (d, $J = 5.3$ Hz, 1H).

Anal. Calcd for $C_{24}H_{27}N_5O_2 \cdot 0.5H_2O$: C, 60.75; H, 5.95; N, 14.76. Found: C, 60.95; H, 5.80; N, 14.80.

*5.1.14. N-[({5-[(6,7-Dimethoxyquinolin-4-yl)oxy]pyridin-2-yl}amino)carbonyl]-2,6-difluorobenzamide (**13**)*

2,6-Difluorobenzoyl isocyanate (0.05 g, 0.3 mmol) was added to a solution of 5-[(6,7-dimethoxyquinolin-4-yl)oxy]pyridin-2-amine (compound **6**, 0.065 g, 0.22 mmol) in DCM (10 mL). The resulting mixture was stirred at room temperature for 12 h under inert atmosphere. The mixture was evaporated and the oil residue was purified by silica gel chromatography (eluting with 1 → 3% CH_3OH in EtOAc) to give compound **13** as a white solid (73 mg; 0.15 mmol; 69.4% yield); MS (APCI) $(M + H)^+$ 481. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 3.93 (s, 3H) 3.94 (s, 3H) 6.54 (d, $J = 5.3$ Hz, 1H) 7.41 (s, 1H) 7.53 (s, 1H) 7.59–7.69 (m, 1H) 7.85 (dd, $J = 9.0$, 2.9 Hz, 1H) 8.10 (d, $J = 9.1$ Hz, 1H) 8.39 (d, $J = 2.8$ Hz, 1H) 8.49 (d, $J = 5.3$ Hz, 1H) 10.74 (s, 1H) 11.68 (s, 1H).

Anal. Calcd for $C_{24}H_{18}F_2N_4O_5 \cdot 0.25CH_2Cl_2$: C, 58.06; H, 3.72; N, 11.17. Found: C, 58.25; H, 3.82; N, 10.88.

*5.1.15. N-[({5-[(6,7-Dimethoxyquinolin-4-yl)-oxy]pyridin-2-yl}amino)carbonyl]benzamide (**14**)*

Benzoyl isocyanate (0.04 g, 0.25 mmol) was added to a solution of 5-[(6,7-dimethoxyquinolin-4-yl)oxy]pyridin-2-amine (compound **6**, 40 mg, 0.12 mmol) in DCM (10 mL). The resulting mixture was stirred at room temperature for 12 h under inert atmosphere. The mixture was evaporated and CH_3OH (5 mL) was added. The precipitate was filtered and washed with more CH_3OH to give compound **14** as a light yellow solid (39.3 mg; 0.09 mmol; 72% yield); MS (APCI) $(M + H)^+$ 445. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 4.03 (s, 3H) 4.03 (s, 3H) 6.99 (d, $J = 6.3$ Hz, 1H) 7.44–7.64 (m, 3H) 7.68 (t, $J = 7.5$ Hz, 1H) 7.76 (s, 1H) 7.91–8.03 (m, 1H) 8.04 (d, $J = 7.1$ Hz, 2H) 8.26 (d, $J = 9.1$ Hz, 1H) 8.50 (d, $J = 2.8$ Hz, 1H) 8.81 (d, $J = 6.6$ Hz, 1H) 11.32 (s, 1H) 11.46 (s, 1H).

Anal. Calcd for $C_{24}H_{20}N_4O_5 \cdot 1CH_2Cl_2 \cdot 0.75H_2O$: C, 55.31; H, 4.36; N, 10.32. Found: C, 55.72; H, 4.60; N, 9.89.

5.2. c-Met tyrosine kinase coupled enzymatic spectrophotometric assay

Human c-Met (Upstate 14-256) was activated by autophosphorylation with ATP prior to use in the enzyme assay. The inhibition of enzyme activity was determined with a coupled enzyme system that monitored for the production of ADP via oxidation of NADH using pyruvate kinase (PK) and lactic dehydrogenase (LDH). The reaction mix contained 300 μM ATP, 500 μM Ac-ARDMYDKEYYSVHNK peptide, 20 mM $MgCl_2$, 1 mM PEP, 300 μM NADH, 2 mM DTT, 15 units/mL LDH, 15 units/mL PK in 100 mM HEPES, pH 7.5, 37 °C. Compound was added to achieve a final DMSO concentration of 2% and the reaction was initiated with c-Met (25 nM final concentration). The coupling system allowed for continuous monitoring of the reaction at 340 nm and initial velocities were calculated by linear regression. K_i values were determined by fitting to the Morrison tight-binding equation [12]. Errors for K_i values are less than 10%.

References

[1] C. Birchmeier, W. Birchmeier, E. Gherardi, G.F. Vande Woude, Nat. Rev. Mol. Cell Biol. 4 (2003) 915.
[2] J. Christensen, J. Burrows, R. Salgia, Cancer Lett. 225 (2005) 1.
[3] K. Furge, Y. Zhang, G.F. Vande Woude, Oncogene 19 (2000) 5582.
[4] Y. Zhang, G.F. Vande Woude, J. Cell Biol. 13 (2003) 328.

[5] S. Corso, P. Comoglio, S. Giordano, Trends Mol. Med. 11 (2005) 284.
[6] Y. Fujiwara, T. Senga, T. Nishitoba, T. Osawa, A. Miwa, K. Nakamura, PCT Int. Appl. (2003) 441.
[7] R. Onderwater, J. Commandeur, W. Menge, N. Vermeulen, Chem. Res. Toxicol. 12 (1999) 396.
[8] (a) S. Nelson, J. Med. Chem. 25 (1982) 753;
(b) C. Ju, J. Uetrecht, Drug Metab. Dispos. 26 (1998) 676.
[9] (a) A. Surrey, H. Hammer, J. Am. Chem. Soc. 68 (1946) 113;
(b) C. Price, R. Roberts, J. Am. Chem. Soc. 68 (1946) 1204.
[10] T. Furuta, T. Sakai, T. Senga, T. Osawa, K. Kubo, T. Shimizu, R. Suzuki, T. Yoshino, M. Endo, A. Miwa, J. Med. Chem. 49 (2006) 2186.
[11] X. Huang, S. Buchwald, Org. Lett. 3 (2001) 3417.
[12] J.W. Williams, J.F. Morrison, Methods Enzymol. 63 (1979) 437.