Structure-Based Design of Novel Class II c-Met Inhibitors: 1. Identification of Pyrazolone-Based Derivatives

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Ⓢ Supporting Information
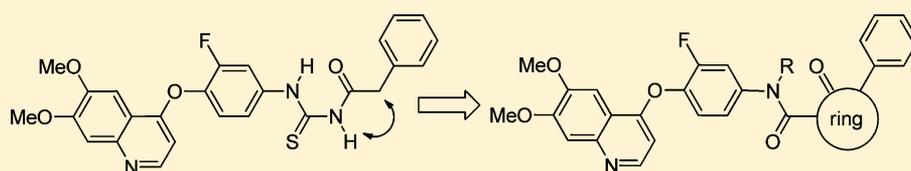
ABSTRACT: Deregulation of c-Met receptor tyrosine kinase activity leads to tumorigenesis and metastasis in animal models. More importantly, the identification of activating mutations in c-Met, as well as *MET* gene amplification in human cancers, points to c-Met as an important target for cancer therapy. We have previously described two classes of c-Met kinase inhibitors (class I and class II) that differ in their binding modes and selectivity profiles. The class II inhibitors tend to have activities on multiple kinases. Knowledge of the binding mode of these molecules in the c-Met protein led to the design and evaluation of several new class II c-Met inhibitors that utilize various 5-membered cyclic carboxamides to conformationally restrain key pharmacophoric groups within the molecule. These investigations resulted in the identification of a potent and novel class of pyrazolone c-Met inhibitors with good in vivo activity.

■ INTRODUCTION

The c-Met receptor tyrosine kinase (RTK) is a commonly deregulated oncogene in human cancers that has been pursued as a drug target for many years.[1] The interest in c-Met originated from its role in cell proliferation, migration, invasion, and survival, all cellular functions associated with cancer progression and metastasis.[2] In human cancers, multiple mechanisms may lead to c-Met activation, including activating mutations in the kinase domain, overexpression of c-Met and/or its ligand, hepatocyte growth factor (HGF), *MET* gene amplification, and cross-talk with other receptor tyrosine kinases such as EGFR.[3] Preclinical data suggest that *MET* gene amplification may lead to oncogene addiction and may render tumors especially sensitive to a c-Met inhibitor.

The reported ATP-competitive c-Met inhibitors have been categorized into two classes based on their chemotype and predicted binding mode.[4a] Class I inhibitors bind in a U-shaped conformation to the ATP-binding site at the entrance of the kinase pocket and wrap around Met1211, while class II inhibitors bind to c-Met with an extended conformation that stretches from the ATP-binding site, delineated by the kinase linker strand (or hinge) to the deep hydrophobic Ile1145 pocket near the C-helix region. In general, class I inhibitors such as compound **1** (c-Met K_i = 4.8 nM) block c-Met kinase activity with high selectivity against other kinases (Figure 1).[4,5] On the other hand, class II c-Met inhibitors may also inhibit other kinases, depending on their substitution patterns.[6] An example of a class II c-Met inhibitor is compound **2** that
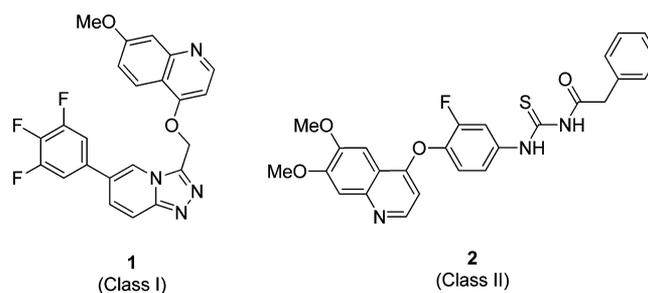
Figure 1. Examples of class I and class II c-Met inhibitors.

inhibited the kinase activity of VEGFR-2 (K_i = 103 nM) as well as c-Met (K_i = 4.0 nM).[7] The different selectivity profiles of these two classes of inhibitors are a direct consequence of their binding mode in the ATP pocket of the c-Met kinase domain.[8] Recent studies have suggested that certain mutations near the active site of c-Met may lead to resistance to class I inhibitors.[9] We postulated that class II inhibitors may be more effective against the mutations that disrupt the class I binding mode because their binding interactions extend beyond the entrance of c-Met's active site. Therefore, our goal was to target c-Met mutations by developing novel c-Met class II inhibitors with increased selectivity over other protein kinases. Our efforts
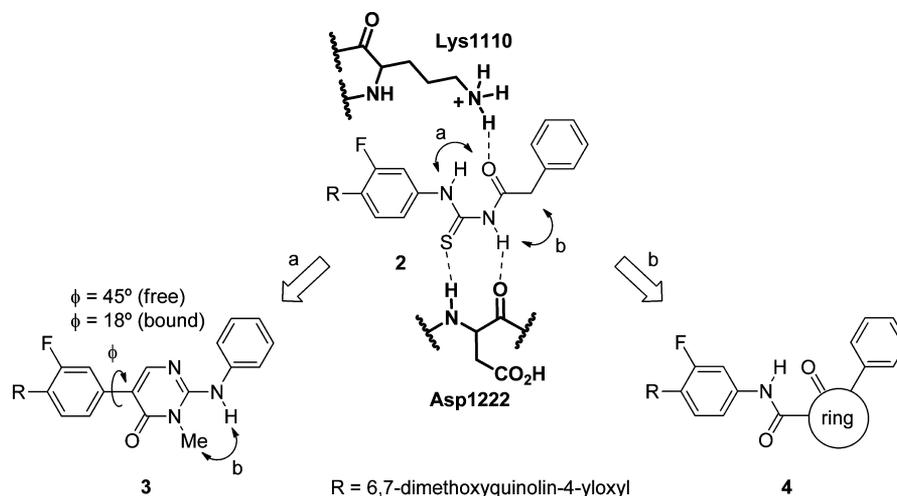
Figure 2. Design of cyclic carboxamides.

toward this goal were 2-fold. In the first phase of our structure–activity relationship (SAR) investigations, we examined various 5-membered cyclic carboxamides to conformationally restrain key pharmacophoric groups within the acylthiourea group of compound **2**. Although the initial molecules examined inhibited both c-Met and VEGFR-2 kinase activity with similar potency, they showed good in vivo activity in a c-Met pharmacodynamic model and, more importantly, provided novel scaffolds for further selectivity enhancement. The results of these initial studies are reported herein. In the second phase of our investigations we utilized a combination of SAR, molecular modeling, and X-ray crystallography to identify potent inhibitors of the c-Met enzyme while gaining significant selectivity over VEGFR-2 and/or IGF-1R. The results of these secondary investigations are outlined in the following article.

■ INHIBITOR DESIGN AND LEAD PROFILING

Compound **2** was one of the first reported class II c-Met inhibitors that showed excellent activity in cells (IC$_{50}$ = 8.7 nM, A431 cell line).[7] We felt that structural modification of **2** could lead to novel scaffolds that still maintained potent activity on c-Met while providing a platform for improving kinase selectivity. A conformational analysis study of **2** suggested that the acylthiourea moiety assumed a pseudocyclic structure through intramolecular hydrogen-bonding between the aniline N–H and the amide C=O functionalities (Figure 2). Furthermore, hydrogen-bond interactions to residues Lys1110 and Asp1222 in c-Met were also predicted to be important for the binding of **2** to c-Met, suggesting that replacement of the intramolecular hydrogen bond of the acylthiourea with a covalent linkage (Figure 2, arrow a) would be a viable structural modification in preserving key interactions with the c-Met backbone.

Following this rationale, we discovered the biaryl series as exemplified by the pyrimidone derivative **3**.[10] Compound **3** inhibited the kinase activity of c-Met with a K_i of 14 nM in the biochemical assay and inhibited HGF-mediated c-Met autophosphorylation in PC3 cells with an IC$_{50}$ of 204 nM. The 4-fold loss in potency against the enzymatic activity relative to **2** (K_i = 4.0 nM) was attributed to biaryl strain created by the pyrimidone ring with the central fluorophenyl ring. In the crystal structure of the *para*-fluoro analogue of **3** bound to c-Met (PDB 3EFK),[9] the torsional angle (ϕ) between the central

fluorophenyl ring and the pyrimidone ring was ~18°, representing an estimated torsional strain of 1.2 kcal/mol relative to the ground state conformation of the free ligand (ϕ ~ 45°, based on gas-phase quantum mechanical calculations). This energy difference represented a predicted 7-fold penalty on activity, which was consistent with the observed 4-fold loss in potency. While the strained conformation of **3** maintained the critical hydrogen bond with the N–H of Asp 1222, the loss of the hydrogen bond donor to the Asp1222 backbone carbonyl due to the pyrimidone N-Me group resulted in little loss of activity. In addition, the pyrimidone N-Me and the aniline N–H bonds in **3** assumed a *syn* coplanar conformation in both the free (modeled) and the bound (crystallographically observed) forms, suggesting that a ring structure in this region would be tolerated (Figure 2, arrow b). This conclusion was supported by the modeling analysis of **2** in terms of eliminating the biaryl torsional strain while maintaining the key hydrogen bonds to the protein. These insights led us to the design of cyclic amides represented by general structure **4** where the *syn* coplanar N-Me and the N–H bonds in **3** are embedded in a ring structure, while the pyrimidone C=C–H responsible for the biaryl torsional strain are replaced by an N–H bond (path b). Although both 5- and 6-membered ring heterocycles were investigated as possible "path-b" conformational restraints, in this work we will focus only on studies in the 5-membered cyclic amide series.[11]

■ CHEMISTRY

In this investigation, we examined several 5-membered cyclic carboxamide derivatives of general structure **4**, including pyrrolidinones, imidazolidinones, and pyrazolones. Substituted N-phenyl and N-benzyl pyrrolidinones **12−15** were prepared as outlined in Scheme 1. Methyl 2-oxo-1-phenylpyrrolidine-3-carboxylate **5**[12] was converted to the corresponding 3-methyl and 3-fluoro derivatives **6** and **7** by enolate formation, followed by treatment with either methyl triflate or N-fluorobenzene-sulfonimide, respectively. Esters **5−7** were hydrolyzed with potassium hydroxide, and the resulting carboxylic acids (**8−10**) were coupled to 4-(6,7-dimethoxyquinolin-4-yloxy)-3-fluoro-benzenamine **11**[13] in the presence of 2-(7-aza-1H-benzotria-zole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU) to give N-phenyl pyrrolidinones **12−14**. The N-benzyl pyrrolidinone derivative, **15**, was prepared by the

Scheme 1[a]
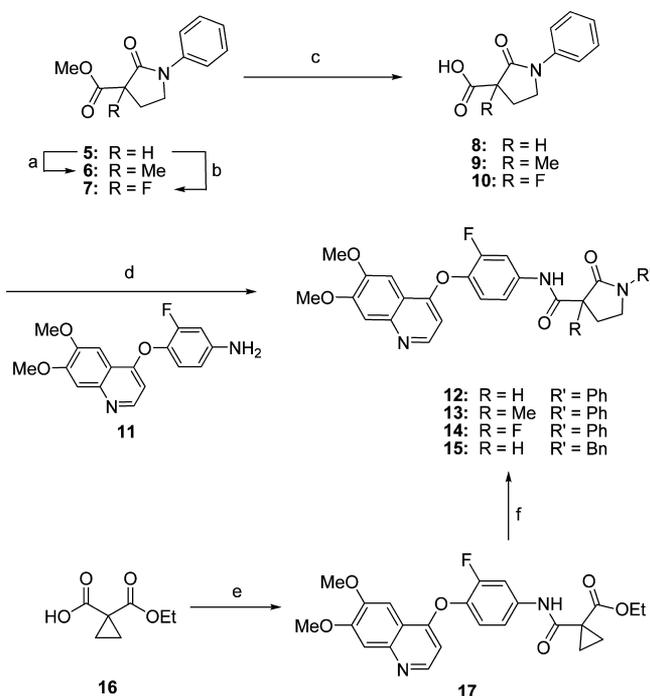
[a]Reagents: (a) LiHMDS, MeOTf, THF, PhMe, −78 °C → rt; (b) LDA, N-fluorobenzenesulfonimide, THF, −78 °C; (c) KOH, MeOH, 80 °C; (d) HATU, DCM; (e) 11, HATU, DCM; (f) BnNH$_2$, 140 °C.

condensation of 1-(ethoxycarbonyl)cyclopropanecarboxylic acid (16) with compound 11, followed by homoconjugate addition of benzylamine to the resulting intermediate 17 using the Danishefsky protocol for lactam formation.[11]

For the preparation of the isomeric pyrrolidinone derivative 21, tert-butyl 2-oxopyrrolidine-1-carboxylate, 18, was first alkylated with benzyl bromide[14] to give compound 19 that was then converted to the p-nitrophenyl (PNP) carbamate 20 (Scheme 2). Treatment of intermediate 20 with compound 11 under microwave heating provided the desired urea-linked pyrrolidinone analogue 21.

The N-phenyl imidazolidinone derivative, 23, was prepared as illustrated in Scheme 3. Treatment of 4-(6,7-dimethoxyquinolin-4-yloxy)-3-fluorobenzenamine 11 with 4-nitrophenyl chloroformate provided the corresponding PNP-carbamate intermediate 22. Carbamate 22 was then converted to

imidazolidinone 23 by the addition of the sodium salt of 1-phenylimidazolidin-2-one. To prepare the final two pyrazolone derivatives, the requisite pyrazolone carboxylic acid 25 was synthesized through a Pinnick oxidation[15] of aldehyde 24 (Scheme 4). Acid 25 was coupled to 4-(6,7-dimethoxyquinolin-4-yloxy)-3-fluorobenzenamine 11 in the presence of HATU to provide pyrazolone 26, which was also methylated with methyl iodide to give 27.

■ RESULTS AND DISCUSSION

The compounds prepared in this study were examined for their ability to inhibit c-Met activity using an enzyme assay with a recombinant c-Met kinase domain and in a cellular assay that determined the inhibition of HGF-mediated c-Met autophosphorylation in PC3 cells.[16] The structure−activity relationships (SAR) of the heterocyclic carboxamides of general structure 4 are summarized in Table 1. A simple 2-oxo-1-phenylpyrrolidine-3-carboxylic amide 12 showed inhibition of c-Met kinase activity (K_i = 13.7 nM) similar to that of compound 3. Replacing the phenyl group with a benzyl group resulted in 4-fold loss of potency (15, K_i = 60.2 nM), suggesting that the hydrophobic pocket is best filled with a simple aromatic ring. However, transposing the lactam function in 15 to the 2-oxo-3-phenylpyrrolidine-1-carboxylic amide 21 led to a slight increase in activity (K_i = 37.8 nM). To probe whether enolization of the α hydrogen of the 1,3-dicarbamide moiety might affect the binding of 12 to c-Met, a 2-methyl or a 2-fluorine group was introduced between the two carbonyls (13 and 14). In both cases, a significant loss of potency (4- to 10-fold) was observed, which likely results from steric hindrance of the 2-substituent with the Leu1157 side chain for one stereoisomer or with the backbone of the DFG motif for the other stereoisomer. Compounds 12 (13.7 nM) and 21 (37.8 nM) each contained sp^3 hybridized carbons, resulting in strong nonplanar conformational preferences, and these compounds showed no improvement over 3 in which the biaryl torsional preferences also favored nonplanarity. The key modification that led to improved potency against c-Met involved replacing the tetrahedral α carbon of compound 12 with an sp^2 hybridized nitrogen. This change resulted in an 8-fold increase in activity (23, K_i = 1.7 nM) and was consistent with the molecular modeling guidance that the c-Met protein preferred a planar conformation for the fluorophenyl-1,3-dicarbamide system.[17] The observation that a planar conformation was preferred in this region led us to the design of pyrazolone carboxamide 26,

Scheme 2[a]
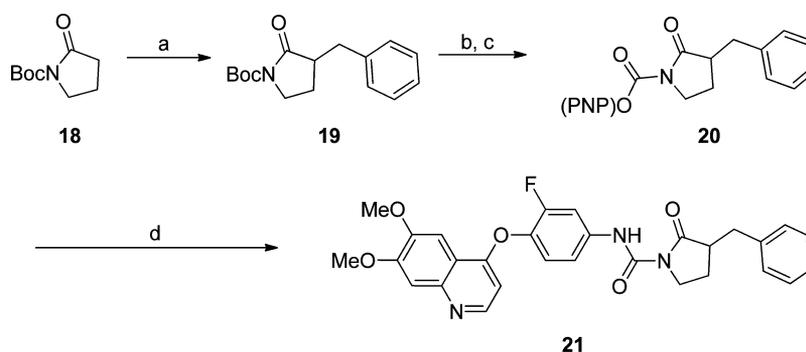
[a]Reagents: (a) LDA, THF, −78 °C → 0 °C, BnBr; (b) TFA, DCM 0 °C, NaOH, rt; (c) 4-nitrophenyl chloroformate, Et$_3$N, THF, 0 °C → rt; (d) 11, DMF, 60 °C (microwave) (60 W).

Scheme 3[a]
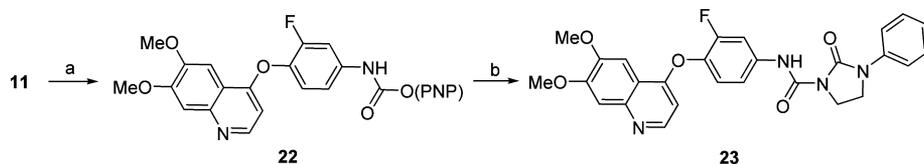
[a]Reagents: (a) 4-nitrophenyl chloroformate, Et₃N, THF, 0 °C → rt; (b) 1-phenylimidazolidin-2-one, NaH, DMF, 0 °C → rt.

Scheme 4[a]
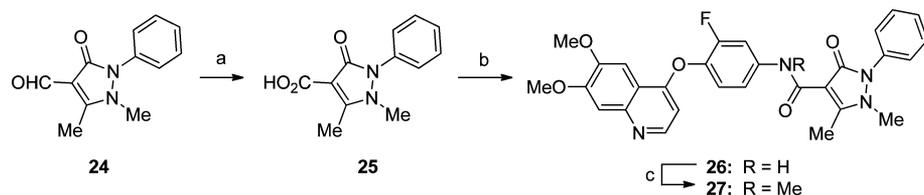
[a]Reagents: (a) 2-methylbut-2-ene, NaClO₂, NaH₂PO₄, t-BuOH, 0 °C → rt; (b) 11, HATU, DCM; (c) NaH, MeI, rt.

Table 1. Activity of Cyclic Carboxamide Derivatives against c-Met[a]

Compound No.	R	Het	c-Met[a] K_i (nM) ±SD	PC3[b] IC_{50} (nM) ±SD
12	H		13.7 ± 0.4	123 ± 48
13	H		56.7 ± 9.8	667 ± 109
14	H		140 ± 18.9	3,925 ± 133
15	H		60.2 ± 0.8	1,111 ± 194
21	H		37.8 ± 4.8	592 ± 50
23	H		1.7 ± 0.4	53.0 ± 24
26	H		1.0 ± 0.3[c]	20 ± 7.5[d]
27	Me		>20,000	>20,000

[a]K_i: inhibitory constant for the phosphorylation of gastrin by c-Met (average of $n > 4$). [b]IC_{50} values for HGF-mediated autophosphoylation in PC3 cells, ($n > 2$). [c]$n = 214$. [d]$n = 303$.

which exhibited enhanced c-Met potency ($K_i = 1.0$ nM). Thus, in agreement with earlier structural analysis of the biaryl dihedral angle, alleviation of torsional strain in going from pyrimidone 3 to pyrazolone 26 enhanced the potency for c-Met by 14-fold. Moreover, pyrazolone 26 demonstrated a 9-fold improvement over compound 2. Molecular modeling studies suggested that the sp³ carbon of the benzylic group in 2 would impart an unfavorable ligand strain in the bound state, in

Figure 3. X-ray structure of **26** bound to c-Met. Only key residues comprising the ligand binding site are displayed. Hydrogen bonds are colored in green and key vdW contacts in black. In contrast to typical kinases that allow for an extended binding mode by adopting a DFG-out conformation, c-Met accommodates this ligand by providing the Ile1145 pocket while leaving Phe1223 of the DFG motif in its cognate hydrophobic pocket.

contrast to pyrazolone **26** that prefers planarity of the entire dicarboxamide system. In addition, the cellular potency of **26** in the inhibition of HGF-mediated c-Met autophosphorylation in PC3 cells was also improved by 10-fold (IC_{50} = 20.2 nM). Methylation of the aniline nitrogen linking the pyrazolone amide to the 4-(6,7-dimethoxyquinolin-4-yloxy)-3-fluorobenzenamine group eliminated the intramolecular hydrogen bond to the pyrazolone carbonyl, which led to disruption of planarity and a dramatic loss of potency on c-Met (pyrazolone **27**). Although pyrazolone **26** exhibited excellent potency against c-Met, it was only modestly selective against VEGFR-2 (6.2 nM) and IGF-1R (65 nM) kinases, a characteristic common among other class II c-Met inhibitors.

A linear binding mode of **26** in the kinase domain of c-Met was unambiguously determined by X-ray crystallography in which two backbone N—H bonds (Met1160 and Asp1222) were desolvated by the inhibitor with hydrogen bonds through the quinoline nitrogen to the backbone N—H of Met1160 and the carboxyamide carbonyl to the N—H of Asp1222 (Figure 3). In addition to the critical hydrogen bond with Met1160, the 6,7-dimethoxy-quinoline formed a number of hydrophobic contacts to other residues on the same strand as Met1160, which links the N- and C-terminal domains of c-Met, a region of the protein that we refer to as simply "the linker strand". The pyrazolone carbonyl formed a pseudoring structure via intramolecular hydrogen bonding with the aniline N—H as well as a hydrogen bond with Lys1110 via a water molecule. The importance of this intramolecular hydrogen bond is underscored by the complete loss of potency upon N-methylation of the amide N—H (**27**, K_i > 20 μM). The N(2)-phenyl ring occupies a hydrophobic pocket defined by Ala1127, Ile1145, Val1155, and Phe1124. As Ile1145 demarcates the back of this pocket, we refer to it as the Ile1145 pocket (also referred to as C-helix pocket), as described previously.[10] This pocket has only been reported in a subset of

kinases and is present due to the uncharacteristic position of the C-helix, which is further away from the ATP binding site than it is in most kinases, even in the unliganded c-Met crystal strucure.[5b,18] The fluorophenyl ring resides between Val1092 and the residue at the tip of the phosphate-binding loop (P-loop), Phe1089.

With its excellent in vitro enzyme and cellular potencies, pyrazolone carboxamide **26** was also evaluated in vivo in both pharmacokinetic (PK) and pharmacodynamic (PD) studies. The pharmacokinetic profile of compound **26** is summarized in Table 2. In rats, iv dosing of **26** demonstrated a low clearance (0.035 L/h/kg; 1.1% of liver blood flow) and a low volume of distribution (0.242 L/kg) with an elimination half-life of 4.6 h.

Table 2. Pharmacokinetic Profile of Pyrazolone Carboxamide 26

in vivo rat PK[a]						
iv				po		
dose[b] (mg/kg)	CL (L/kg/h)	Vss (L/kg)	t1/2 (h)	dose[c] (mg/kg)	%F	AUC (μM·h)
2	0.035	0.242	4.6	5	94	258

[a]Pharmacokinetic parameters following administration of compound **26** in male Sprague–Dawley rats: 3 animals per study. [b]Dosed as a solution in DMSO. [c]Dosed as a suspension in 1% Tween 80, 99% OraPlus.

Pyrazolone carboxamide **26** showed good oral bioavailability (94%) and high plasma exposure when dosed orally in rats at 5 mg/kg.

Pyrazolone **26** was also evaluated in a pharmacodynamic assay measuring the inhibition of HGF-mediated c-Met phosphorylation in mouse liver (Figure 4). The compound was administered to Balb/c mice by oral gavage at 10, 30, or 100 mg/kg and, 2 h postdose, human HGF was injected iv to

Figure 4. The effect of compound **26** on HGF-mediated c-Met phosphorylation in the liver of Balb/c mice at 2 h. Data points represent the mean ± SD, $n = 3$; * = $p < 0.0001$ versus vehicle + HGF by ANOVA with Bonferroni/Dunn post hoc test. Bars represent phosphorylated c-Met levels. Terminal plasma concentrations are indicated by the black circles.

stimulate c-Met phosphorylation. The livers were harvested 5 min post-HGF injection, and c-Met phosphorylation levels were quantified by electrochemiluminescent assay. HGF-mediated c-Met phosphorylation was inhibited in a dose-dependent manner with an ED_{90} of <30 mg/kg and an associated plasma exposure of **26** of approximately 1000 ng·h/mL. In this study, administration of compound **26** resulted in significant c-Met inhibition (85%) even at 10 mg/kg, and there was a correlation between the inhibition of liver c-Met phosphorylation and plasma concentrations.

◼ SUMMARY

We have described the design, synthesis, and biological evaluation of a series of conformationally constrained analogues of compound **2** that replace the acylthiourea moiety with various 5-membered ring carboxamides. Collectively, the acylthiourea (**2**) → pyrimidone (**3**) → pyrazolone carboxamide (**26**) evolution resulted in a novel scaffold that exhibited potent inhibition of c-Met, superior to that of thiourea **2**. Although pyrazolone carboxamide **26** was not as selective as desired against VEGFR-2 and IGF-1R kinases, it exhibited good in vitro and in vivo profiles and set the stage for further optimization within this novel series. In part 2 of this investigation, we extend our structure−activity investigations with additional molecular modeling studies and X-ray structural analysis to uncover a number of factors that govern the in vitro selectivity profiles of this series in regard to VEGFR-2 and IGF-1R.[19]

◼ EXPERIMENTAL SECTION

Chemistry. *General.* Unless otherwise noted, all materials were obtained from commercial suppliers and used without further purification. Anhydrous solvents were obtained from Aldrich, Acros, or EM Science and used directly. All reactions involving air- or moisture-sensitive reagents were performed under a nitrogen or argon atmosphere. Microwave-assisted reactions were conducted either with an Initiator from Biotage, Uppsala, Sweden, or Explorer from CEM, Matthews, North Carolina. Silica gel chromatography was performed using either glass columns packed with silica gel (200−400 mesh, Aldrich Chemical) or prepacked silica gel cartridges (Biotage or Redisep) mounted on a medium pressure liquid chromatography instrument from ISCO [MPLC (ISCO)]. All final compounds were purified to >95% purity as determined by

LC/MS obtained on an Agilent 1100 spectrometer using a Phenomenex Synergi column (MAX-RP, 50 mm × 2.0 mm, 4μ, 40 °C). The solvent systems were A, 0.1% TFA in water; B, 0.1% TFA in MeCN; 0.8 mL/min. The method was as follows: 0.0−0.2 min, 10% B; 0.2−3.0 min, 10−100% B; 3.0−4.5 min, 100% B; 4.5−5.0 min, 100−10%; 3.0 μL injection; 215, 254 nm detection; MSD, positive mode. Low-resolution mass spectral (MS) data were obtained at the same time of the purity determination on the LC/MS instrument using ES ionization mode (positive). NMR spectra were determined with a Bruker 300 MHz or DRX 400 MHz spectrometer. Chemical shifts were reported in parts per million (ppm, δ units). Elemental analyses (C, H, N) were obtained from Atlantic Microlab in Norcross, Georgia.

N-(4-(6,7-Dimethoxyquinolin-4-yloxy)-3-fluorophenyl)-2-oxo-1-phenylpyrrolidine-3-carboxamide (12). 4-(6,7-Dimethoxyquinolin-4-yloxy)-3-fluorobenzenamine (0.300 g, 0.954 mmol), 2-oxo-1-phenyl-pyrrolidine-3-carboxylic acid (0.255 g, 1.24 mmol), and HATU (0.436 g, 1.15 mmol) were combined in dichloromethane and stirred overnight. The mixture was filtered, and the filtrate was concentrated and purified via column chromatography (aminopropyl column, 40 g, 35 min, 0−5% MeOH/dichloromethane) to give the title compound (0.400 g, 84%). MS (ESI pos ion) *m/z*: calcd for $C_{28}H_{24}FN_3O_5$, 501.2; found, 502.1 (M + H). ^{1}H NMR (300 MHz, CDCl₃) δ ppm: 2.53−2.77 (m, 2H), 3.71 (t, J = 9.5 Hz, 1H), 3.95 (dd, J = 8.4, 6.1 Hz, 2H), 4.06 (s, 3H), 4.07 (s, 3H), 6.42 (d, J = 5.1 Hz, 1H), 7.20−7.35 (m, 3H), 7.40−7.50 (m, 3H), 7.57−7.65 (m, 3H), 7.84 (dd, J = 12.1, 2.5 Hz, 1H), 8.50 (d, J = 5.3 Hz, 1H), 9.94 (s, 1 H).

N-(4-(6,7-Dimethoxyquinolin-4-yloxy)-3-fluorophenyl)-3-methyl-2-oxo-1-phenylpyrrolidine-3-carboxamide (13). Methyl 2-oxo-1-phenylpyrrolidine-3-carboxylate (0.100 g, 0.457 mmol) was dissolved in toluene and THF, and the mixture was cooled to −78 °C. A solution of LiHMDS in THF (1.0 M, 0.639 mL, 0.639 mmol) and MeOTf (0.050 mL, 0.44 mmol) were added. The mixture was allowed to warm to room temperature and then recooled in an ice water bath. More LiHMDS in THF (1.0 mL, 1.0 mmol) and MeOTf (0.050 mL, 0.44 mmol) were added, and the reaction was continued until LCMS analysis indicated the reaction was nearly complete. The mixture was diluted with dichloromethane and water. The organic layer was separated, washed with saturated ammonium chloride, dried over sodium sulfate, and concentrated to give methyl 3-methyl-2-oxo-1-phenylpyrrolidine-3-carboxylate (**6**). MS (ESI pos ion) *m/z*: calcd for $C_{13}H_{15}NO_3$, 233.1; found, 234.1 (M + H). ^{1}H NMR (300 MHz, CDCl₃) δ ppm: 1.55 (s, 3H), 2.05 (ddd, J = 13.0, 8.4, 7.2 Hz, 1H), 2.67 (ddd, J = 13.0, 7.8, 4.1 Hz, 1H), 3.75 (s, 3H), 3.73−3.83 (m, 1H), 3.95 (dt, J = 9.4, 7.6 Hz, 1H), 7.13−7.20 (m, 1H), 7.33−7.41 (m, 2H), 7.60−7.66 (m, 2H).

The crude methyl 3-methyl-2-oxo-1-phenylpyrrolidine-3-carboxylate (**6**) was mixed with KOH (0.260 g, 4.57 mmol) in MeOH and water and heated at 80 °C overnight. The mixture was then cooled to room temperature, diluted with dichloromethane, and treated with aqueous 5 N HCl to lower the pH of the aqueous phase to ~5. The layers were separated, and the aqueous phase was extracted with dichloromethane. The combined organic phases were washed with brine, dried over sodium sulfate, filtered, and concentrated to give 3-methyl-2-oxo-1-phenylpyrrolidine-3-carboxylic acid (**9**) (0.084 g, 84% over 2 steps). MS (ESI pos ion) m/z: calcd for $C_{12}H_{13}NO_3$, 219.1; found, 220.1 (M + H). ^{1}H NMR (300 MHz, CDCl$_3$) δ ppm: 1.27 (s, 1H), 1.58 (s, 3H), 2.14 (ddd, J = 13.2, 7.8, 5.3 Hz, 1H), 2.67 (ddd, J = 13.2, 8.2, 6.4 Hz, 1H), 3.81−3.97 (m, 2H), 7.17−7.24 (m, 1H), 7.36−7.43 (m, 2H), 7.61 (dd, J = 8.7, 0.9 Hz, 2H).

3-Methyl-2-oxo-1-phenylpyrrolidine-3-carboxylic acid (**9**) (0.084 g, 0.384 mmol), 4-(6,7-dimethoxynaphthalen-1-yloxy)-3-fluorobenzenamine (**11**) (0.093 g, 0.296 mmol), and HATU (0.135 g, 0.355 mmol) were dissolved in dichloromethane and stirred overnight. The reaction mixture was loaded directly onto an aminopropyl column and purified by chromatography (0−5% MeOH in dichloromethane over 20 min followed by 5% MeOH in dichloromethane for 10 min) to give the title compound (0.073 g, 48%). MS (ESI pos ion) m/z: calcd for $C_{29}H_{26}FN_3O_5$, 515.2; found, 516.2 (M + H). ^{1}H NMR (300 MHz, CDCl$_3$) δ ppm: 1.70 (s, 3H), 2.18−2.27 (m, 1H), 2.80−2.95 (m, 1H), 3.85−3.93 (m, 2H), 4.08 (s, 6H), 6.45 (d, J = 4.7 Hz, 1H), 7.20−7.36 (m, 3H), 7.41−7.48 (m, 2H), 7.54 (s, 1H), 7.58−7.65 (m, 3H), 7.86 (dd, J = 12.2, 2.4 Hz, 1H), 8.49 (d, J = 5.4 Hz, 1H), 9.92 (s, 1H).

N-(4-(6,7-Dimethoxynaphthalen-1-yloxy)-3-fluorophenyl)-3-fluoro-2-oxo-1-phenylpyrrolidine-3-carboxamide (14). Lithium diisopropylamide (0.74 mL, 2.0 M, 1.5 mmol) was added to THF at −78 °C, followed by methyl 2-oxo-1-phenylpyrrolidine-3-carboxylate (0.250 g, 1.1 mmol) in THF. After 45 min, *N*-fluorobenzenesulfonimide (0.50 g, 1.6 mmol) in THF was added. The mixture was stirred at −78 °C for 30 min, and the reaction was quenched with saturated ammonium chloride. The mixture was allowed to warm to room temperature overnight. The solvent was evaporated, and the reaction was diluted with EtOAc and water. The aqueous phase was extracted with EtOAc. The organic layers were combined, dried over sodium sulfate, and evaporated. The crude product was purified by silica gel chromatography (40 g column, 0−5% MeOH/dichloromethane over 30 min) to afford methyl 3-fluoro-2-oxo-1-phenylpyrrolidine-3-carboxylate (**7**) (0.170 g, 64%). MS (ESI pos ion) m/z: calcd for $C_{12}H_{12}FNO_3$, 237.1; found, 238.1 (M + H). ^{1}H NMR (300 MHz, CDCl$_3$) δ ppm: 2.48−2.66 (m, 1H), 2.88 (dddd, J = 13.9, 13.0, 6.9, 4.3 Hz, 1H), 3.91 (s, 3H), 3.96−4.08 (m, 2H), 7.23−7.31 (m, 1H), 7.41−7.46 (m, 2H), 7.66−7.73 (m, 2H).

Methyl 3-fluoro-2-oxo-1-phenylpyrrolidine-3-carboxylate (**7**) (0.148 g, 0.624 mmol) and KOH (0.350 g, 6.2 mmol) were combined in MeOH (38 mL), and the mixture was stirred at reflux for 4 h. The mixture was concentrated to give 3-fluoro-2-oxo-1-phenylpyrrolidine-3-carboxylic acid (**10**), which was used in the next step without further purification. MS (ESI pos ion) m/z: calcd for $C_{11}H_{10}FNO_3$, 223.1; found, 224.1 (M + H). ^{1}H NMR (300 MHz, CDCl$_3$) δ ppm: 2.43−2.63 (m, 1H), 2.82−2.95 (m, 1H), 3.88−4.09 (m, 2H), 7.21−7.29 (m, 1H), 7.41 (t, J = 8.0 Hz, 2H), 7.62 (d, J = 8.3 Hz, 2H), 10.06 (br s, 1H).

3-Fluoro-2-oxo-1-phenylpyrrolidine-3-carboxylic acid (**10**) (0.109 g, 0.489 mmol), 4-(6,7-dimethoxynaphthalen-1-yloxy)-3-fluorobenzenamine (**11**) (0.118 g, 0.376 mmol), and HATU (0.171 g, 0.451 mmol) were mixed in dichloromethane and stirred overnight. The reaction mixture was filtered, and the solids were washed with dichloromethane. The filtrate was concentrated and purified by silica gel chromatography (0−5% MeOH in dichloromethane over 20 min, followed by 5% MeOH in dichloromethane for 10 min to give the title compound (0.177 g, 91%). MS (ESI pos ion) m/z: calcd for $C_{28}H_{23}F_2N_3O_5$, 519.2; found, 520.1 (M + H). ^{1}H NMR (300 MHz, CDCl$_3$) δ ppm: 2.45−2.61 (m, 1H), 3.11 (tdd, J = 13.2, 13.2, 7.8, 3.3 Hz, 1H), 4.03 (s, 3H), 4.04 (s, 3H), 3.94−4.15 (m, 2H), 6.38 (d, J = 4.5 Hz, 1H), 7.16−7.27 (m, 2H), 7.33 (dd, J = 8.8, 1.02 Hz, 1H), 7.37−7.46 (m, 3H), 7.56 (s, 1H), 7.66 (d, J = 7.9 Hz, 2H), 7.79 (dd, J

= 12.0, 2.3 Hz, 1H), 8.49 (d, J = 5.3 Hz, 1H), 8.88 (d, J = 4.7 Hz, 1H). Anal. Calcd for $(C_{28}H_{23}F_2N_3O_5 \cdot 0.5CH_2Cl_2)$: C, H, N.

1-Benzyl-N-(4-(6,7-dimethoxyquinolin-4-yloxy)-3-fluorophenyl)-2-oxopyrrolidine-3-carboxamide (15). A mixture of 4-(6,7-dimethoxyquinolin-4-yloxy)-3-fluorobenzenamine (**11**) (0.400 g, 1.27 mmol), 1-(ethoxycarbonyl)cyclopropanecarboxylic acid (**16**) (0.260 g, 0.83 mmol), and HATU (0.290 g, 0.76 mmol) was stirred at room temperature for 5 h. The mixture was purified on silica gel to give ethyl 1-((4-(6,7-dimethoxyquinolin-4-yloxy)-3-fluorophenyl)carbamoyl)-cyclopropanecarboxylate (**17**) (0.200 g, ~80% pure) that was used directly in the next step. MS (ESI pos ion) m/z: calcd for $C_{24}H_{23}FN_2O_6$, 454.2; found, 455.1 (M + H).

A mixture of ethyl 1-((4-(6,7-dimethoxyquinolin-4-yloxy)-3-fluorophenyl)carbamoyl)cyclopropanecarboxylate (**17**) (0.200 g, 0.44 mmol) and benzylamine (0.047 g, 0.44 mmol, 1.0 equiv) was added. After 1 h, the reaction was concentrated and an additional portion of benzylamine (0.5 mL, 4.6 mmol, 10 equiv) was added and the solution was heated at 140 °C. After the reaction was complete, the mixture was allowed to cool to room temperature and the crude material was purified by HPLC (gradient of 5−95%, MeCN/water with 0.1% TFA over 70 min). The fractions containing the product were washed with saturated aqueous NaHCO$_3$ and extracted with dichloromethane. The organic layers were dried over magnesium sulfate, filtered, and concentrated to give the title compound (0.045 mg, 20%). MS (ESI pos. ion) m/z: calcd for $C_{29}H_{26}FN_3O_5$, 515.2; found, 516.1 (M + H). ^{1}H NMR (300 MHz, CDCl$_3$) δ ppm: 2.30−2.64 (m, 2H), 3.25−3.46 (m, 2H), 3.56 (t, J = 9.4 Hz, 1H), 4.04 (2s, 6H), 4.43−4.62 (m, 2H), 6.41 (d, J = 5.3 Hz, 1H), 7.11−7.42 (m, 7H), 7.44 (s, 1H), 7.58 (s, 1H), 7.82 (dd, J = 12.2, 2.1 Hz, 1H), 8.49 (d, J = 5.3 Hz, 1H), 10.18 (s, 1H).

3-Benzyl-N-(4-(6,7-dimethoxyquinolin-4-yloxy)-3-fluorophenyl)-2-oxopyrrolidine-1-carboxamide (21). tert-Butyl 2-oxopyrrolidine-1-carboxylate (**18**) (2.56 g, 13.8 mmol) was dissolved in THF (70 mL) and cooled under argon to −78 °C. A solution of LDA (1.8 M solution in heptane/THF, 7.9 mL, 14.2 mmol) was added via a syringe. After 1 h, benzyl bromide (1.65 mL, 14 mmol) was added via a syringe. The mixture was placed in an ice bath and stirred under an argon atmosphere for 1 h and then treated with saturated ammonium chloride (75 mL). A second reaction using 5.45 g of tert-butyl 2-oxopyrrolidine-1-carboxylate (**18**) was performed, and the crude material was combined with the first batch. The aqueous phase was extracted with EtOAc (100 mL), and the organic phases were combined, dried over magnesium sulfate, filtered, concentrated, and purified on silica gel to afford tert-butyl 3-benzyl-2-oxopyrrolidine-1-carboxylate (**19**) (2.35 g, 15%). MS (ESI pos ion): calcd for $C_{12}H_{13}NO_3$, 219.1; found, 220.1 (M − C_4H_9)[+]. ^{1}H NMR (400 MHz, CDCl$_3$) δ ppm: 1.54 (s, 9H), 1.70 (dq, J = 12.7 Hz, 9.3 Hz, 1H), 1.97−2.05 (m, 1H), 2.61−2.72 (m, 1H), 2.74−2.87 (m, 1H), 3.28 (dd, J = 13.8, 3.8 Hz, 1H), 3.52 (ddd, J = 10.8, 9.1, 7.2 Hz, 1H), 3.66 (ddd, J = 10.7, 8.4, 2.9 Hz, 1H), 7.15−7.36 (m, 5H).

tert-Butyl 3-benzyl-2-oxopyrrolidine-1-carboxylate (**19**) (2.30 g, 8.35 mmol) was dissolved in dichloromethane (30 mL) and cooled in an ice water bath. Trifluoroacetic acid (6 mL) was added. The solution was stirred under argon while being allowed to warm to room temperature. After 2 h, the mixture was concentrated and dried under high vacuum to give 3-benzylpyrrolidin-2-one, which was taken directly to the next step without further purification. MS (ESI pos ion) m/z: calcd for $C_{11}H_{13}NO$, 175.1; found, 176.1 (M + H).

The crude 3-benzylpyrrolidin-2-one was dissolved in THF (32 mL), and triethylamine (2.4 mL, 17 mmol) was added. The flask was cooled in an ice water bath, and 4-nitrophenyl chloroformate (2.53 g, 12.6 mmol) was added. The mixture was allowed to warm to room temperature while being stirred overnight. The reaction was then quenched with water (60 mL), and the layers were separated. The aqueous phase was extracted with EtOAc (2 × 30 mL). The combined organic phases were sequentially washed with 2% HCl (50 mL), saturated sodium bicarbonate (20 mL), and brine (40 mL). The organic phase was dried over magnesium sulfate, filtered, and concentrated, and the crude material was purified by silica gel chromatography (4:4:1 hexanes/dichloromethane/EtOAc) to afford 4-

nitrophenyl 3-benzyl-2-oxopyrrolidine-1-carboxylate (**20**) (1.43 g, 45%). MS (ESI pos ion) m/z: calcd for $C_{18}H_{16}N_2O_5$, 340.1; found, 341.1 (M + H). ^{1}H NMR (400 MHz, CDCl$_3$) δ ppm: 1.82−1.91 (m, 1 H), 2.12−2.22 (m, 1H), 2.66−2.72 (m, 2H), 3.17−3.31 (m, 3H), 6.92 (d, J = 9.0 Hz, 2H), 7.20−7.33 (m, 5H), 8.19 (d, J = 9.0 Hz, 2H).

4-(6,7-Dimethoxyquinolin-4-yloxy)-3-fluorobenzenamine (0.253 g, 0.805 mmol) and 4-nitrophenyl 3-benzyl-2-oxopyrrolidine-1-carboxylate (**20**) (0.661 g, 1.94 mmol) were dissolved in DMF (3 mL) in a microwave vial and heated in a microwave at 60 °C and 60 W for 40 min. The vial was allowed to cool to room temperature, and the contents were poured into water (20 mL) and extracted with dichloromethane (3 × 30 mL). The organic phases were combined, dried over magnesium sulfate, filtered, and concentrated, and the crude material was purified on reverse phase HPLC (10% → 95% MeCN/ water with 0.1% TFA) to afford the title compound (0.006 g, 1%). MS (ESI pos ion) m/z: calcd for $C_{29}H_{26}FN_3O_5$, 515.2; found, 516.1 (M + H). ^{1}H NMR (400 MHz, CDCl$_3$) δ ppm: 1.78−1.92 (m, 1H), 2.12− 2.25 (m, 1H), 2.83 (dd, J = 13.9, 9.2 Hz, 1H), 3.02−3.14 (m, 1H), 3.28 (dd, J = 13.8, 4.6 Hz, 1H), 3.65−3.78 (m, 1H), 3.92 (ddd, J = 11.4, 8.8, 2.7 Hz, 1H), 4.13 (s, 3H), 4.16 (s, 3H), 6.76 (d, J = 6.1 Hz, 1H), 7.19−7.43 (m, 7H), 7.69 (s, 1H), 7.85 (dd, J = 12.0, 2.2 Hz, 1H), 7.91 (s, 1H), 8.70 (d, J = 6.6 Hz, 1H), 10.91 (s, 1H).

N-(4-(6,7-Dimethoxyquinolin-4-yloxy)-3-fluorophenyl)-2-oxo-3-phenylimidazolidine-1-carboxamide (23). To a mixture of 4-(6,7-dimethoxyquinolin-4-yloxy)-3-fluorobenzenamine (1.17 g, 3.71 mmol) in dichloromethane (13.5 mL) and pyridine (0.60 mL, 7.4 mmol) was added *p*-nitrophenyl chloroformate (1.01 g, 5.00 mmol). The flask was placed in a water bath and stirred at room temperature under nitrogen. After 1 h, the reaction was quenched with water (20 mL). The mixture was filtered, and the solid was washed with methanol and diethyl ether. The layers of the filtrate were separated, and the aqueous phase was extracted with dichloromethane (3 × 20 mL). The organic extracts were combined and washed with aqueous HCl (40 mL). The organic phase was dried over magnesium sulfate, filtered, and concentrated to afford 4-nitrophenyl 4-(6,7-dimethoxyquinolin-4-yloxy)-3-fluorophenylcarbamate (**22**) (1.54 g, 87%). MS (ESI pos ion) m/z: calcd for $C_{24}H_{18}FN_3O_7$, 479.1; found, 480.1 (M + H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 4.00 (s, 6H), 6.74 (d, J = 5.5 Hz, 1H), 7.42−7.80 (m, 7H), 8.34 (d, J = 9.0 Hz, 2H), 8.68 (d, J = 5.9 Hz, 1H), 10.90 (br s, 1H).

To a solution of 1-phenylimidazolidin-2-one (0.217 g, 1.34 mmol) in DMF (9.0 mL) under nitrogen at 0 °C was added sodium hydride (0.768 g, 60% in mineral oil, 1.92 mmol). After 15 min, the reaction was warmed to room temperature and stirred for 15 min before 4-nitrophenyl 4-(6,7-dimethoxyquinolin-4-yloxy)-3-fluorophenylcarbamate (**22**) (0.519 g, 1.08 mmol) was added. After 25 min at room temperature, the mixture was quenched with water (20 mL) and filtered. The solid was purified using silica gel chromatography (30:1 → 20:1 dichloromethane/MeOH), followed by HPLC (10% → 95% MeCN in water with 0.1% TFA over 25 min) to afford title compound (0.173 g, 32% yield). MS (ESI pos ion) m/z: calcd for $C_{27}H_{23}FN_4O_5$, 502.2; found, 503.1 (M + H). ^{1}H NMR (400 MHz, CDCl$_3$) δ ppm: 3.99−4.07 (m, 2H), 4.10−4.18 (m, 2H), 4.13 (s, 3H), 4.16 (s, 3H), 6.77 (d, J = 6.5 Hz, 1H), 7.22−7.30 (m, 2H), 7.33−7.38 (m, 1H), 7.45 (t, J = 7.9 Hz, 2H), 7.56 (d, J = 8.0 Hz, 2H), 7.68 (s, 1H), 7.86 (dd, J = 12.1, 2.4 Hz, 1H), 7.92 (s, 1H), 8.70 (d, J = 6.6 Hz, 1H), 10.76 (s, 1H). Anal. Calcd for ($C_{27}H_{23}FN_4O_5$·2.0CH$_2$Cl$_2$): C, H. Found: 3.48. Calcd: 4.05 N. Found: 7.76. Calcd: 8.33.

N-(4-(6,7-Dimethoxyquinolin-4-yloxy)-3-fluorophenyl)-1,5-di-methyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxamide (26). To a 100-mL round-bottomed flask was added 1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carbaldehyde (**24**) (1.00 g, 4.6 mmol, Aldrich), sodium phosphate monobasic, monohydrate (1.4 mL, 20 mmol), and *t*-BuOH (20 mL). The well-stirred slurry was cooled to 0 °C, and 2-methylbut-2-ene (5.0 mL, 47 mmol) was added. A solution of sodium chlorite (0.760 g, 6.7 mmol) in 20 mL of water was added slowly. After 5 min, the reaction mixture was allowed to warm to room temperature and stirred for 4 h. An additional portion of sodium chlorite was added, and the solution was stirred overnight. The reaction mixture was treated with 1N HCl (2 mL) and extracted

with chloroform (3×). The combined organic layers were extracted with 1N NaOH (15 mL). The aqueous layer was acidified with aqueous 5N HCl (5 mL) and extracted with chloroform (3×). The combined organic layers were dried over sodium sulfate, filtered, and concentrated to give 5-methyl-1-methyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxylic acid (**25**) (0.960 g, 87%) as a yellow solid. MS (ESI pos ion) m/z calcd for $C_{12}H_{12}N_2O_3$, 232.1; found, 233.1 (M + H). ^{1}H NMR (300 MHz, CDCl$_3$) δ ppm: 2.70 (s, 3H), 3.38 (s, 3H), 7.35 (dd, J = 8.2, 1.3 Hz, 2H), 7.40−7.71 (m, 3 H), 12.08 (br s, 1 H).

To a solution of 5-methyl-1-methyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxylic acid (**25**) (0.223 g, 96 μmol) and 4-(6,7-dimethoxynaphthalen-1-yloxy)-3-fluorobenzenamine (**11**) (0.200 g, 64 μmol) in DMF (10 mL) at 0 °C was added triethylamine (0.13 mL, 96 μmol) followed by HATU (0.365 g, 96 μmol) in portions. The reaction mixture was allowed to warm to room temperature and then stirred at room temperature for 16 h. The solution was diluted with EtOAc (60 mL) and water (30 mL). The organic phase was separated and washed with 30 mL of brine and dried over Na$_2$SO$_4$. The solution was filtered and concentrated in vacuo. The crude product was purified by silica gel chromatography (EtOAc to 10% MeOH/EtOAc) to afford the title compound (0.180 g, 53%) as a white solid. MS (ESI pos ion) m/z calcd for $C_{29}H_{25}FN_4O_5$, 528.2; found, 529.1(M + H). ^{1}H NMR (300 MHz, CDCl$_3$) δ ppm: 2.81 (s, 3 H), 3.38 (s, 3H), 4.06 (2s, 6H), 6.44 (dd, J = 5.3, 1.0 Hz, 1H), 7.12−7.23 (m, 1H), 7.28−7.34 (m, 1H), 7.34−7.40 (m, 2H), 7.44 (s, 1H), 7.47−7.52 (m, 1H), 7.52−7.66 (m, 3H), 7.93 (dd, J = 12.6, 2.5 Hz, 1H), 8.49 (d, J = 5.4 Hz, 1H),10.89 (s, 1H). Anal. Calcd for ($C_{29}H_{25}FN_4O_5$·0.2 CH$_2$Cl$_2$): C, H, N.

N-(4-(6,7-Dimethoxyquinolin-4-yloxy)-3-fluorophenyl)-N,1,5-tri-methyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxamide (27). A solution of *N*-(4-(6,7-dimethoxyquinolin-4-yloxy)-3-fluoro-phenyl)-1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-car-boxamide (**26**) (0.500 g, 0.950 mmol) in a mixture of THF/DMF (3:1) was placed under a nitrogen atmosphere and cooled to 0 °C. Sodium hydride (60% in mineral oil, 45 mg) was added to the cooled solution. After stirring for 30 min, methyl iodide (0.148 g 1.04 mmol) was added and the reaction mixture was allowed to stir at room temperature for 2 d. Water was added, and the mixture was extracted with dichloromethane. The organic layer was dried and concentrated. The residue was purified by silica gel chromatography with 0−5% MeOH in dichloromethane as eluant to give the title compound (0.036 g, 7%) (a less polar byproduct corresponding to C-methylation was also observed). MS (ESI pos ion) m/z: calcd for $C_{30}H_{27}FN_4O_5$, 542.2; found, 543.2 (M + H). ^{1}H NMR (300 MHz, CDCl3) δ ppm: 2.54 (s, 3H), 3.22 (s, 3H), 3.52 (s, 3H), 4.06 (s, 6H), 6.26 (d, J = 5.4 Hz, 1H), 7.12−7.24 (m, 5H), 7.35−7.52 (m, 4 H), 7.56 (s, 1H), 8.28 (d, J = 5.3 Hz, 1H).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Biological assays, in vivo study protocols, selectivity data, and X-ray crystallographic data for compound **26**. This material is available free of charge via the Internet at http://pubs.acs.org.

Accession Codes

The cocrystal structure of c-Met + compound **26** has been deposited in the Protein Data Bank with PDB code 3U6H.

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Notes

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■ ABBREVIATIONS USED

RTK, receptor tyrosine kinase; EGFR, epidermal growth factor receptor; VEGFR-2, vascular endothelial growth factor receptor 2; IGF-1R, insulin-like growth factor receptor 1; ATP, adenosine-5′-triphosphate; DCM, dichloromethane; BSA, bovine serum albumin; HGF, hepatocyte growth factor; HLM, human liver microsomes; RLM, rat liver microsomes; iv, intravenous; SAR, structure—activity relationship; PK, pharmacokinetic; PD, pharmacodynamic; TFA, trifluoroacetic acid; LDA, lithium diisopropylamide; HATU, 2-(7-aza-1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluoro-phosphate; rt, room temperature

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