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Structure-Based Design of Novel Class II c-Met Inhibitors: 2. SAR and Kinase Selectivity Profiles of the Pyrazolone Series

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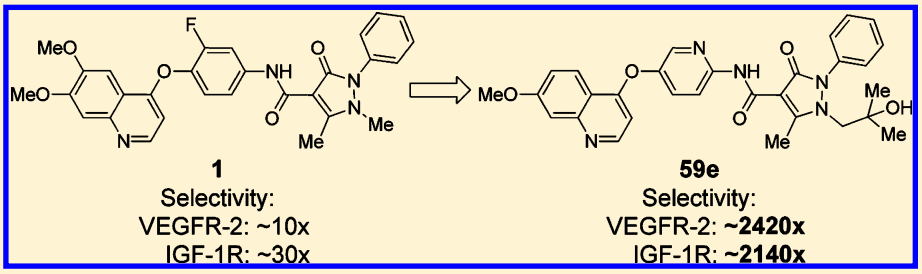
Supporting Information



ABSTRACT: As part of our effort toward developing an effective therapeutic agent for c-Met-dependent tumors, a pyrazolone-based class II c-Met inhibitor, *N*-(4-((6,7-dimethoxyquinolin-4-yl)oxy)-3-fluorophenyl)-1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carboxamide (**1**), was identified. Knowledge of the binding mode of this molecule in both c-Met and VEGFR-2 proteins led to a novel strategy for designing more selective analogues of **1**. Along with detailed SAR information, we demonstrate that the low kinase selectivity associated with class II c-Met inhibitors can be improved significantly. This work resulted in the discovery of potent c-Met inhibitors with improved selectivity profiles over VEGFR-2 and IGF-1R that could serve as useful tools to probe the relationship between kinase selectivity and in vivo efficacy in tumor xenograft models. Compound **59e** (AMG 458) was ultimately advanced into preclinical safety studies.

INTRODUCTION

The receptor tyrosine kinase (RTK) c-Met is mainly expressed by epithelial cells. Activation of c-Met is regulated by its ligand, hepatocyte growth factor (HGF), also known as scatter factor (SF).[1] Upon binding of HGF at the extracellular domain, c-Met receptor undergoes dimerization that results in transphosphorylation of the intracellular tyrosine residues (Y1234, Y1235) within the catalytic site.[2] Further phosphorylation of residues Y1349 and Y1356 mobilizes the intracellular C-terminal docking domain that recruits and subsequently activates a wide range of downstream signaling molecules (e.g., Grb2, Gab1, PI3K, Akt, Ras, Erk, and STAT3) that modulate the survival, proliferation, migration, and invasion of cells. As such, normal HGF/c-Met signaling plays an important role during embryogenesis and tissue injury repair.[3] On the other hand, dysregulation of this pathway (through, e.g., either overexpression of HGF/c-Met or activating mutation of *MET* gene) can render many cellular processes unchecked and promote tumorigenesis. It has been established that aberrant signaling of the HGF/c-Met pathway correlates with aggressive tumor growth and poor prognosis in cancer patients.[4] Different approaches to inhibition of the HGF/c-Met pathway in cancer cells have been documented.[5] These include antagonistic ligands to c-Met, antibodies against either HGF or c-Met, and small molecule kinase inhibitors targeting the intracellular kinase domain. Numerous c-Met kinase inhibitors have been reported in the literature.[6] These inhibitors can be categorized into either class I or class II based on their binding mode in the c-Met kinase domain (vide infra). While class I molecules tend to be very selective for c-Met, thus far, a majority of the class II molecules are multikinase inhibitors. Improving the selectivity of class II c-Met inhibitors has been a significant challenge. In fact, until recently, no selective class II c-Met inhibitors have been reported and little is known as to whether the kinase selectivity profiles of class II c-Met inhibitors can be improved. Schroeder et al. reported the design of a pyridone-based c-Met inhibitor that was selective over a number of kinases, including IGF-1R.[7] The selectivity over VEGFR-2 was modest (46-fold). We postulated that knowledge from kinase structural analysis

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coupled with SAR and X-ray crystallography studies on c-Met complexes would enable us to better understand and optimize kinase selectivity within this family of class II c-Met inhibitors. In the preceding paper, we reported the structure-based design of a class II c-Met inhibitor that led to compound **1** (Figure 1),

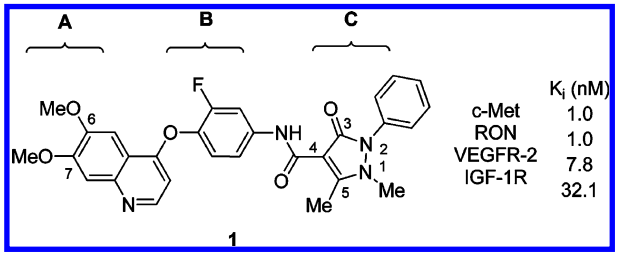

Figure 1. Structure and activity of compound **1**, a pyrazolone-based class II c-Met inhibitor (numbering conventions used in the text for the quinoline and the pyrazolone rings are shown).

which represented the most potent c-Met inhibitor in that series (K_i = 1.0 nM).[8] In this paper, we will detail our efforts toward enhancing the kinase selectivity profile of compound **1** by modifying the quinoline (A), the fluorophenyl (B), and particularly the pyrazolone (C) regions of the molecule.[9]

Structural Basis for SAR Exploration of the Pyrazolone Ring. In general, the extended structure of class II c-Met inhibitors beyond the ATP binding pocket in the c-Met kinase domain tends to render them less selective over other kinases.[10] Mindful of this observation, pyrazolone **1** was tested for selectivity against a panel of tyrosine and serine/threonine kinases. In addition to the potent inhibition of c-Met and RON, a member of the MET proto-oncogene family,[11] pyrazolone **1** also showed activity toward a number of other kinases.[12] In particular, it was a potent inhibitor of VEGFR-2 (K_i = 8 nM), itself an important and clinically proven cancer therapy target,[13] and of the insulin-like growth factor 1 receptor (IGF-1R, K_i = 32 nM), another RTK that is upregulated in both primary and metastatic cancers.[14] To develop these types of inhibitors as potential probes for c-Met driven tumors, higher levels of selectivity over other kinases were desired. Given the extensive structural information of inhibitor-bound VEGFR-2 available in the literature, we set out to identify structural differences between c-Met and VEGFR-2 within the kinase binding pockets as a means of enhancing selectivity.

Examination of publicly available VEGFR-2 crystal structures indicated that this protein, like most other kinases, lacked the presence of a hydrophobic pocket equivalent to the Ile1145 pocket in c-Met. This suggested that **1** would bind VEGFR-2 in a well-established binding mode in which the inhibitor would induce the protein to adopt a DFG-out conformation by replacing the cognate phenylalanine of the DFG motif with the *N*-phenyl ring of the pyrazolone, as shown in Figure 2A.[15] Moreover, because our structural analysis of the kinome suggested that the Ile1145 pocket may be unique to c-Met, we hypothesized that **1** would adopt the same DFG-out binding mode in other kinases as well. Subsequent X-ray crystallography studies of **1** bound to VEGFR-2 confirmed this prediction and clearly showed the expected DFG-out binding mode (Figure 2B). Specifically, the quinoline and the fluorophenyl ring of the inhibitor assume essentially the same orientation in VEGFR-2 as seen in c-Met (cf. Figure 2C).[8] In contrast, the pyrazolone carboxyl amide rotates 180° away from the C-helix of VEGFR-2, displacing the DFG-Phe1047 residue with the *N*-phenyl group. In this orientation, the oxygen atom of the carboxyl amide forms a hydrogen bond to catalytic Lys868 and the pyrazolone carbonyl group forms a hydrogen bond to the backbone NH of Asp1046 from the DFG sequence. The N(1)-Me group on the pyrazolone ring resides ∼3.6 Å away from Ile888 on the C-helix, forming a close van der Waals contact. The difference between the two binding modes (c-Met vs VEGFR-2) is highlighted by an overlay of the two crystal structures (Figure 2C).

The DFG-out conformation of VEGFR-2 bound to **1** suggested that the pyrazolone ring in **1** could be exploited as a selectivity handle. For example, due to the close proximity of the C(5)-Me and N(1)-Me of the pyrazolone ring to the γ carbons of Glu885 and Ile888, respectively, substitutions (especially large, polar ones) at these positions should create unfavorable interactions with the C-helix of VEGFR-2 and most other kinases. On the other hand, these same substitutions were expected to be well tolerated upon binding to c-Met based on the X-ray crystal structure of the **1** bound to c-Met.[8] The binding mode in c-Met showed the N(1)-Me projecting out toward a largely solvent accessible region of the protein where there would be opportunities for introducing additional contacts with the protein (Figure 2C). Additionally, the C(5)-Me was observed to project directly toward Phe1223 of the DFG sequence, which had been shown from previous crystal structures to be capable of adopting a DFG-out conformation, indicating that c-Met could tolerate a larger C(5)-substituents.[16]

On the basis of this understanding of the structural differences between c-Met and VEGFR-2, modification of the pyrazolone ring (region C, Figure 1) represented a logical approach to enhancing the selectivity profile of the pyrazolone-based class II c-Met inhibitors against VEGFR-2 and other kinases. Additionally, our SAR efforts in other parts of the molecule (i.e., A, B regions, Figure 1) aimed at improving the physicochemical properties of **1** also uncovered subtle influences of modifications on selectivity profiles. To better assess selectivity/off-target liability over other RTKs, a second counterscreen target, IGF-1R, was chosen along with VEGFR-2 in this study. Following discussion of the chemical synthesis of various analogues, we will briefly highlight the SAR investigations in the quinoline (A) and in the central *F*-phenyl ring (B) of **1**. We then present our major SAR work in the pyrazolone core (C) as guided by the aforementioned hypotheses.

■ CHEMISTRY

Analogues with substitution at the 6-position of the quinoline were prepared as shown in Scheme 1. The requisite quinoline ring was constructed following the protocol of Lin and Loo.[17] Thus, 4-bromo-3-methoxybenzenamine **2** was condensed with diethyl ethoxymethylenemalonate at 100 °C followed by cyclization in diphenyl ether at 245 °C to give ethyl 6-bromo-4-hydroxy-7-methoxyquinoline-3-carboxylate (**3a**). This crude material was subjected to hydrolysis followed by decarboxylation over a short reaction time (to minimize the *O*-demethylation during prolonged heating) to yield 6-bromo-7-methoxyquinolin-4-ol (**3b**), which was converted to chloride **4** using $POCl_3$. Biaryl ether-formation with **4** and 2-fluoro-4-nitrophenol (**5**) was best achieved in chlorobenzene to give 6-bromo-4-(2-fluoro-4-nitrophenoxy)-7-methoxyquinoline **6**.[18] The latter was converted to either the 6-methyl or the 6-vinylquinoline derivatives (**7** and **8**) under the Negishi[19] or

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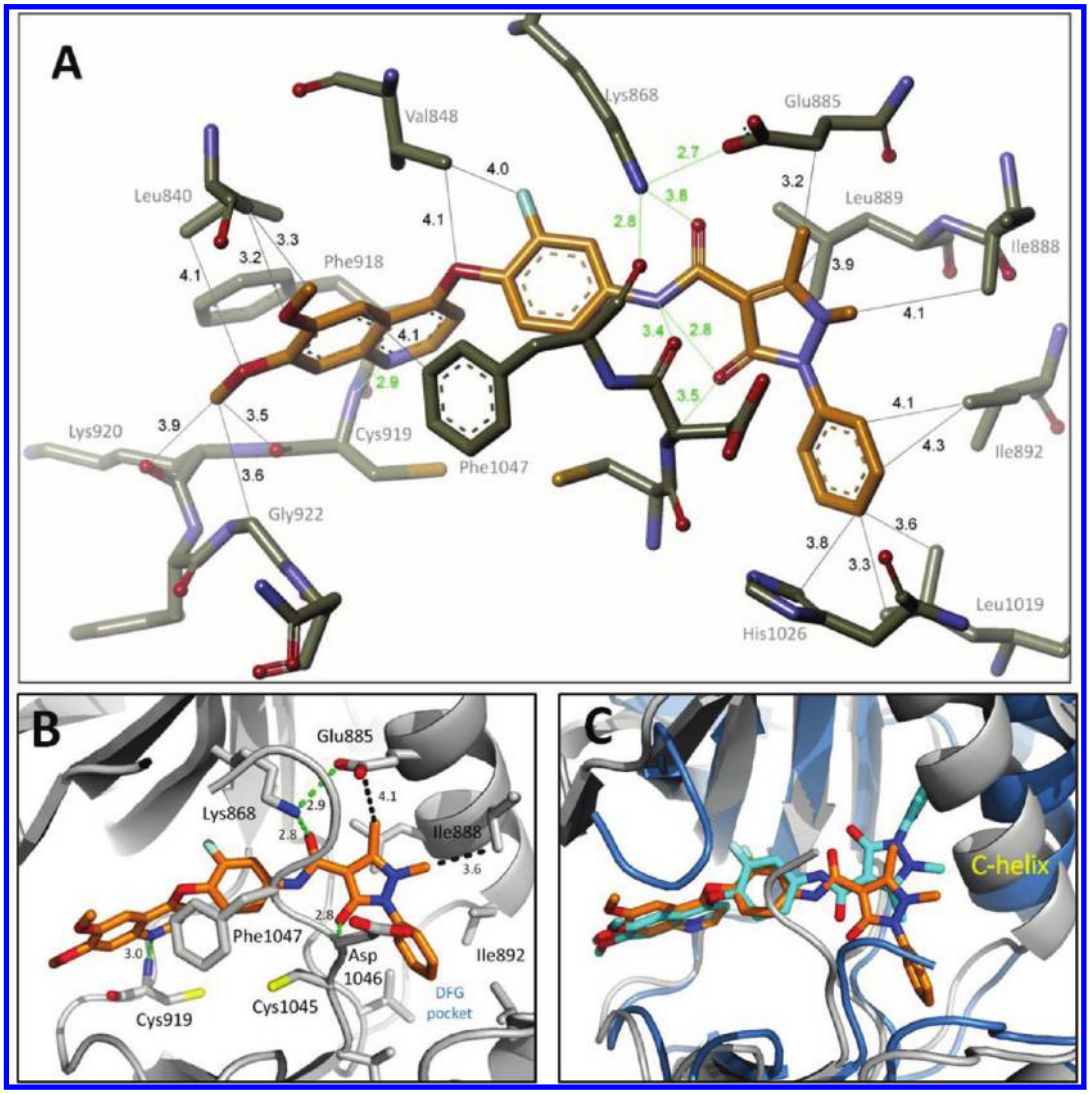

Figure 2. (A) Model of **1** in VEGFR-2 indicating key contacts. Hydrogen bonds are colored in green and key van der Waals contacts in black. Distances are in Å. (B) X-ray cocrystal structure of **1** in VEGFR-2 (PDB: 3U6J). Phe1047 of the DFG-motif adopts a DFG-out conformation as predicted. (C) Overlay of c-Met (blue) and VEGFR-2 (gray) cocrystal structures showing the relative orientations of **1** and the 3−4 Å "movement" of the C-helix.

the Molander[20] protocols, respectively. Alternatively, selective reduction of the nitro group in **6** with $SnCl_2$ provided bromoaniline **9a**, whereas hydrogenation over Pd catalyst led to the *des*-bromo aniline **9d**. Similarly, hydrogenation of the nitro groups in **7** and **8**, with concomitant hydrogenolysis of the vinyl group in **8**, afforded alkyl anilines **9b** and **9c**. Amide coupling of **9a−d** with 1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carboxylic acid (**10**)[8] in the presence of HATU furnished analogues **11a−d**.

The syntheses of analogues with modifications in the central "B-ring" region are shown in Scheme 2. Thus 6,7-dimethoxyquinoline-based anilines 2-chloro-4-(6,7-dimethoxyquinolin-4-yloxy)aniline (**12**),[21] 6-(6,7-dimethoxyquinolin-4-yloxy)-pyridin-3-amine (**13**),[22] and 5-(6,7-dimethoxyquinolin-4-yloxy)pyridin-2-amine (**14**)[23] were coupled with either 1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carboxylic acid (**10**) or its acid chloride to give dimethoxyquinolines **15a−c**. Monomethoxyl quinoline-based aniline 5-(7-methoxyquinolin-4-yloxy)pyridin-2-amine (**16**) was prepared as described previously.[9] Biaryl ether formation from 4-chloro-7-methoxyquinoline (**17**)[24] and 3-methoxy-4-nitrophenol under SN_{Ar} conditions gave nitro derivative **18a**, which was reduced to aniline **18b**. A modified Ullmann coupling followed by benzoylation allowed for the conversion of 2-amino-5-iodopyrimidine **19** to **20a**.[25] *O*-Debenzylation of the latter to **20b**, followed by SN_{Ar} biaryl ether formation to **21a**, and final debenzoylation afforded aminopyrimidine **21b**. Amide coupling of **16**, **18b**, and **21b** with **10** provided monomethoxyquinolines **22a−c**.

Several synthetic routes were developed for C(5)-substituted pyrazolones. In the first method, simple amino groups at the C-5 carbon were installed via the bromide intermediate **24**, which was readily prepared via bromination[26] of methyl 1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carboxylate **23**[27] (Scheme 3). Substitution of the bromine with either sodium azide, followed by reduction, or secondary amines led to the formation of esters **25a−d**. Saponification and amide coupling with either **9d** or **16** afforded compounds **26a−d** and **27**.

In the second method, the C(5)-substituents were introduced via de novo pyrazolone synthesis featuring an amido Dieckmann condensation (Scheme 4). Thus, Boc-protected

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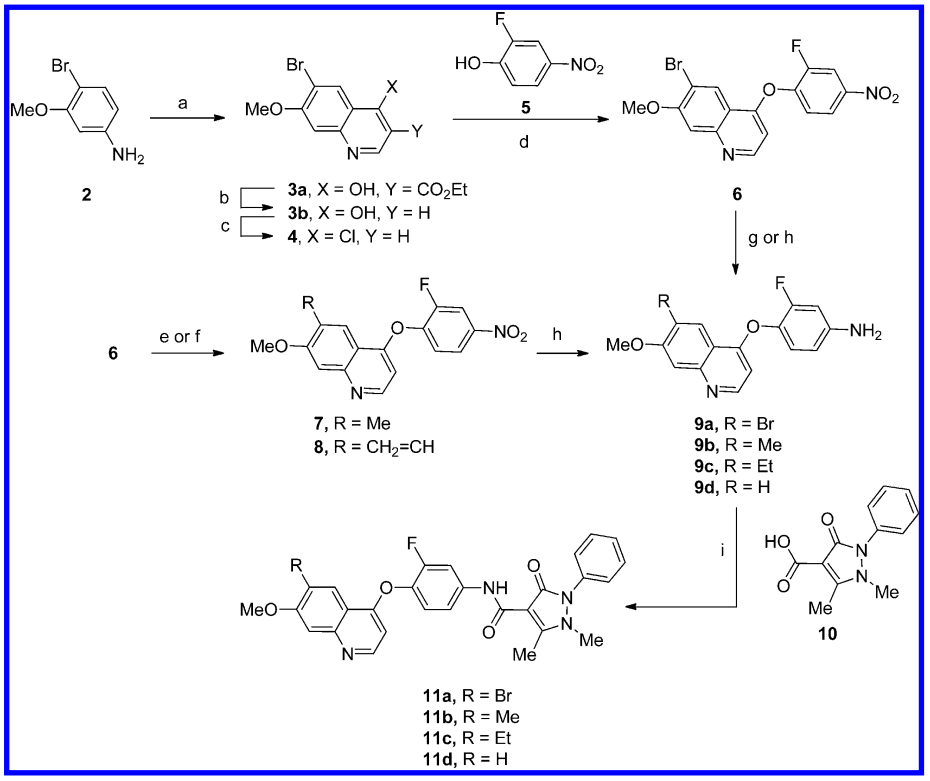
Scheme 1. [a]



[a]Reagents and conditions: (a) (1) diethyl ethoxymethylenemalonate, 100 °C, 17 h, (2) Ph_2O, 245 °C, 2 h; (b) (1) NaOH (aq), 100 °C, 50 min, HCl, (2) Ph_2O, reflux, 30 min; (c) $POCl_3$, 110 °C, 2 h; (d) PhCl, 140 °C, 16 h; (e) Me_2Zn, $Pd(dppf)Cl_2$, dioxane, 105 °C; (f) $(CH_2{=}CH)BF_3K$, $Pd(dppf)Cl_2$, PrOH, 95 °C; (g) $SnCl_2$, EtOH, 70 °C; (h) H_2, $Pd(OH)_2/C$ (20%), EtOH; (i) HATU, DCM.

amino acids **28a–b** were coupled with phenyl hydrazine to give **29a–b**. The β-NH of the acyl hydrazides were protected as N(Cbz) (**30a–b**), setting the stage for methylation at the α-NH to give hydrazides **31a–b**. After removal of the Cbz groups, the β-NH's of **32a–b** were acylated with ethyl malonoyl chloride. The resulting intermediates **33a–b** were subjected to sodium ethoxide-mediated cyclization followed by in situ saponification to furnish C-5 substituted pyrazolone-4-carboxylic acids **34a–b**. Amide coupling as described earlier with anilines **9d** and **16** afforded **35a–b** and **36** after removal of the Boc-protecting groups.

In the final method (Scheme 5), ketoesters that were either commercially available (**38g–i**) or readily accessible from acids **37a–f** under the Masomune conditions (**38a–f**)[28] were subjected to Knorr condensations with methyl-2-phenyl-hydrazine[29] to give pyrazolones **39a–i**. Subsequent Vilsmeier formylation[30] and Pinnick[31] oxidation at C(4) furnished pyrazolone-4-carboxylic acids **41a–i**. HATU-mediated amide coupling with aniline **9d** or **16** yielded analogues **42a–c** and **43c–i**.

Alkyl substitutions at the pyrazolone N(1) position were installed by the direct *N*-alkylation of 5-methyl-2-phenyl-1*H*-pyrazol-3(2*H*)-one (**44**) at fusion temperatures (Scheme 6). This reaction worked best with either alkyl iodides or alkyl tosylates. Vilsmeier formylation of pyrazolones **45a–c** and subsequent oxidation of aldehydes **46a–c** provided the carboxylic acids **47a–c**. The methylallyl group in **47c** was readily converted to the saturated derivative **47d** via hydrogenation. Amide coupling with either **9d** or **16** afforded final products **48a–d**, **49a**, and **50b**. At the early stage of our work, the olefin **48c** served as a precursor to hydroxylated analogues. Thus, the 2-methylallyl function in **48c** was further transformed, via intermediates **51** and **52**, to the 2-hydroxypropyl analogue **53**.

To expedite efforts on the synthesis of N(1)-modified analogues containing a β-hydroxyl ethyl moiety, we developed a general method for the selective hydroxyethylation of pyrazolone **54** with oxarines **55** (Scheme 7).[32] The resulting benzyl esters **56a–e** were cleaved under hydrogenolysis conditions to acids **57a–e** that were in turn coupled with aniline **9d** or **16** to give the desired products. Using this methodology, both the racemic and the enantiomers of **53** [(*R*)-**58a**, (*S*)-**58a**] were readily prepared. Similarly, a variety of β-hydroxyl ethyl derivatives such as primary (**58b**, **59b**), secondary (**58c**, **58d**, **59a**), and tertiary (**58e**, **59e**) alcohols were synthesized. Additionally, the primary alcohol **58b** was converted through the Mitsunobu reaction to amine **61** via phthalimide **60**.

Modification of the alcohols obtained from the oxirane opening was also explored to expand the structural diversity at N(1) (Scheme 8). Thus, alcohol **56b** was treated with TMS-diazomethane to afford methyl ether **62a**, which was then converted, via acid **62b**, to analogue **63**. For the synthesis of 3-amino-2-hydroxypropyl substituted pyrazolones at N(1), the 3-chloro-2-hydroxypropyl derivative **64**[32] was converted via the azido intermediate (**65a**) to amino alcohol **65b**. Boc-protection of the free amine (to **66a**) and *O*-debenzylation (to **66b**) followed by amide coupling afforded, after deprotection, the amino alcohol analogue **67**. In addition, **65b** was sequentially

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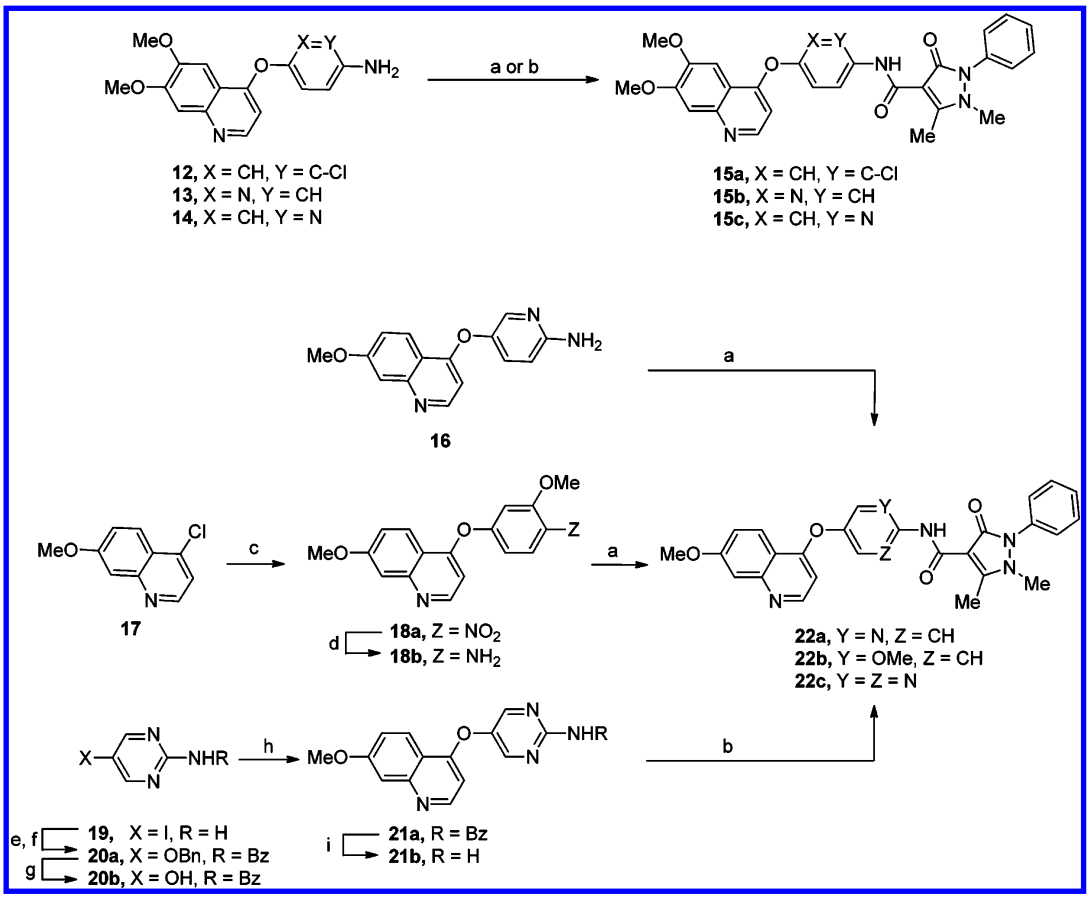
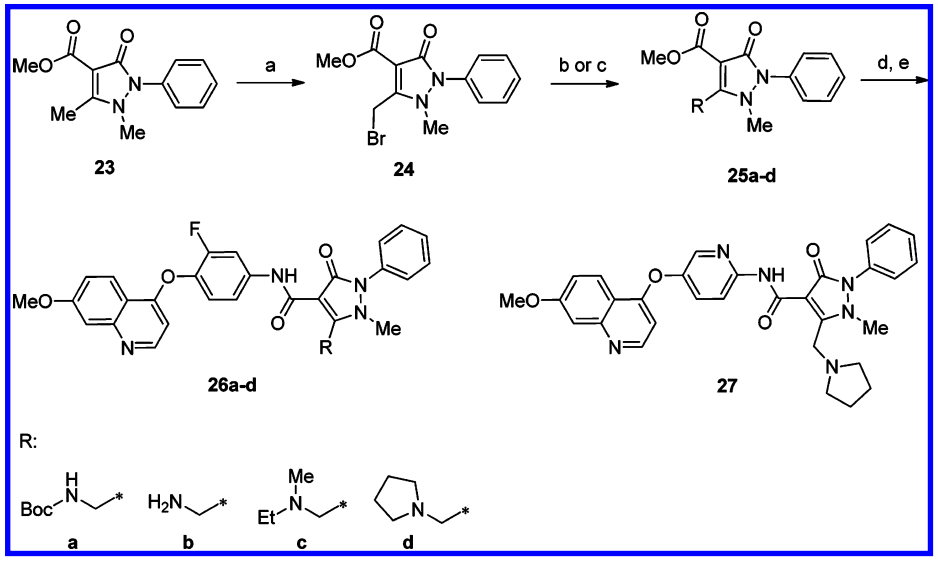
Scheme 2. [a]



[a]Reagents and conditions: (a) **10**, HATU, Et_3N, DCM; (b) **10**, $(CO)_2Cl_2$, DMF, DCM; (c) 3-methoxy-4-nitrophenol, PhCl, reflux; (d) H_2, Pd/C (20%), EtOAc; (e) BnOH, Cs_2CO_3, CuI, 1,10-phenanthroline, 110 °C; (f) BzCl, pyridine, DCM; (g) H_2, Pd/C (10%), MeOH; (h) **17**, PPTS, 2-BuOH, 100 °C; (i) NaOH, MeOH, 70 °C.

Scheme 3. [a]



[a]Reagents and conditions: (a) NBS, $CHCl_3$; (b) (1) NaN_3, DMF, (2) PPh_3, THF, H_2O; (3) Boc_2O, DCM; (c) R_1R_2NH, DCM; (d) NaOH, H_2O, MeOH, 80 °C; (e) HATU, **9d** or **16**, DMF or DCM.

converted to intermediates **68a–b** and the final oxazolidinone analogue **69**.

SAR of the Quinoline 6-MeO Group (A-Region). Di- or trimethoxy substituted aryl appendages are commonly employed in the linker strand region of the ATP binding site to boost the potency of kinase inhibitors.[33] While useful for SAR purposes, these poly methoxy-substituted aryls often introduce metabolic instabilities. In the case of **1**, we recognized

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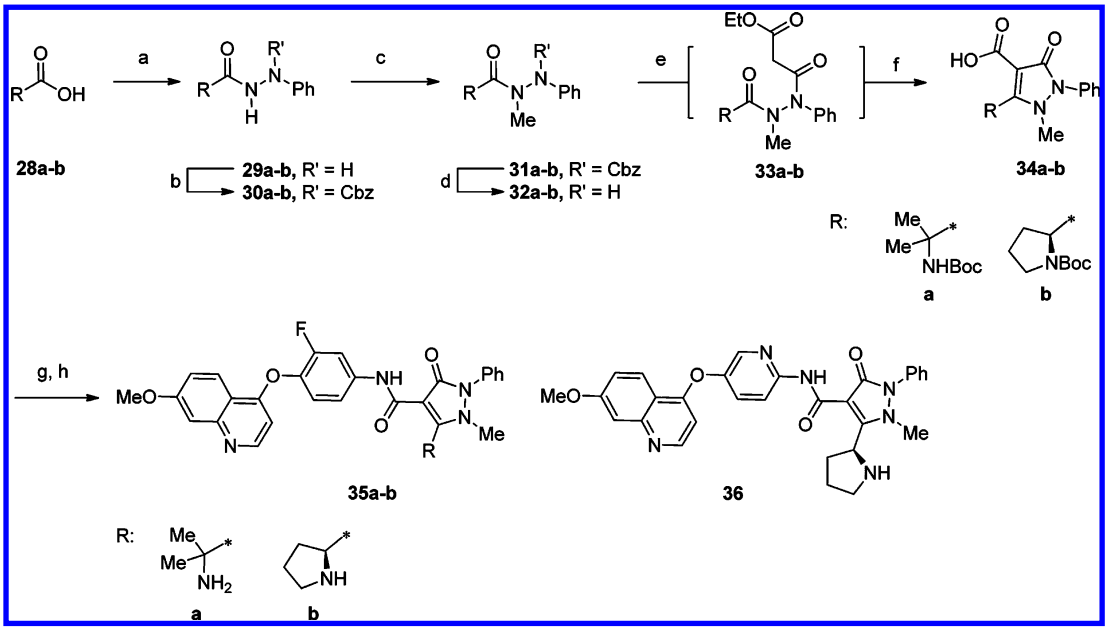
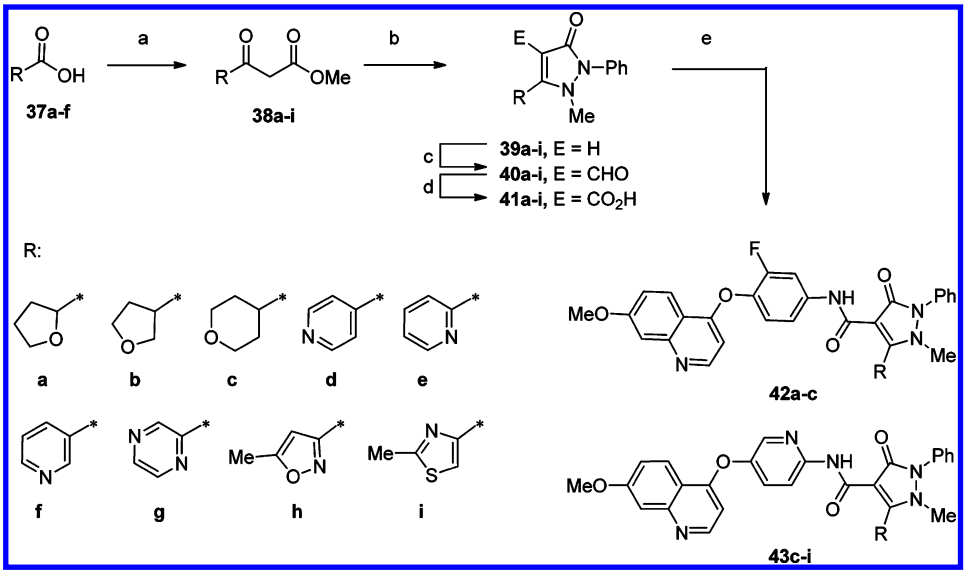
Scheme 4. [a]



[a]Reagents and conditions: (a) HOBt, EDCI, Et_3N, $PhNHNH_2$, DCM; (b) BnOC(O)Cl, NaOH (aq), THF; (c) NaH, DMF; MeI, 0 °C → rt; (d) H_2, Pd/C, MeOH; (e) DMAP, ethyl malonoyl chloride, DCM, 0 °C → rt; (f) NaOEt, EtOH, 90 °C; NaOH, MeOH, 90 °C; (g) **9d** or **16**, $^{i}Pr_2NEt$, HATU, DMF or DCM; (h) TFA, DCM.

Scheme 5. [a]



[a]Reagents and conditions: (a) CDI, methyl malonate potassium salt, $MgCl_2$, THF; (b) PhNHNHMe, HOAc, pyridine, 100 °C; (c) DMF, $POCl_3$; (d) $NaClO_2$, 2-methylbut-2-ene, NaH_2PO_4, ^{t}BuOH, 0→20 °C; (e) **9d** or **16**, HATU or EDCI-HOAt, DMF, or DCM.

that the *ortho*-dimethoxy quinoline represented a latent *ortho*-quinone surrogate that might lead to undesired safety complications.[34] To mitigate this concern, we elected to first investigate monomethoxy substituted quinolines in the linker strand region.

As shown from the crystal structure in Figure 3,[8] the 7-methoxy group of **1** is buried in the ATP-binding pocket and forms numerous van der Waals contacts with the linker strand of the protein. In contrast, the 6-methoxy group is more exposed to the solvent and forms only two protein contacts, including one with Phe1089 at the tip of the P-loop, a residue known to be flexible and likely less important for inhibitor potency. We speculated that modifications at the 6-position would likely have less of an impact on potency than those at the 7-position.[35] Additionally, replacing the 6-methoxy group would also eliminate the possibility of both *ortho*-quinone and *para*-quinone-imine formations in vivo.[36] Consistent with our structural understanding, as indicated in Table 1, the 6-methoxy group in **1** could be replaced with a halogen (**11a**), small alkyls (**11b**, **11c**), or even completely eliminated (**11d**) with minimal loss of biochemical activity (<5-fold). However, the cellular activity in PC3 cells was significantly reduced in most cases (**11a**−**c**), with the exception of the 6-H analogue (**11d**) where marginal impact was observed. With respect to

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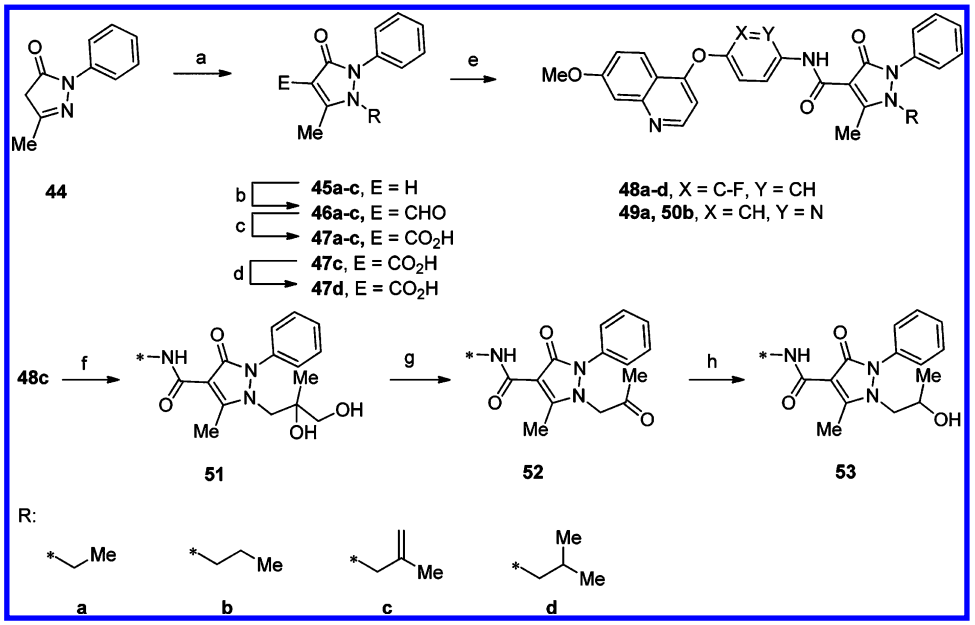
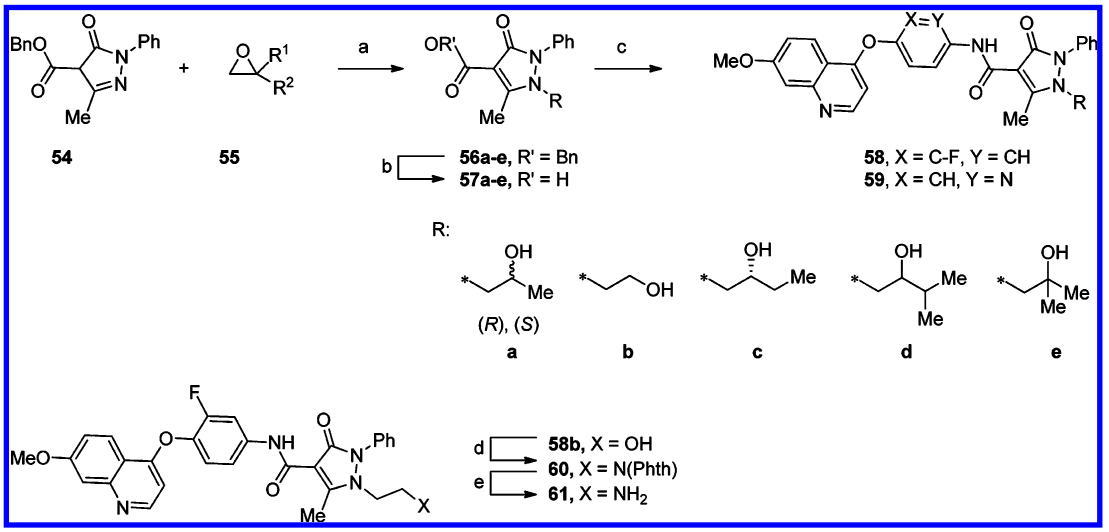
Scheme 6. [a]



[a]Reagents and conditions: (a) RX (X = I, OTs, or Br), Δ; (b) $POCl_3$, DMF, 50 °C; (c) $NaClO_2$, KH_2PO_4, 2-methyl-2-butene, ^tBuOH, H_2O, 0 °C → rt; (d) H_2, Pd/C, EtOAc; (e) **9d** or **16**, Et_3N, HATU, DMF; (f) OsO_4, NMO, $^tBuOH–H_2O$; (g) $NaIO_4$, $^tBuOH–H_2O$; (h) $NaBH_4$, MeOH.

Scheme 7. [a]



[a]Reagents and conditions: (a) $Mg(ClO_4)_2$ or $AlCl_3$, ACN; (b) Pd/C, H_2, EtOAc; (c) **9d** or **16**, HATU, Et_3N, DMF; (d) phthalimide, Ph_3P, DEAD, DCM; (e) hydrazine, $EtOH/H_2O$, 50 °C.

kinase selectivity, replacing the 6-methoxy group generally resulted in a 2-fold improvement in selectivity over VEGFR-2. Although the bromo- and alkyl analogues **11a–c** showed no impact on the selectivity over IGF-1R, the *des*-methoxy analogue **11d** exhibited an improved selectivity over IGF-1R (>150-fold), representing about a 5-fold improvement from **1**.

SAR of the Central Fluorophenyl Ring (B-Region). In the c-Met-bound form, the central fluorophenyl ring in **1** connecting the quinoline and the pyrazolone carboxyamide resides between the gatekeeper Leu1157 and the P-loop Phe1089. As shown in Figure 4, the fluorine atom occupies a shallow hydrophobic nitch demarcated by the Val1092 isopropyl side chain, indicating there is little room for substitution at this position. Replacing the CF group in **1** with a nitrogen atom resulted in 50-fold loss of activity (**15b**, Table 2). This change not only removed occupancy of the Val1092 cavity but perhaps more significantly imparted a dramatic change in the conformational preferences of the molecule. Modeling studies indicated that this nitrogen atom prefers to form an intramolecular CH–N hydrogen bond with C(3) of the quinoline ring, thereby bringing the two rings into a coplanar conformation in the ground state and destabilizing the bound-state orthogonal conformation. Therefore, we explored modifying the adjacent position (Y in Table 2 structure). It was found that bulkier groups such as chlorine (**15a**) or methoxy (**22b**) reduces the potency of **1** by ∼10–15-fold. This is likely a result from both the loss of occupancy of the Val1092 cavity and a slight steric clash with the δ carbon of Lys1110 that resides ∼3.9 Å from position Y. In contrast to **15b**, the isomeric pyridine (**15c**) still maintained the bound-state

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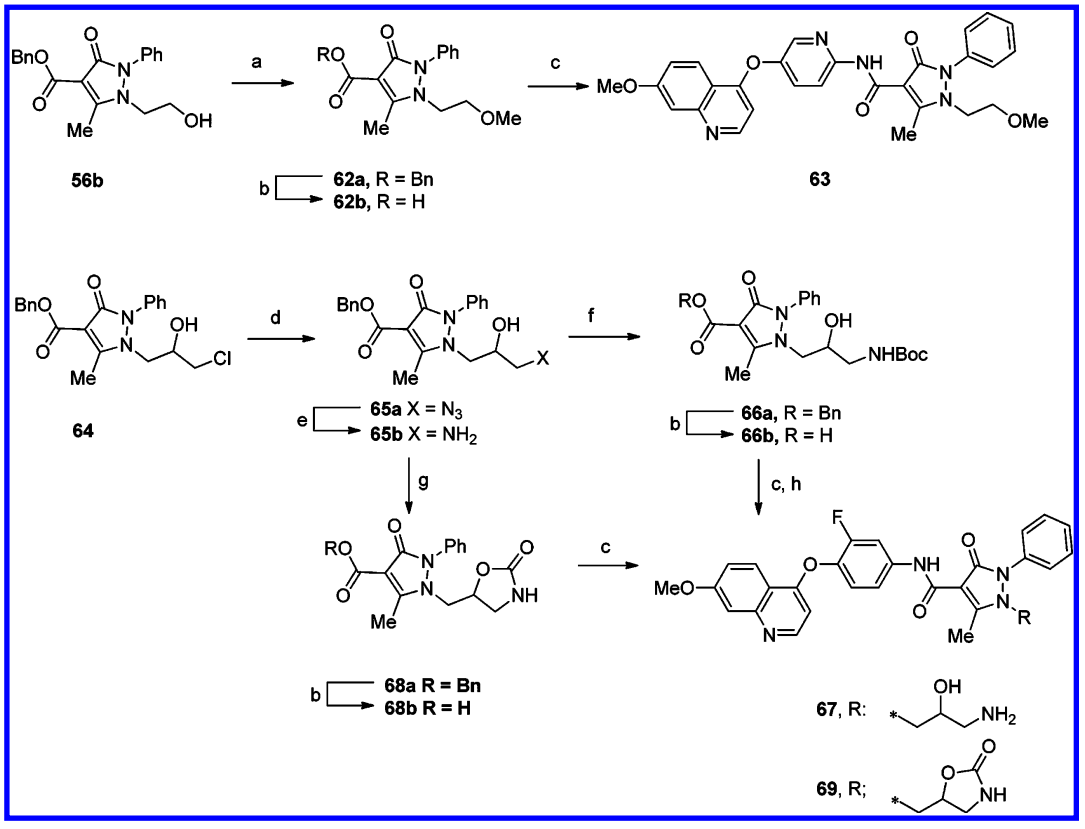
Scheme 8. [a]



[a](a) $TMSCHN_2$, HBF_4, DCM; (b) H_2, Pd/C, EtOAc; (c) **9b** or **16**, HATU, Et_3N, DMF; (d) NaN_3, DMF/water, 90 °C, 18 h; (e) HSC_3H_6SH, DIEA, MeOH, 23 °C, 48 h; (f) Boc_2O, DCM; (g) disuccinimidyl carbonate (DSC), DBU, 1,4-dioxane, 23 °C, 2 h; (h) TFA, DCM.

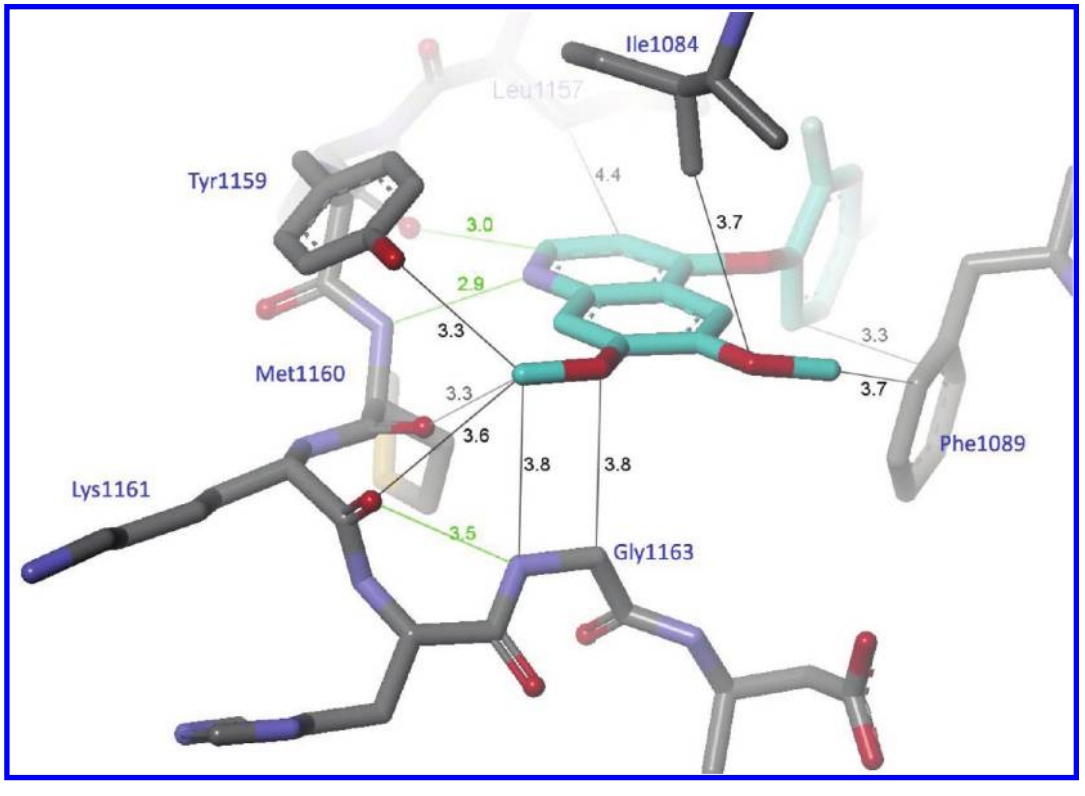


Figure 3. X-ray structure of **1** bound to c-Met highlighting key interactions of the 6- (right-hand side) and 7- (left-hand side) methoxyl groups of the quinoline ring (A-region). Hydrogen bonds are colored in green and key van der Waals contacts in black. Distances are in Å.

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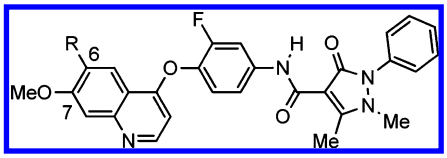
Table 1. Modification of the Quinoline Ring[a]



		c-Met	VEGFR-2		IGF-1R		PC3
compd	R	K_i	K_i	fold	K_i	fold	IC_{50}
1	OMe	1	7.8	8	32.1	32	20.2
11a	Br	5.1	78.9	16	149	29	652
11b	Me	3.4	–	–	146	43	461
11c	Et	2.4	38	16	70.2	29	534
11d	H	1.1	23.7	22	178	162	37.1

[a] K_i (nM): inhibitory constant for the phosphorylation of gastrin by c-Met, VEGFR-2, or IGF-1R. Fold: ratio of K_i(kinase)/K_i(c-Met). PC3 IC_{50} (nM): inhibitory concentration for HGF-mediated c-Met phosphorylation in PC3 cells. Both K_i and IC_{50} values are reported as an average for $n > 2$. See Supporting Information for standard deviations.

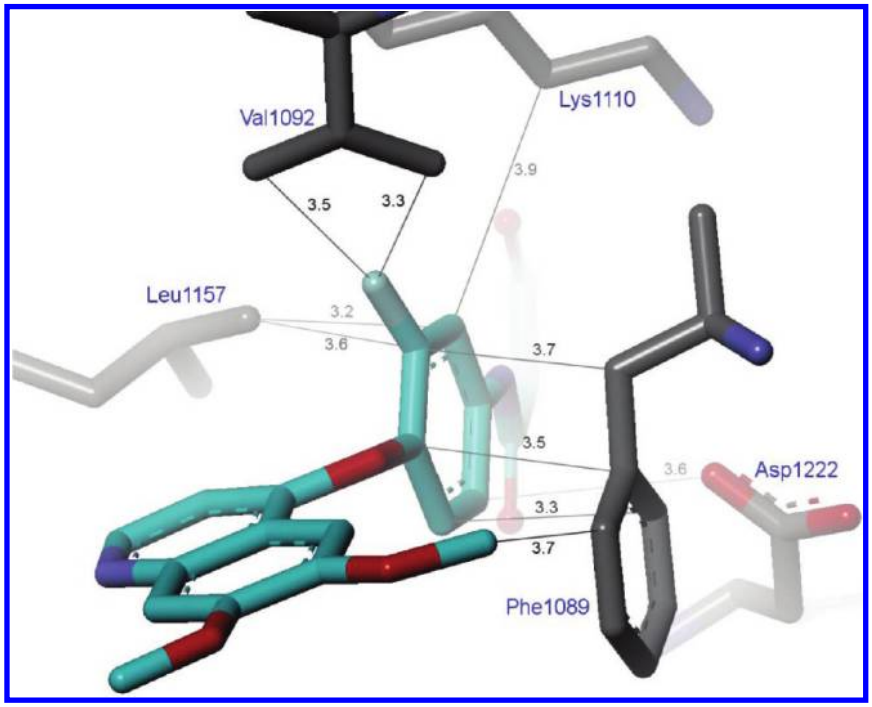


Figure 4. X-ray structure of **1** bound to c-Met highlighting key interactions of the central fluorophenyl ring (B-region). Hydrogen bonds are colored in green and key van der Waals contacts in black. Distances are in Å.

conformational preference and led to only a minor loss of activity. Notably, the pyridine analogue **15c** effected an unanticipated improvement in selectivity over IGF-1R (>4-fold) relative to the fluorophenyl analogue **1**. Combination of this feature with the superior selectivity associated with the mono methoxyquinoline (see Table 1, **11d**) led to analogue **22a**, which had the best overall activity and selectivity up to this point. In addition, we recognized that this pyridine-based central ring not only conferred better physicochemical characteristics to the molecule (e.g., lower logP, molecular weight, and protein binding) but also significantly reduced potential metabolic liabilities associated with the *para*-aminophenol moiety.[37] For the SAR purposes, both the fluorophenyl- (e.g., **1**) and the pyridine- (e.g., **15c**, **22a**) based central rings are included in subsequent discussions. Interestingly, the pyrimidine analogue (**22c**) with a nitrogen at both Y- and Z-positions showed 13-fold reduced c-Met activity relative to the pyridine derivative. One possible explanation is that by forcing a nitrogen atom into the Z-position, the carboxylate of Asp1222, which is 3.6 Å away, may experience electrostatic repulsion.

C-Region Overview. In parallel to establishing SAR in the A- and B-regions, we focused much of our medicinal chemistry efforts in the C-region, where our structural analysis suggested a path for improving kinase selectivity. Figure 5 illustrates the three different areas of the C-region that we investigated: (i) the Ile1145 pocket, occupied by the N(2)-phenyl ring of **1**, (ii) the solvent channel, slightly accessed by the N(1)-methyl group of **1**, and (iii) a DFG-out pocket, occluded by c-Met's DFG-in motif in complex with **1**.

With the N(2) SAR shown in the preceding paper,[8] we found the hydrophobic Ile1145 pocket to be best accommodated by aryl rings. As previously discussed, our structural analysis had suggested that most kinases lack an equivalent to the Ile1145 pocket but that some may have the ability to tolerate N(2)-aryl rings by placing them in the DFG-out pocket. Thus, the finding that N(2)-aryl rings also engendered

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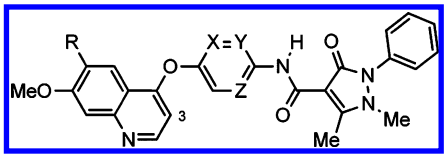
Table 2. SAR of the Central Ring[a]



					c-Met	VEGFR-2		IGF-1R		PC3
compd	R	X	Y	Z	K_i	K_i	fold	K_i	fold	IC_{50}
1	OMe	CF	CH	CH	1	7.8	8	32.1	32	20.2
15b	OMe	N	CH	CH	53.5	1980	37	1570	29	417
15a	OMe	CH	CCl	CH	15.8	35.9	2	26.5	2	177
22b	H	CH	COMe	CH	12.8	702	55	93.6	7	114
15c	OMe	CH	N	CH	1.9	18.4	10	233	123	71.2
22a	H	CH	N	CH	1.2	42.0	35	618	515	83.0
22c	H	CH	N	N	16.7	1630	97	217	13	–

[a] K_i (nM): inhibitory constant for the phosphorylation of gastrin by c-Met, VEGFR-2, or IGF-1R. Fold: ratio of K_i(kinase)/K_i(c-Met). PC3 IC_{50} (nM): inhibitory concentration for HGF-mediated c-Met phosphorylation in PC3 cells. Both K_i and IC_{50} values are reported as an average for $n > 2$. See Supporting Information for standard deviations.

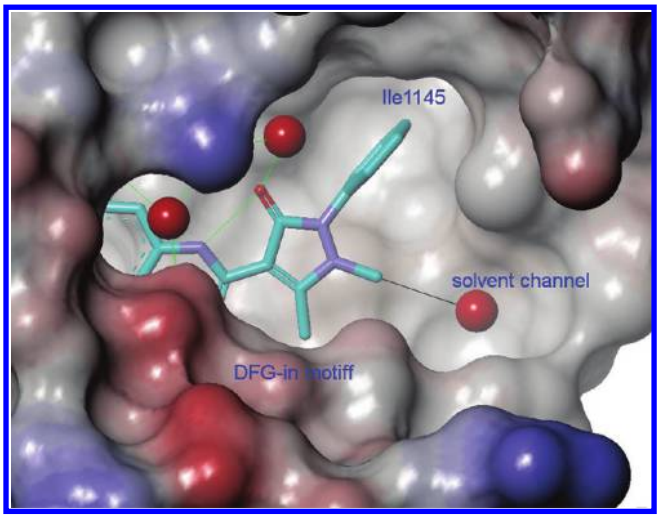


Figure 5. C-region of X-ray structure of **1** bound to c-Met, with three distinct areas annotated. Note that the side chain of Glu1127, between the solvent channel and Ile1145 pocket, was not resolved and is treated artificially in this surface representation as an alanine.

affinity in other kinases was not surprising because these aryl rings were predicted and subsequently observed to bind DFG-out. With the N(2)-substitution putatively occupying an altogether different pocket in off-target kinases, further exploration of the N(2)-substitution offered the potential to exploit these structural differences. However, both the Ile1145 pocket of c-Met and the DFG-out pockets of other kinases demonstrated a preference for aromatic rings. A more promising approach to enhance kinase selectivity in this series appeared to involve preservation of the N(2)-phenyl group with concomitant functionalization of either N(1) into the solvent channel or C(5) into an induced DFG-out pocket.

SAR at C(5). The effects of targeting the DFG-out pocket with C(5) substitutions on c-Met activity as well as on selectivity against VEGFR-2 and IGF1-R are shown in Table 3. As described earlier (cf. Figure 2), we predicted that C(5)-substitutions, particularly polar groups, were less likely to be tolerated in VEGFR-2. This is because VEGFR-2 (and other kinases) would only be able to accommodate compounds from this series in a DFG-out binding mode in which bulky C(5)-substitution would disrupt a well conserved salt-bridge between a glutamic acid on the C-helix and the catalytic lysine. Moreover, our prior experience with kinases found to be capable of forsaking this lysine–glutamate salt bridge suggested that the resultant opening would be hydrophobic, thus incompatible with polar groups. Consistent with this analysis, a simple amino methyl group at C(5) was well tolerated in c-Met (**26b**: K_i = 1.4 nM; PC3 cell, 42 nM) and led to significant loss of activity in VEGFR-2 and IGF-1R relative to **11d**, resulting in 378- and 649-fold selectivity over the two kinases. Capping the amine of **26b** with the bulky Boc group further attenuated the off-target activity but also resulted in a 20-fold loss of c-Met activity (**26a**). However, less drastic size increases of C(5), as in the dialkyl aminomethyl (**26c**) and cyclic dialkyl aminomethyl groups (**26d**, **27**), were well tolerated in c-Met and maintained robust selectivity against VEGFR-2 and IGF-1R. These data confirmed the prediction that branched (up to six heavy atoms) basic groups at C(5) could enhance selectivity over VEGFR-2 and IGF-1R.

Distinct from most kinases, the DFG-out pocket of c-Met was predicted to adopt a more open shape that would tolerate modest polarity at C(5). While Table 3 largely corroborates this idea, it shows that small α-branched basic NH groups were not well tolerated. Loss of c-Met activity was observed in the cases of the *gem*-dimethyl derivative (**35a**) and the 2′-pyrrolidinyl derivatives (**35b**, **36**). Molecular modeling suggests that compounds **26b–d** and **27**, which are unsubstituted at the α-position, are able to position their basic amines in well solvated areas of the C-region. In contrast, their α-branched derivatives (**35a–b** and **36**) show a significant conformational preference to form an intramolecular hydrogen bond between the basic amine and the amide carbonyl, as illustrated in Figure 6. The conformational impact of α-branching is likely driven by sterics: while the α-unsubstituted molecule can place its lone β-heavy atom out of plane with the pyrazolone, the α-branched molecule is unable to simultaneously position both β-heavy atoms away from the N(1)-methyl of the pyrazolone and the amide carbonyl. The energetically favorable option for the α-branched molecules is then to form an intramolecular hydrogen bond. While such intramolecular hydrogen bonding leads to the most favorable conformer in the unbound state, this conformation would interfere with the ligand's ability to bind in c-Met's DFG-out pocket. Consistent with the well-established DFG-out

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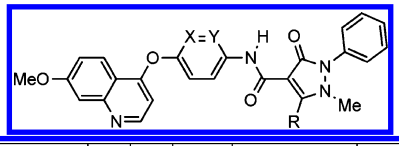
Table 3. Effects of C5-Substituents on Selectivity Profiles[a]



compd	R	X	Y	c-Met	VEGFR-2		IGF-1R		PC3
				K_i	K_i	Fold	K_i	Fold	IC_{50}
11d	CH_3-	CF	CH	1.1	23.7	22	178	162	37.1
22a	CH_3-	CH	N	1.2	42	35	618	515	83
26b	NH_2CH_2-	CF	CH	1.4	541	378	928	649	42
26a	$BocNHCH_2$-	CF	CH	29	1240	43	>6600	>230	–
26c	$Et(Me)NCH_2$-	CF	CH	2.3	903	386	744	317	76.7
26d		CF	CH	1.5	1310	879	1800	1206	83.9
27		CH	N	1.4	2020	1465	887	643	66.4
35a		CF	CH	28.4	3350	118	3100	109	–
35b		CF	CH	7.2	2240	313	680	95	327
36		CH	N	22	>6600	>300	948	43	–
42a		CF	CH	0.9	708	781	190	209	64.6
42b		CF	CH	0.6	131	214	250	407	33.7
42c		CF	CH	1.2	945	786	144	120	39.8
43c		CH	N	1.1	2720	2440	42.7	38	37.6
43d		CH	N	0.6	>6600	>6600	35.9	65	18.4
43e		CH	N	0.6	1380	2380	18.5	32	21.6
43f		CH	N	0.8	2830	3397	27	32	24.1
43g		CH	N	1.2	4730	3989	87.7	74	31.5
43h		CH	N	0.7	501	688	30.9	42	29.5
43i		CH	N	0.7	588	831	24.8	35	23.4

[a] K_i (nM): inhibitory constant for the phosphorylation of gastrin by c-Met, VEGFR-2, or IGF-1R. Fold: ratio of K_i(kinase)/K_i(c-Met). PC3 IC_{50} (nM): inhibitory concentration for HGF-mediated c-Met phosphorylation in PC3 cells. Both K_i and IC_{50} values are reported as an average for $n > 2$. See Supporting Information for standard deviations.

binding mode of kinases, in order for the α-branched **35a–b** and **36** to bind, these ligands must provide the DFG-out Asp1222-NH with a hydrogen bond acceptor. While the ground state conformation of these compounds precludes this interaction, the predicted energetic penalty of breaking the intramolecular hydrogen bond to satisfy the Asp1222-NH with the amide carbonyl is qualitatively in agreement with the observed loss of potency. When the pyrrolidine ring in **35b** was replaced with a furan ring as in **42a–b**, thereby excluding possible intramolecular

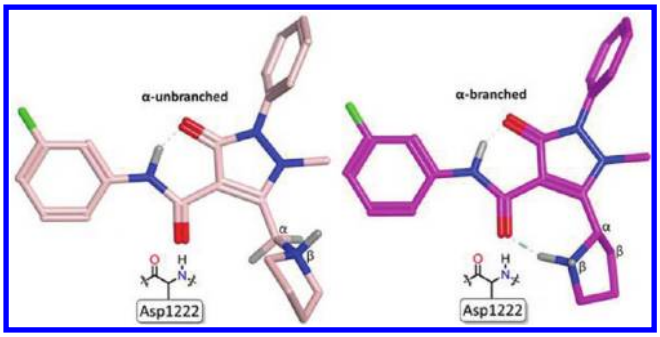


Figure 6. Impact of α-branching of C(5)-substitution on conformational preferences. The conformation of the *α-unbranched* fragment is dictated by the strong preference of the sp^3 carbon to place the nitrogen atom *orthogonal* to the pyrazolone plane. In contrast, the ground state conformer for the α-branched fragment forms an intramolecular H-bond between the β-NH and the amide carbonyl, thereby interrupting its ability to satisfy the DFG motif-Asp1222 backbone amide-NH and rendering it incompatible with binding to c-Met. α-Branched molecules presumably pay a conformational penalty to bind in a different higher energy conformation that does not interfere with DFG-out binding.

hydrogen-bond formation, the c-Met activity was recovered. Pyrans **42c** and **43c** were also potent in c-Met enzyme (K_i < 2 nM) and cell (IC_{50} < 40 nM) assays, and were selective over VEGFR-2.

To mimic the phenylalanine of c-Met, heteroaromatic groups at C(5) were also investigated. Introducing a 4-pyridinyl ring at C(5) improved the c-Met activity at both the biochemical and cellular levels (**43d** vs **22a**). In addition, the selectivity over VEGFR-2 was enhanced by >100-fold, although selectivity over IGF-1R dropped by 9-fold. The position of the pyridine attachment at C(5) did not affect the activity or selectivity profiles (cf., **43e** and **43f**), nor did the introduction of another nitrogen atom to the pyridine ring (cf., pyrazine **43g**). Five-membered heteroaryl groups at C(5) such as 5-methylisoxazol-3-yl (**43h**) and 2-methylthiazol-4-yl (**43i**) behaved similarly in their c-Met activity and selectivity over VEGFR-2 and IGF-1R.

In summarizing our C(5) exploration, we found that high selectivity over VEGFR-2 could be achieved with both aryl and alkyl groups at C(5) containing polar functionality, while the selectivity over IGF-1R was generally lower with an aryl substituent than with an alkyl substituent.

SAR at N(1). The effect of targeting the solvent channel as depicted in Figure 5, through N(1)-substitution, on c-Met activity and selectivity over VEGFR-2 and IGF-1R is shown in Table 4. For this purpose, the SAR is limited to the 7-methoxyquinoline based linker binder as represented by **11d**. As discussed earlier (Figure 2), we anticipated that modifications at N(1) would provide a means for improving kinase selectivity by introducing unfavorable steric overlap with the C-helix of the VEGFR-2 protein and other kinases in the traditional DFG-out binding mode. The most conservative change, replacing the methyl group at N(1) with an ethyl group (**48a**), effectively increased the VEGFR-2 selectivity by 4-fold but led to a 2–3-fold decrease in c-Met enzymatic and cellular potency. Consistent with results on the analogues described earlier, the central pyridine ring (**49a**) enhanced selectivity over both VEGFR-2 and IGF-1R by an additional 2-fold. Extending further into the solvent channel through homologation to the *n*-propyl analogues (**48b** and **50b**) slightly improved the c-Met enzymatic and cellular potency by ∼1.5-fold over the ethyl

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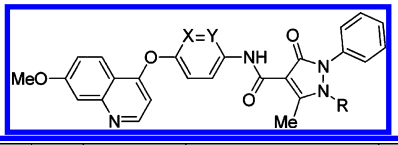
Table 4. Effects of N1-Substituents on Selectivity Profiles[a]



compd	R	X	Y	c-Met	VEGFR-2		IGF-1R		PC3
				K_i	K_i	Fold	K_i	Fold	IC_{50}
11d		CF	CH	1.1	23.7	22	178	162	37.1
48a		CF	CH	2.3	207	90	557	244	62.5
49a		CH	N	1.6	343	210	708	433	106
48b		CF	CH	1.0	161	157	419	409	48.8
50b		CH	N	1.1	309	290	730	685	69.5
48d		CF	CH	7.9	1000	126	915	116	205
48c		CF	CH	0.9	74.1	81	249	272	23.9
61		CF	CH	3.9	452	115	872	223	195
58b		CF	CH	1.4	191	140	864	632	47.5
59b		CH	N	0.4	234	579	1100	2726	95.8
63		CH	N	1.4	325	231	2890	2060	89.3
53		CF	CH	1.9	257	135	1330	698	52.0
(*R*)-**58a**		CF	CH	1.0	396	390	744	735	23.9
(*S*)-**58a**		CF	CH	1.2	386	337	695	607	23.0
59a		CH	N	0.8	932	1205	1290	1667	45.4
58c		CF	CH	0.9	246	282	575	659	38.0
58d		CF	CH	1.3	389	307	637	502	56.0
67		CF	CH	0.8	382	512	104	140	63.1
69		CF	CH	4.4	519	117	1660	376	116
58e		CF	CH	2.7	1160	435	887	332	50.5
59e		CH	N	1.0	2430	2422	2150	2144	60.1

[a] K_i (nM): inhibitory constant for the phosphorylation of gastrin by c-Met, VEGFR-2, or IGF-1R. Fold: ratio of K_i(kinase)/K_i(c-Met). PC3 IC_{50} (nM): inhibitory concentration for HGF-mediated c-Met phosphorylation in PC3 cells. Both K_i and IC_{50} values are reported as an average for $n > 2$. See Supporting Information for standard deviations.

analogues (**48a** and **49a**) to the same level as in the unsubstituted parent **11d**. The additional γ carbons of **48b** and **50b** also appeared to have enhanced, by an additional 1.5−2-fold over the ethyl, selectivities over VEGFR-2 and IGF-1R now at >150- and >400-fold, respectively. However, attaching a second γ carbon as in the isobutyl analogue (**48d**) was accompanied by significant loss of c-Met activity (>7-fold), possibly reflecting unfavorable desolvation penalty associated

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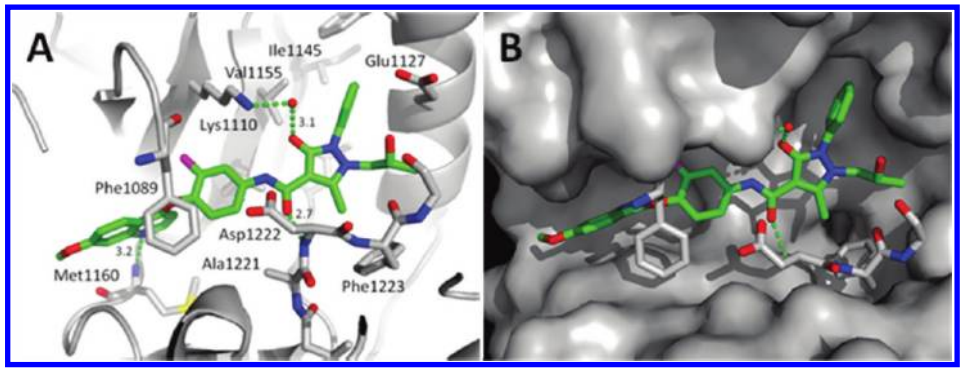

Figure 7. X-ray cocrystal structure of (*R*)-**58a** bound to c-Met (PDB: 3U6I). (A) Key interactions of the pyrazolone region with the protein. Hydrogen bond (green dashed lines) distances are in Å; (B) surface of the c-Met active site pocket. The surfaces of Phe1089, Asp1222, Phe1223, and Gly1224 are not depicted for clarity.

with the increased hydrophobicity. Interestingly, the loss of c-Met activity in **48d** was recovered by simply removing the sp^3-center at the branching point, as shown with the 2-methylallyl analogue (**48c**). Nevertheless, the β-branched analogues (**48d** and **48c**) clearly showed that the selectivities begin to taper off. Overall, among simple alkyl derivatives, the *n*-propyl analogues offered the best combination of potency and selectivity.

Encouraged by the SAR of simple alkyl groups at the N(1) position of the pyrazolone ring, polar functionalities were introduced to better satisfy this highly solvated area as well as to modulate the overall physicochemical properties of the molecules. A terminal amino group on the ethyl chain (**61**) caused a 4-fold loss in c-Met activity in both the enzyme and the cellular assays. Compound **61** was also ~2-fold less selective over IGF-1R. On the other hand, the corresponding hydroxyl analogue (**58b**) was better tolerated in c-Met and was more selective over IGF-1R. With the pyridine central ring, the β-hydroxyl analogue **59b** showed an increased selectivity over both VEGFR-2 (3-fold) and IGF-1R (6-fold) when compared to the ethyl analogue (**49a**). Capping the hydroxyl group in **59** as a methoxy (**63**) led to slight decrease in both c-Met activity and selectivity over VEGFR-2. These results suggested that a β-hydroxyl group was the optimal polar group in the N(1) region. Having already established that the optimal hydrocarbon chain length was an *n*-propyl group (cf., **48b** vs **48a**), combining these two structural features at the N(1) position was examined next. While the racemic 2-hydroxypropyl analogue with a central fluorophenyl ring (**53**) showed similar potency and selectivity when compared to either the hydroxyethyl or the propyl derivatives (**58b** and **48b**, respectively), the analogue with a central pyridine ring (**59a**) showed the highest selectivity over VEGFR-2 (1200-fold) to this point. Compound **59a** was also more selective over IGF-1R (1670-fold) than the propyl analogue **50b** (685-fold). The chirality of hydroxyl group (or derivatives thereof) had little effect on c-Met activity or selectivity: both the (*R*)- and the (*S*)- enantiomers of **53** [(*R*)-**58a**, (*S*)-**58a**] showed similar c-Met activities and selectivities over VEGFR-2 and IGF-1R.[9] The *R*-enantiomer, (*R*)-**58a**, was cocrystallized with c-Met and the structure was solved at 2.0-Å resolution (Figure 7A). The structure showed that the carbinol chain occupied the solvent channel as anticipated, with the secondary hydroxyl protruding out from the pyrazolone ring, flanked above by Glu-1127 from the C-Helix and below by the backbone carbonyl groups of Phe-1223 and Gly-1224 (of the DFG motif). The X-ray structure also suggested that the region surrounding the methyl group of the propyl chain could accommodate substitution (Figure 7B). Indeed, compounds with groups flanking the secondary hydroxyl such as ethyl (**58c**) and isopropyl (**58d**) derivatives were well tolerated and selective. The amino alcohol function as in **67** was also tolerated but led to 5-fold loss in selectivity over IGF-1R. When the amino alcohol in **67** was cyclized as the oxazolidinone **69**, erosion in both c-Met activity and the selectivity over VEGFR-2 were observed.

Discovery of 59e (AMG 458).[9] The superior activity/selectivity profile provided by the hydroxypropyl side chain prompted extensive investigations of (*R*)-**58a** in vivo. It was found that in rat and mouse, the secondary hydroxyl group in (*R*)-**58a** was prone to oxidation to the corresponding ketone which was subsequently shown to be nonselective over VEGFR-2.[9] Therefore, it was concluded that 2-hydroxyl propyl derivatives were not viable candidates for in vivo studies. However, the observation that chirality of the 2-hydroxyl group had little influence on activity/selectivity, combined with our understanding of the structural information, led us to believe that a tertiary hydroxyl group would be tolerated in c-Met and potentially resistant to biotransformations. It was further hypothesized that good selectivity would be retained based on the selectivity data from the isobutyl analogue (**48d**). Indeed, this was the case; both tertiary alcohols **58e** and **59e** showed c-Met activities similar to the 2-hydroxylpropyl derivative (**53**, **59a**). In addition, they were more selective against VEGFR-2 (2−3-fold) than the secondary alcohols. On the basis of these results, both **58e** and **59e** were selected for in vivo pharmacological evaluations.[9,38] Overall, compound **59e** was the most selective class II c-Met inhibitor we had synthesized. The broad spectrum kinase profile of **59e** is represented in the form of heat map in Figure 8 using internal IC_{50} data for kinases that have been counterscreened against. On the basis of the excellent selectivity profile, as well as favorable PK profiles in both the rodent and primate species, compound **59e** was advanced into preclinical safety studies.[9]

SUMMARY

In summary, we demonstrated that the selectivity profiles of class II c-Met inhibitors can be dramatically improved. Through extensive molecular modeling studies and X-ray structural analysis of the lead structure **1**, we uncovered a number of factors that govern the kinase selectivity profiles of this series using VEGFR-2 and IGF-1R as examples. Specifically, we showed that: (1) both the 6-desmethoxy quinoline in the linker region (A) and the pyridine in the central ring (B) enhanced selectivity, but more so over IGF-1R than over VEGFR-2, (2)

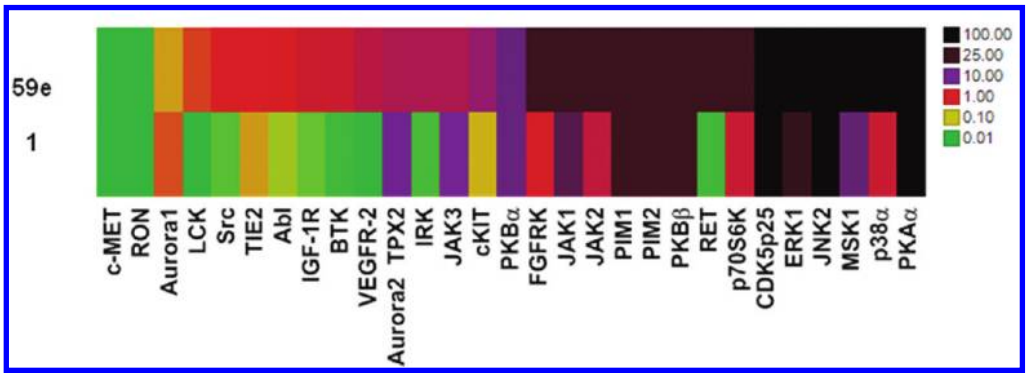

Figure 8. Heat map of kinase activity (IC_{50}) of compounds **1** and **59e** (activity units are in micromolar).

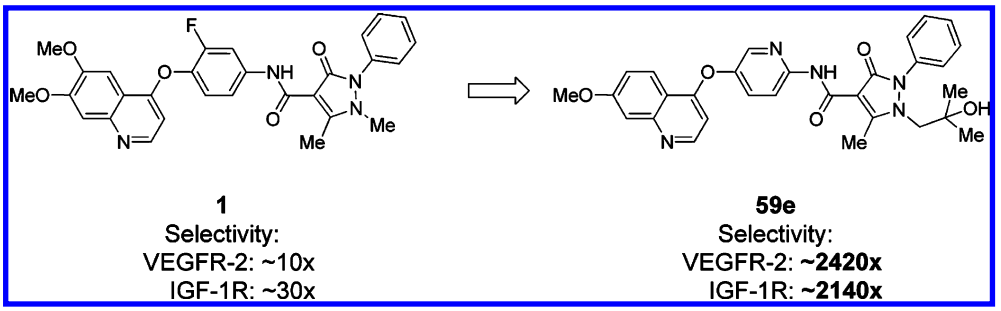

Figure 9. Structural evolution from **1** to **59e**.

polarity at C(5) of the pyrazolone (C) was essential for good selectivity over VEGFR-2, whereas steric bulk was important for selectivity over IGF-1R, and (3) a 2-hydroxypropyl side chain at N(1) was optimal for overall selectivity and activity. These efforts ultimately led to the identification of **59e** which was >2000-fold selective over VEGFR-2 and IGF-1R and significantly more selective over other kinases than the initial lead compound (Figure 9).

EXPERIMENTAL SECTION[39]

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 N_2 or Ar 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 H_2O; 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.

General Method for Amide Coupling between 1,5-Dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carboxylic Acid (10) and Anilines. A mixture of an aniline (1.0 equiv), acid **10** (1.5 equiv), Et_3N (1.5 equiv), and HATU (1.5 equiv) in DCM or DMF (substrate [c] ~0.1 M) was stirred at rt for 24 h. The mixture was either filtered, and the filtrate was concentrated (when DCM was the solvent) or partitioned between EtOAc and H_2O (when DMF was the solvent). The organic residue was purified by silica gel chromatography (eluent: MeOH in DCM or MeOH in EtOAc) to afford the title compounds.

***N*-(4-(6-Bromo-7-methoxyquinolin-4-yloxy)-3-fluorophenyl)-1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carboxamide (11a).** *(A) Ethyl 6-Bromo-4-hydroxy-7-methoxyquinoline-3-carboxylate (**3a**).* A mixture of diethyl ethoxymethylenemalonate (22 mL, 102 mmol) and 4-bromo-3-methoxybenzenamine **2** (20.2 g, 100 mmol) was heated at 100 °C in a sand bath under N_2 for 17 h. Ph_2O (100 mL) was added, and the mixture was heated with a heating gun at ~245 °C (internal probe). After 5 min, the boiling red solution turned cloudy. After 2 h, the mixture was allowed to cool to rt, diluted with hexanes (100 mL), and filtered. The solid was washed with hexanes (2 × 100 mL) to give the crude product (28 g, 84%), which was used directly in the next step.

*(B) 6-Bromo-7-methoxyquinolin-4-ol (**3b**).* A mixture of ethyl 6-bromo-4-hydroxy-7-methoxyquinoline-3-carboxylate (28 g, 86 mmol) and NaOH (15 g, 375 mmol) in H_2O (150 mL) was heated at 100 °C in an oil bath for 50 min. The solution was allowed to cool to rt and was acidified with HCl (concd). The slurry was filtered, and the resulting solid was washed with H_2O and air-dried to give the acid intermediate. The acid was suspended in Ph_2O (150 mL) and was heated with a heating gun. At 120 °C, rapid foaming occurred, which continued until after the internal temperature reached 140 °C; thereafter rapid rises in temperature were observed. The mixture was heated at reflux for 30 min, cooled to rt, and diluted with hexanes (100 mL). The mixture was filtered hot (60 °C), and the residue was washed with hexanes (3×). The solid was suspended in H_2O (150 mL) and treated with NaOH (5 N, 25 mL). After being heated at 100 °C for 20 min, the dark mixture was filtered hot. The filtrate was quenched with HCl (5 N, 20 mL) and the resulting slurry was let cool to rt before it was filtered and the resulting solid residue was washed with H_2O (20 mL). The solid contained the desired product plus the side-product resulting from *O*-demethylation (>50:1 ratio, >96% pure at 215 nm). MS (ESI pos ion) calcd for $C_{10}H_8BrNO_2$, 253.0/255.0; found, 254.0/256.0 (M + H). ^{1}H NMR (400 MHz, DMSO-d_6)

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δ 3.93 (s, 3 H), 5.99 (d, J = 7.4 Hz, 1 H), 7.06 (s, 1 H), 7.87 (d, J = 7.4 Hz, 1 H), 8.11−8.21 (m, 1 H).

*(C) 6-Bromo-4-chloro-7-methoxyquinoline (**4**).* A mixture of 6-bromo-7-methoxyquinolin-4-ol (2.2 g, 8.7 mmol) and $POCl_3$ (15 mL, 161 mmol) was heated at 110 °C in an oil bath for 2 h. The reaction mixture was allowed to cool to rt and concentrated. The residue was washed with hot EtOAc (2 × 15 mL) and dried in the air to give a brown powder (2.6 g, 97% as HCl salt). MS (ESI pos ion) calcd for $C_{10}H_7BrClNO$, 270.9/272.9/274.9; found, 271.9/273.9/275.9 (M + H). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.87 (bd, 1 H), 8.42 (s, 1 H), 7.73 (s, 1 H), 7.64 (bd, 1 H), 4.06 (s, 3 H).

*(D) 6-Bromo-4-(2-fluoro-4-nitrophenoxy)-7-methoxyquinoline (**6**).* A mixture of 6-bromo-4-chloro-7-methoxyquinoline-HCl (600 mg, 1942 μmol) and 2-fluoro-4-nitrophenol (915 mg, 5825 μmol) in chlorobenzene (5 mL) was heated to reflux (140 °C oil bath). After 16 h, the solution was allowed to cool to rt and the mixture was diluted with ether (10 mL) to form a white slurry that was filtered through a fritted funnel. The solid residue was suspended in NaOH (3 N, 15 mL), and the mixture was stirred for 20 min. The solid was collected and washed first with MeOH/H_2O (1:8) and then with ether to give a light-yellow solid (490 mg, >95% pure). MS (ESI pos ion) calcd for $C_{16}H_{10}BrFN_2O_4$, 392.0/394.0; found, 393.0/395.0 (M + H). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.07 (s, 3 H), 6.51 (d, J = 5.1 Hz, 1 H), 7.39 (t, J = 8.2 Hz, 1 H), 7.49 (s, 1 H), 8.18 (t, J = 10.6 Hz, 2 H), 8.52 (s, 1 H), 8.69 (d, J = 5.1 Hz, 1 H).

*(E) 4-(6-Bromo-7-methoxyquinolin-4-yloxy)-3-fluorobenzenamine (**9a**).* A mixture of 6-bromo-4-(2-fluoro-4-nitrophenoxy)-7-methoxyquinoline (100 mg, 254 μmol) in EtOH (6 mL) was treated with tin(II) chloride dihydrate (140 mg, 615 μmol). The resulting brown slurry was heated at 70 °C for 4 h. The orange mixture was allowed to cool to rt and diluted with NaOH (1 N, 10 mL). The mixture was extracted with EtOAc (3 × 10 mL), and the combined organic layers were washed with NaOH (1 N, 10 mL), H_2O, and brine. After drying over Na_2SO_4, filtering, and concentrating of the organic phase, the resulting yellow solid (92.4 mg, 100%) was used directly in the next step. MS (ESI pos ion) calcd for $C_{16}H_{12}BrFN_2O_2$, 362.0/364.0; found, 363.0/365.0 (M + H).

*(F) N-(4-(6-Bromo-7-methoxyquinolin-4-yloxy)-3-fluorophenyl)-1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxamide (**11a**).* A mixture of 4-(6-bromo-7-methoxyquinolin-4-yloxy)-3-fluorobenzenamine (9a, 92.4 mg, 254 μmol), 1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carboxylic acid (10, 85 mg, 366 μmol), and HATU (135 mg, 356 μmol) in $CHCl_3$ (5 mL) was heated at 70 °C for 2 d. During this period, more reagents were added to drive the reaction to completion. The mixture was allowed to cool to rt and diluted with EtOAc (15 mL). The mixture was washed with NaOH (0.5 N, 2×), H_2O, brine, and dried over Na_2SO_4. The organic phase was filtered and concentrated. The residue was purified by chromatography on silica gel with (2 N NH_3-MeOH)−DCM (4%) as eluents. The major, less polar fraction was collected to give a crystalline solid that was further triturated with EtOAc/hexanes (1:1) to give a brown powder (30 mg, 20%). MS (ESI pos ion) calcd for $C_{28}H_{22}BrFN_4O_4$, 576.1/578.1; found, 577.0/579.0 (M + H). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.81 (s, 3 H), 3.38 (s, 3 H), 4.05 (s, 3 H), 6.42 (d, J = 5.1 Hz, 1 H), 7.17 (t, J = 8.6 Hz, 1 H), 7.31 (d, J = 8.8 Hz, 1 H), 7.37 (d, J = 7.4 Hz, 2 H), 7.47 (t, J = 7.5 Hz, 1 H), 7.44 (s, 1 H), 7.57 (t, J = 7.8 Hz, 2 H), 7.93 (dd, J = 1.7, 12.5 Hz, 1 H), 8.6 (m, 2 H), 10.9 (s, 1 H).

***N*-(3-Fluoro-4-(7-methoxy-6-methylquinolin-4-yloxy)-phenyl)-1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carboxamide (11b).** *(A) 4-(2-Fluoro-4-nitrophenoxy)-7-methoxy-6-methylquinoline (**7**).* In a 25 mL round-bottomed flask was added Pd(dppf)Cl_2−DCM (6.2 mg, 7.6 μmol), 6-bromo-4-(2-fluoro-4-nitrophenoxy)-7-methoxyquinoline (100 mg, 254 μmol), and dioxane (2 mL) under Ar. Dimethylzinc (1.0 M in heptane, 509 μL, 509 μmol) was then added. After gas evolution ceased, the mixture was heated at 105 °C. After 18 h, more dimethylzinc (509 μL, 509 μmol) was added. After an additional 3 h, the reaction was allowed to cool to rt. The mixture was quenched with MeOH (0.1 mL) and diluted with DCM (5 mL)−MeOH (1 mL). The mixture was filtrated, and the resulting solids were washed with MeOH−DCM (10%). The combined filtrates were concentrated. The residue was purified by chromatography on silica gel with EtOAc as eluent to afford a white solid (54 mg, 65%). MS (ESI pos ion) m/z: calcd for $C_{17}H_{13}FN_2O_4$, 328.1; found, 329.2 (M + H). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.42 (s, 3 H), 4.01 (s, 3 H), 6.54 (d, J = 4.6 Hz, 1 H), 7.29 (m, 1 H), 7.41 (s, 1 H), 7.95 (s, 1 H), 8.12 (d, J = 9.0 Hz, 1 H), 8.18 (d, J = 9.8 Hz, 1 H), 8.64 (d, J = 4.7 Hz, 1 H).

*(B) 3-Fluoro-4-(7-methoxy-6-methylquinolin-4-yloxy)aniline (**9b**).* A mixture of 4-(2-fluoro-4-nitrophenoxy)-7-methoxy-6-methylquinoline (50 mg, 152 μmol) and Pd(OH)$_2$/C (20%, 80 mg) in EtOH (15 mL) was purged with H_2 (3×). The mixture was stirred at rt under an atmosphere of H_2 (balloon) for 6 h. The mixture was filtered, and the filtrate was concentrated. The crude product was used immediately in the next step. MS (ESI pos ion) m/z: calcd for $C_{17}H_{15}FN_2O_2$, 298.1; found, 299.1 (M + H).

*(C) N-(3-Fluoro-4-(7-methoxy-6-methylquinolin-4-yloxy)phenyl)-1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxamide (**11b**).* A mixture of 3-fluoro-4-(7-methoxy-6-methylquinolin-4-yloxy)benzenamine (50 mg, 168 μmol), 1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carboxylic acid (65 mg, 280 μmol), and HATU (127 mg, 335 μmol) in DCM (4 mL) was stirred at 40 °C for 20 h. During this period, more HATU (127 mg, 335 μmol) was added. The mixture was diluted with EtOAc (15 mL) and washed with NaOH (1 N, 10 mL), H_2O (5 mL), and brine. The organic layer was dried with Na_2SO_4, filtered, and concentrated. The residue was purified by chromatography on silica gel using (2 N NH_3 in MeOH)/EtOAc (0 to 4%) as eluents to give an off-white solid (20 mg, 23%). MS (ESI pos ion) m/z: calcd for $C_{29}H_{25}FN_4O_4$, 512.2; found, 513.1 (M + H). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.42 (s, 3 H), 2.80 (s, 3 H), 3.38 (s, 3 H), 3.99 (s, 3 H), 6.40 (d, J = 5.0 Hz, 1 H), 7.16 (t, J = 8.6 Hz, 1 H), 7.28 (m, 1 H), 7.37 (m, 3 H), 7.48 (t, J = 6.6 Hz, 1 H), 7.57 (t, J = 7.2 Hz, 2 H), 7.92 (d, J = 12.3 Hz, 1 H), 8.10 (s, 1 H), 8.53 (d, J = 5.3 Hz, 1 H), 10.88 (s, 1 H).

***N*-(4-(6-Ethyl-7-methoxyquinolin-4-yloxy)-3-fluorophenyl)-1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carboxamide (11c).** *(A) 4-(2-Fluoro-4-nitrophenoxy)-7-methoxy-6-vinylquinoline (**8**).* In a 25 mL round-bottomed flask was charged Pd(dppf)Cl_2−DCM (48 mg, 66 μmol), potassium vinyltrifluoroborate (220 mg, 1642 μmol), 6-bromo-4-(2-fluoro-4-nitrophenoxy)-7-methoxyquinoline (520 mg, 1323 μmol), and Et_3N (300 μL, 2135 μmol) in 1-propanol (4 mL). The mixture was heated at 90 °C under Ar for 15 h. The reaction mixture was allowed to cool to rt and was diluted with EtOAc (15 mL). The mixture was filtered through a pad of Celite, and the solid residue was washed with MeOH−DCM (1%). The filtrate was concentrated, and the residue was purified by chromatography on silica gel using MeOH−DCM (0−2%) as eluent to afford a mixture of the desired product and the debromination byproduct (5:1). MS (ESI pos ion) calcd for $C_{18}H_{13}FN_2O_4$, 340.1; found, 341.1 (M + H). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.02 (s, 3 H), 5.45 (d, J = 11.4 Hz, 1 H), 5.97 (d, J = 17.6 Hz, 1 H), 6.51 (d, J = 5.1 Hz, 1 H), 7.16 (dd, J = 17.6, 11.2 Hz, 1 H), 7.38 (t, J = 8.2 Hz, 1 H), 7.45 (s, 1 H), 8.12−8.24 (m, 2 H), 8.31 (s, 1 H), 8.64 (d, J = 5.3 Hz, 1 H).

*(B) 4-(6-Ethyl-7-methoxyquinolin-4-yloxy)-3-fluoroaniline (**9c**).* To a solution of 4-(2-fluoro-4-nitrophenoxy)-7-methoxy-6-vinylquinoline (130 mg, 382 μmol) in a mixture of EtOH (20 mL) and EtOAc (25 mL) under N_2 was added Pd(OH)$_2$/C (20%, 105 mg, 748 μmol). The mixture was purged with H_2 and stirred under an atmosphere of H_2 (balloon) for 23 h. The mixture was filtered through a pad of Celite, and the solid residue was washed with EtOAc. The filtrate was concentrated, and the residue was purified by chromatography on silica gel gel using MeOH/EtOAc (0 to 5%) as eluents to afford the product (65 mg, 100%) containing ~30% *des*-ethyl derivative (carried through from the last step). MS (ESI pos ion) calcd for $C_{18}H_{17}FN_2O_2$, 312.1; found, 313.1 (M + H). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.32 (t, J = 7.3 Hz, 3 H), 2.83 (q, J = 7.4 Hz, 2 H), 3.99 (s, 3 H), 6.37 (d, J = 5.3 Hz, 1 H), 6.50 (dd, J = 8.5, 2.6 Hz, 1 H), 6.57 (dd, J = 11.7, 2.5 Hz, 1 H),

7.03 (t, J = 8.6 Hz, 1 H), 7.37 (s, 1 H), 8.10 (s, 1 H), 8.52 (d, J = 5.1 Hz, 1 H).

*(C) N-(4-(6-Ethyl-7-methoxyquinolin-4-yloxy)-3-fluorophenyl)-1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxamide (**11c**).* A mixture of 4-(6-ethyl-7-methoxyquinolin-4-yloxy)-3-fluorobenzenamine (65 mg, 208 μmol), 1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carboxylic acid (97 mg, 416 μmol), and HATU (180 mg, 473 μmol) in DCM (5 mL) was stirred overnight. More HATU (180 mg, 473 μmol) and Et_3N (0.5 mL) were added. After 4 d, the mixture was diluted with EtOAc (15 mL) and washed with NaOH (0.5 N, 10 mL), $NaHCO_3$ (saturated), dried with Na_2SO_4, filtered, and concentrated to a red oil. The product mixture after chromatography on silica gel using MeOH/EtOAc (0–4%) as eluent was further purified on HPLC (10–90% gradient/15 min). The product fractions were concentrated and the residue was neutralized with NaOH (1N). The aqueous layer was saturated with $NaHCO_3$ and extracted with DCM to afford the product (30 mg, 27%). MS (ESI pos ion) calcd for $C_{30}H_{27}FN_4O_4$, 526.2; found, 527.2 (M + H). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.32 (t, J = 7.5 Hz, 3 H), 2.81 (s, 3 H), 2.84 (m, 2 H), 3.38 (s, 3 H), 3.99 (s, 3 H), 6.39 (d, J = 4.9 Hz, 1 H), 7.17 (t, J = 8.8 Hz, 1 H), 7.32 (d, 1 H), 7.37 (m, 2 H), 7.48 (t, J = 7.2 Hz, 1 H), 7.57 (t, J = 7.5 Hz, 2 H), 7.92 (dd, J = 2.0, 13.8 Hz, 1 H), 8.09 (s, 1 H), 8.54 (d, J = 5.1 Hz, 1 H), 10.88 (1 H).

***N*-(4-(6-Bromo-7-methoxyquinolin-4-yloxy)-3-fluorophenyl)-1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carboxamide (11d).** *(A) 3-Fluoro-4-(7-methoxyquinolin-4-yloxy)-aniline (**9d**).*[9] A mixture of 6-bromo-4-(2-fluoro-4-nitrophenoxy)-7-methoxyquinoline (440 mg, 1119 μmol) and Pd(OH)$_2$/C (20%, 200 mg) in EtOH (30 mL) was purged with H_2 and stirred under an atmosphere of H_2 for 20 h. The reaction content was purged with N_2, filtered through a pad of Celite, and concentrated to a brown residue. Because of the potential oxidative decomposition of the highly electron rich system, the crude product was carried directly into the next step. MS (ESI pos ion) m/z: calcd for $C_{16}H_{13}FN_2O_2$, 284.1; found, 285.1 (M + H).

*(B) N-(3-Fluoro-4-(7-methoxyquinolin-4-yloxy)phenyl)-1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxamide (**11d**).* A mixture of 3-fluoro-4-(7-methoxyquinolin-4-yloxy)-benzenamine (318 mg, 1119 μmol), 1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carboxylic acid (390 mg, 1678 μmol), and HATU (638 mg, 1678 μmol) in DCM (9 mL)–DMF (3 mL) was stirred for 4 h. Et_3N (0.5 mL) was added and the mixture was stirred overnight. The mixture was diluted with EtOAc (30 mL) and washed with NaOH (1 N, 20 mL), H_2O, and saturated $NaHCO_3$. The organic layer was dried over Na_2SO_4, filtered, and concentrated. The residue was purified by chromatography on silica gel with MeOH/EtOAc (0–4%) as eluent to give the desired product as a white solid (190 mg, 34%). MS (ESI pos ion) m/z: calcd for $C_{28}H_{23}FN_4O_4$, 498.1; found, 499.1 (M + H). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.80 (s, 3 H), 3.38 (s, 3 H), 3.97 (s, 3 H), 6.41 (d, J = 5.3 Hz, 1 H), 7.17 (t, J = 8.6 Hz, 2 H), 7.22 (dd, J = 2.4, 9.2 Hz, 1 H), 7.29 (d, 1 H), 7.37 (d, J = 7.6 Hz, 2 H), 7.41 (d, J = 2.4 Hz, 1 H), 7.48 (t, J = 7.4 Hz, 1 H), 7.57 (t, J = 7.8 Hz, 2 H), 7.92 (dd, J = 2.1, 12.5 Hz, 1 H), 8.27 (d, J = 9.2 Hz, 1 H), 8.58 (d, J = 5.7 Hz, 1 H), 10.88 (s, 1 H).

***N*-(2-Chloro-4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carboxamide (15a).** To a solution of 1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carboxylic acid (0.04 g, 0.2 mmol) in DCM was added oxalyl chloride (0.02 mL, 0.2 mmol) followed by a drop of DMF. The mixture was stirred at rt for 4 h, and the solvent was evaporated. The crude material was added to a solution of 2-chloro-4-(6,7-dimethoxyquinolin-4-yloxy)benzenamine[40] (0.05 g, 0.2 mmol) in DCM (1 mL), followed by the addition of Et_3N (0.02 mL, 0.2 mmol). The mixture was stirred at rt for 3 d. Water was added, and the mixture was extracted with DCM. The organic phase was dried over Na_2SO_4, filtered, and evaporated. The residue was purified by preparative TLC using MeOH–DCM (5%) as eluent to give the desired product (35 mg, 40%). MS (ESI pos ion) m/z calcd for $C_{29}H_{25}ClN_4O_5$, 544.2; found, 545.0 (M + H). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.81 (s, 3 H), 3.37 (s, 3 H), 3.48 (s, 1 H), 4.04 (s, 3 H), 4.07 (s, 3 H), 6.55 (d, J = 3.9 Hz, 1 H), 7.11 (dd, J = 9.3, 1.9 Hz, 1 H), 7.38 (d, J = 7.3 Hz, 2 H), 7.43–7.63 (m, 5 H), 8.50 (d, J = 5.4 Hz, 1 H), 8.70 (d, J = 8.8 Hz, 1 H), 11.12 (s, 1 H).

***N*-(6-(6,7-Dimethoxyquinolin-4-yloxy)pyridin-3-yl)-1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carboxamide (15b).** To a solution of 1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carboxylic acid (0.046 g, 0.20 mmol) in DCM (2 mL) was added oxalyl chloride (0.017 mL, 0.20 mmol) followed by a drop of DMF. The mixture was stirred at rt for 4 h, and the solvent was evaporated. A solution of 6-(6,7-dimethoxyquinolin-4-yloxy)pyridin-3-amine (0.04 g, 0.1 mmol) in DCM (2 mL) was added followed by Et_3N (0.03 mL, 0.2 mmol). The resulting mixture was stirred at rt overnight. Water was added, and the mixture was extracted with DCM. The organic phase was dried over Na_2SO_4, filtered, and evaporated. The residue was purified by preparative TLC using MeOH–DCM (5%) as eluent to give the desired product (25 mg, 36%). MS (ESI pos ion) m/z calcd for C_{28} H_{25} N_5O_5, 511.2; found, 512.1 (M + H). ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.71 (s, 3 H), 3.38 (s, 3 H), 3.89 (s, 3 H), 3.95 (s, 3 H), 6.84 (d, J = 5.2 Hz, 1 H), 7.31 (d, J = 8.7 Hz, 1 H), 7.7–7.38 (m, 7 H), 8.27 (dd, J = 2.9, 5.8 Hz, 1 H), 8.50 (d, J = 2.6 Hz, 1 H), 8.56 (d, J = 5.0 Hz, 1 H), 10.86 (s, 1 H).

***N*-(5-(6,7-Dimethoxyquinolin-4-yloxy)pyridin-2-yl)-1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carboxamide (15c).** A mixture of 5-(6,7-dimethoxyquinolin-4-yloxy)pyridin-2-amine (130 mg, 437 μmol), 1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carboxylic acid (120 mg, 517 μmol), HATU (280 mg, 736 μmol), and Et_3N (1.0 mL) in DCM (5 mL) was stirred at rt for 24 h to give, after aqueous workup and purification by chromatography on silica gel with MeOH–DCM (4–6%) as eluent, the desired product as a white solid (37 mg, 17%). MS (ESI pos ion) m/z calcd for C_{28} H_{25} N_5O_5, 511.2; found, 512.1 (M + H). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.81 (s, 3 H), 3.38 (s, 3 H), 4.06 (s, 6 H), 6.46 (d, J = 5.23 Hz, 1 H), 7.38 (d, J = 8.2 Hz, 2 H), 7.41–7.58 (m, 6 H), 8.25 (d, J = 2.7 Hz, 1 H), 8.38 (d, J = 9.0 Hz, 1 H), 8.46–8.54 (m, 1 H), 11.28 (s, 1 H).

***N*-(5-(7-Methoxyquinolin-4-yloxy)pyridin-2-yl)-1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carboxamide (22a).** A mixture of 5-(7-methoxyquinolin-4-yloxy)pyridin-2-amine (**16**, 400 mg, 1497 μmol), 1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carboxylic acid (521 mg, 2245 μmol), Et_3N (1.0 mL), and HATU (854 mg, 2245 μmol) in DCM (3 mL)–DMF (3 mL) was stirred at rt. After 20 h, more 1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carboxylic acid (521 mg, 2245 μmol) was added, and the mixture was heated at 65 °C for 3 h. The mixture was allowed to cool to rt, diluted with EtOAc (20 mL), and stirred overnight. The mixture was filtered, and the solid was washed with Et_2O/EtOAc (1:1), aqueous NaOH (1 N, 5 mL), and lyophilized to give the product as a white power (606 mg, 84%). MS (ESI pos ion) m/z: calcd for $C_{27}H_{23}N_5O_4$, 481.2; found, 482.1 (M + H). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.80 (s, 3 H), 3.37 (s, 3 H), 3.97 (s, 3 H), 6.42 (d, J = 5.1 Hz, 1 H), 7.23 (dd, J = 2.4, 9.7 Hz, 1 H), 7.37 (d, J = 7.4 Hz, 2 H), 7.41 (m, 1 H), 7.47 (m, 1 H), 7.53 (m, 3 H), 8.23 (m, 2 H), 8.38 (d, J = 9.0 Hz, 1 H), 8.60 (d, J = 5.1 Hz, 1 H), 11.27 (s, 1 H).

***N*-(2-Methoxy-4-(7-methoxyquinolin-4-yloxy)phenyl)-1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carboxamide (22b).** *(A) 7-Methoxy-4-(3-methoxy-4-nitrophenoxy)-quinoline (**18a**).* To a solution of 3-methoxy-4-nitrophenol (0.51 g, 3.0 mmol) in chlorobenzene (15 mL) was added 4-chloro-7-methoxyquinoline **17** (0.70 g, 3.6 mmol). The reaction mixture was heated at reflux under N_2 for 20 h. The reaction mixture was allowed to cool to rt, diluted with H_2O, and basified to pH ∼8 with NaOH (5 N). The resulting mixture was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by chromatography on silica gel using EtOAc in hexanes (30 to 70%) as eluent to obtain the product as pale-yellow solid (430 mg, 44%). (ESI pos ion) m/z calcd for $C_{17}H_{14}N_2O_5$, 326.1; found, 326.8. ^{1}H NMR (300 MHz, CD_3OD) δ 3.96 (s, 3 H), 3.99 (s, 3 H), 6.78 (d, J = 5.3 Hz, 1 H), 6.88 (dd, J = 8.85, 2.3 Hz, 1 H), 7.21 (d, J = 2.3 Hz, 1 H), 7.31 (dd, J = 9.2, 2.4 Hz, 1 H),

7.40 (d, J = 2.4 Hz, 1 H), 8.01 (d, J = 9.0 Hz, 1 H), 8.21 (d, J = 9.2 Hz, 1 H), 8.65 (d, J = 5.3 Hz, 1 H).

*(B) 2-Methoxy-4-(7-methoxyquinolin-4-yloxy)aniline (**18b**).* To a solution of 7-methoxy-4-(3-methoxy-4-nitrophenoxy)quinoline (0.43 g, 1.3 mmol) in EtOAc (15 mL) under N_2 was added Pd/C (10%, 0.042 g). The reaction mixture was purged with N_2 (3×) and was exposed to H_2 in a balloon. After 20 h at rt, the solvent was separated by filtration and evaporated. The crude product was purified by chromatography on silica gelusing MeOH−DCM (3:97) as eluent to obtain the product as brown foam. MS (ESI pos ion) m/z calcd for $C_{17}H_{16}N_2O_3$, 296.1; found, 296.9. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.84 (bs, OMe and NH_2, 5 H), 3.97 (s, 3 H), 6.43 (d, J = 5.3 Hz, 1 H), 6.58−6.69 (m, 2 H), 6.72−6.82 (m, 1 H), 7.21 (dd, J = 9.1, 2.5 Hz, 1 H), 7.40 (d, J = 2.4 Hz, 1 H), 8.26 (d, J = 9.0 Hz, 1 H), 8.56 (d, J = 5.3 Hz, 1 H).

*(C) N-(2-Methoxy-4-(7-methoxyquinolin-4-yloxy)phenyl)-1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxamide (**22b**).* To a solution of 1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carboxylic acid (0.11 g, 0.48 mmol) in DMF (10 mL) was added 2-methoxy-4-(7-methoxyquinolin-4-yloxy)benzenamine (0.095 g, 0.32 mmol), 1*H*-benzo[*d*][1,2,3]triazol-1-ol hydrate (0.074 g, 0.48 mmol), EDCI-HCl (0.068 g, 0.35 mmol), and ^{i}Pr$_2$NEt (0.11 mL, 0.64 mmol). The reaction was heated at 60 °C for 20 h and then partitioned between EtOAc and saturated $NaHCO_3$. The aqueous layer was extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by chromatography on silica gel using MeOH−DCM (5:95) as eluent to give the product as an off-white solid (110 mg, 67%). MS (ESI pos ion) m/z calcd for $C_{29}H_{26}N_4O_5$, 510.2; found, 511.2. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.82 (s, 3 H), 3.35 (s, 3 H), 3.88 (s, 3 H), 3.98 (s, 3 H), 6.50 (d, J = 5.3 Hz, 1 H), 6.73 (d, J = 2.4 Hz, 1 H), 6.79 (dd, J = 8.7, 2.45 Hz, 1 H), 7.22 (dd, J = 9.2, 2.4 Hz, 1 H), 7.38 (s, 1 H), 7.39−7.44 (m, 2 H), 7.47 (d, J = 7.4 Hz, 1 H), 7.55 (t, J = 7.4 Hz, 2 H), 8.25 (d, J = 9.0 Hz, 1 H), 8.59 (d, J = 5.3 Hz, 1 H), 8.62 (d, J = 8.8 Hz, 1 H), 10.96 (s, 1 H).

***N*-(5-(7-Methoxyquinolin-4-yloxy)pyrimidin-2-yl)-1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carboxamide (22c).** *(A) N-(5-(Benzyloxy)pyrimidin-2-yl)benzamide (**20a**).* A mixture of CuI (861.8 mg, 4525 μmol), 2-amino-5-iodopyrimidine (1000 mg, 4525 μmol), Cs_2CO_3 (2949 mg, 9050 μmol), and 1,10-phenanthroline (815.4 mg, 4525 μmol) in benzyl alcohol (4696 μL, 45249 μmol) in a 50 mL sealed tube under N_2 was stirred and heated at 110 °C. After 1 h, the reaction mixture was directly purified by chromatography on silica gel with [NH_3/MeOH (1%)]−DCM (0−10%) to afford the title compound contaminated with 1,10-phenanthroline. This material was used without further purification in the next step. MS (ESI pos ion) m/z calcd for $C_{11}H_{11}N_3O$, 201.1; found, 202.0 (M + H).

In a 50 mL round-bottomed flask was added 5-(benzyloxy)pyrimidin-2-amine (910 mg, 4522 μmol) and DCM (10 mL) followed by pyridine (3658 μL, 45223 μmol) and benzoyl chloride (1575 μL, 13567 μmol). After stirring at rt for 3 h, the reaction mixture was evaporated and the residue was purified by chromatography on silica gel with MeOH−DCM (0−10%) as eluent to afford the title compound. MS (ESI pos ion) m/z calcd for $C_{18}H_{15}N_3O_2$, 305.1; found, 306.1 (M + H).

*(B) N-(5-Hydroxypyrimidin-2-yl)benzamide (**20b**).* In a 50 mL round-bottomed flask under N_2 was added *N*-(5-(benzyloxy)-pyrimidin-2-yl)benzamide (322 mg, 1055 μmol) and a suspension of Pd/C (10%, 112 mg) in MeOH (4 mL). The reaction mixture was purged with H_2 and stirred under an atmosphere of H_2 (balloon). After 4 h, the reaction mixture was purged with N_2 and then filtered over Celite and concentrated under reduced pressure. The crude product was used without further purification in the next step. MS (ESI pos ion) m/z calcd for $C_{11}H_9N_3O_2$, 215.1; found, 215.9 (M + H).

*(C) N-(5-(7-Methoxyquinolin-4-yloxy)pyrimidin-2-yl)benzamide (**21a**).* In a 50 mL sealed tube under N_2 were added 4-chloro-7-methoxyquinoline (254 mg, 1313 μmol), *N*-(5-hydroxypyrimidin-2-yl)benzamide (226 mg, 1050 μmol), PPTS (330 mg, 1313 μmol), and 2-BuOH (4 mL). The mixture was stirred and heated at 100 °C for1 h. After cooling to rt, the reaction mixture was diluted with DCM and neutralized with NaOH (1 N). The aqueous phase was extracted with DCM−MeOH (90:10, 3×). The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude mixture was purified by chromatography on silica gel with MeOH−DCM (0−5%) as eluent to afford the title compound (163 mg, 41.7%) as yellow oil. MS (ESI pos ion) m/z calcd for $C_{21}H_{16}N_4O_3$, 372.1; found, 373.0 (M + H).

*(D) 5-(7-Methoxyquinolin-4-yloxy)pyrimidin-2-amine (**21b**).* A mixture of *N*-(5-(7-methoxyquinolin-4-yloxy)pyrimidin-2-yl)-benzamide (163 mg, 438 μmol), MeOH (10 mL), and NaOH (1N, 10 mL) in a 50 mL sealed tube was heated at 70 °C. After 1 h, the reaction mixture was diluted with DCM and neutralized with NH_4Cl (saturated). The aqueous phase was extracted with DCM−MeOH (90:10, 3×). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude mixture was purified by chromatography on silica gel with MeOH−DCM (0 to 5%) as eluent to afford the title compound (57 mg, 49%) as a white solid. MS (ESI pos ion) m/z calcd for $C_{14}H_{12}N_4O_2$, 268.1; found, 269.0 (M + H).

*(E) N-(5-(7-Methoxyquinolin-4-yloxy)pyrimidin-2-yl)-1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxamide (**22c**).* In a 10 mL sealed tube under N_2 was added 1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carboxylic acid (36 mg, 157 μmol), DCM (1 mL), and a catalytical amount of DMF, followed by oxalyl chloride (46 μL, 522 μmol). The reaction mixture was stirred at rt for 30 min and then evaporated under high vacuum for 2 h. The resulting acyl chloride was dissolved in DCM and transferred to a flask containing 5-(7-methoxyquinolin-4-yloxy)pyrimidin-2-amine (28 mg, 104 μmol). ^{i}Pr$_2$NEt (55 μL, 313 μmol) was added, and the mixture was heated at 50 °C for 3 h. The crude reaction mixture was directly purified by chromatography on silica gel with MeOH/EtOAc (20:80) as eluent to afford the title compound. MS (ESI pos ion) m/z calcd for $C_{26}H_{22}N_6O_4$, 482.2; found, 483.1 (M + H). ^{1}H NMR (400 MHz, DMSO-d_6/$CDCl_3$) δ 2.72 (s, 3 H), 3.38 (s, 3 H), 3.95 (s, 3 H), 6.65−6.74 (m, 1 H), 7.28−7.36 (m, 1 H), 7.40−7.46 (m, 3 H), 7.48−7.54 (m, 1 H), 7.55−7.62 (m, 2 H), 8.22−8.28 (m, 1 H), 8.64−8.69 (m, 1 H), 8.71 (s, 2 H), 11.50 (s, 1 H).

***tert*-Butyl (4-((3-Fluoro-4-(7-methoxyquinolin-4-yloxy)-phenyl)carbamoyl)-1-methyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-5-yl)methylcarbamate (26a).** *(A) Methyl 5-(Bromomethyl)-1-methyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxylate (**24**).* Methyl 1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carboxylate (7.82 g, 31.8 mmol) was dissolved in $CHCl_3$ (150 mL), and NBS (6.91 g, 38.8 mmol) was added. After 1.5 h at rt, more NBS (6.23 g, 35.2 mmol) was added. After stirring for 1 h, the reaction mixture was filtered, and the solid was washed with $CHCl_3$. The filtrate was concentrated, treated with DCM, and filtered. The filtrate was concentrated, and purified again by chromatography on silica gel using MeOH−DCM (0−10%) as eluent to give the desired product (4.11 g, 33%). MS (ESI pos ion) m/z: calcd for $C_{13}H_{13}BrN_2O_3$, 324.0; found, 325.0 (M + H). ^{1}H NMR (400 MHz, CD_3OD) δ 3.46 (s, 3 H), 3.85 (s, 3 H), 4.99 (s, 2 H), 7.38−7.42 (m, 2 H), 7.56−7.64 (m, 3 H).

(B) Methyl 5-(Azidomethyl)-1-methyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxylate. Methyl 5-(bromomethyl)-1-methyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carboxylate (3.494 g, 10.75 mmol) was dissolved in DMF (20 mL) and cooled in an ice−water bath under N_2. Then, sodium azide (842 mg, 12.96 mmol) was added and the reaction was allowed to warm to rt and stirred for 50 min. The mixture was quenched with H_2O (70 mL), stirred overnight, and extracted with DCM (3 × 75 mL). The organic phases were combined, washed with H_2O (6 × 100 mL), brine, dried over Na_2SO_4, filtered, and concentrated. The residue was dried under high vacuum to afford the title compound (2.592 g, 61%). MS (ESI pos ion) m/z: calcd for $C_{13}H_{13}N_5O_3$, 287.1; found, 288.1 (M + H).

*(C) Methyl 5-(Aminomethyl)-1-methyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxylate (**25b**).* Methyl 5-(azidomethyl)-1-methyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carboxylate (1.802 g, 6.27 mmol) was dissolved in THF (60 mL) and H_2O (2.0 mL).

Triphenyl phosphine (1.913 g, 7.29 mmol) was added over 5 min, resulting in gas evolution. After stirring under N_2 at rt overnight, the mixture was concentrated. The residue was purified by chromatography on silica gel [MeOH−DCM (1:50 to 1:20), then (2 N NH_3 in MeOH)−DCM (1:10 to 1:5)] to afford the title compound (1.245 g, 66%). MS (ESI pos ion) m/z: calcd for $C_{13}H_{15}N_3O_3$, 261.1; found, 262.1 (M + H). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.43 (s, 3 H), 3.89 (s, 3 H), 4.15 (s, 2 H), 7.33 (d, J = 9.0 Hz, 2 H), 7.41 (t, J = 7.3 Hz, 1 H), 7.50 (d, J = 8.0 Hz, 2 H).

*(D) Methyl 5-((tert-Butoxycarbonyl)methyl)-1-methyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxylate (**25a**).* To a solution of methyl 5-(aminomethyl)-1-methyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carboxylate (1.214 g, 4.65 mmol) in DCM (40 mL), cooled in an ice water bath, was added a solution of di-*tert*-butyl dicarbonate (1.175 g, 5.38 mmol) in DCM (5 mL), followed by DCM rinsing (~2 mL). After about 30 min, the reaction was allowed to warm to rt and stirred for another 30 min. The reaction mixture was poured into H_2O (30 mL), and the layers were separated. The aqueous phase was extracted with DCM (30 mL). The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated to afford the title compound. MS (ESI pos ion) m/z: calcd for $C_{18}H_{23}N_3O_5$, 361.2; found, 362.1 (M + H). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.46 (s, 9 H), 3.57 (s, 3 H), 3.89 (s, 3 H), 4.50 (d, J = 6.6 Hz, 2 H), 5.83 (br s, 1 H), 7.30 (d, J = 7.4 Hz, 2 H), 7.39−7.46 (m, 1 H), 7.47−7.58 (m, 2 H).

(E) 5-((tert-Butoxycarbonyl)methyl)-1-methyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxylic Acid. A mixture of methyl 5-((*tert*-butoxycarbonyl)methyl)-1-methyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carboxylate in MeOH (25 mL) and NaOH (1 N, 6.0 mL) was stirred at rt. After 70 min, NaOH pellets (0.683 g, 17.1 mmol) were added. After stirring for 1 h at rt, the flask was fitted with a reflux condenser and placed in a preheated oil bath (80 °C). After 45 min, the mixture was allowed to cool to rt and treated with HCl (10%) to adjust the pH to about 2−4. The mixture was concentrated. The residue was treated with DCM−MeOH (1:1), and the resultant suspension was filtered. The filtrate was concentrated and the solid was again treated with DCM−MeOH (1:1), and the suspension was filtered. The filtrate was concentrated and the residue was dried under high vacuum to afford the title compound (1.573 g, 97%). MS (ESI pos ion) m/z: calcd for $C_{17}H_{21}N_3O_5$, 347.2; found, 348.1 (M + H). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.45 (s, 9 H), 3.63 (s, 3 H), 4.53 (d, J = 6.6 Hz, 2 H), 6.03 (br s, 1 H), 7.34 (d, J = 1.2 Hz, 2 H), 7.48−7.62 (m, 3 H), 12.03 (br s, 1 H).

*(F) tert-Butyl (4-((3-Fluoro-4-(7-methoxyquinolin-4-yloxy)-phenyl)carbamoyl)-1-methyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-5-yl)methylcarbamate (**26a**).* The general procedure for amide coupling between 1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carboxylic acid and anilines was followed to prepare the title compound (1.197 g, 31%). Part of this material (0.5 g) was further purified on HPLC (10−95% MeCN/H_2O with 0.1% TFA) to provide an analytically pure sample. MS (ESI pos ion) m/z: calcd for $C_{33}H_{32}FN_5O_6$, 613.2; found, 614.1 (M + H). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.47 (s, 9 H), 3.66 (s, 3 H), 4.09 (s, 3 H), 4.62 (d, J = 6.6 Hz, 2 H), 6.11 (t, J = 6.6 Hz, 1 H), 6.72 (d, J = 6.5 Hz, 1 H), 7.19−7.25 (m, 1 H), 7.38 (d, J = 7.6 Hz, 3 H), 7.44 (dd, J = 9.4, 2.2 Hz, 1 H), 7.55−7.63 (m, 3 H), 7.95−8.13 (m, 2 H), 8.41 (d, J = 9.2 Hz, 1 H), 8.81 (d, J = 6.6 Hz, 1 H), 10.96 (s, 1 H).

5-(Aminomethyl)-*N*-(3-fluoro-4-(7-methoxyquinolin-4-yloxy)phenyl)-1-methyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carboxamide (26b). *tert*-Butyl (4-((3-fluoro-4-(7-methoxyquinolin-4-yloxy)phenyl)carbamoyl)-1-methyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-5-yl)methylcarbamate (667 mg, 1.09 mmol) was dissolved in DCM (10 mL), and TFA (0.50 mL, 6.5 mmol) was added. The mixture was stirred in a water bath under N_2 for 90 min, and then more TFA (0.50 mL, 6.5 mmol) was added, and stirring was continued. After 3.5 h, the reaction mixture was concentrated, treated with NH_3 in MeOH (2 N, 10 mL), and concentrated. The residue was purified by chromatography on silica gel [MeOH−DCM (1:50), then (2 N NH_3 in MeOH)−DCM (1:10 to 1:5)] to afford the title compound (336 mg, 60%). MS (ESI pos ion) m/z: calcd for $C_{28}H_{24}FN_5O_4$, 513.2; found, 514.1 (M + H). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.01 (br s, 2 H), 3.51 (s, 3 H), 3.98 (s, 3 H), 4.30, (s, 2 H), 6.43 (d, J = 5.3 Hz, 1 H), 7.16−7.26 (m, 2 H), 7.32 (d, J = 8.4 Hz, 1 H), 7.39 (d, J = 8.0 Hz, 2 H), 7.44 (s, 1 H), 7.48−7.54 (m, 1 H), 7.56−7.64 (m, 2 H), 7.92 (d, J = 12.3 Hz, 1 H), 8.28 (d, J = 9.0 Hz, 1 H), 8.61 (d, J = 5.1 Hz, 1 H), 10.93 (s, 1 H).

5-((Ethyl(methyl)amino)methyl)-*N*-(5-(7-methoxyquinolin-4-yloxy)pyridin-2-yl)-1-methyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carboxamide (26c). *(A) Methyl 5-((Ethyl(methyl)-amino)methyl)-1-methyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxylate (**25c**).* Methyl 5-(bromomethyl)-1-methyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carboxylate (368 mg, 1.13 mmol) was suspended in DCM (8 mL), and *N*-ethylmethylamine (0.12 mL, 1.4 mmol) was added. The mixture was stirred under N_2 at rt for 75 min, and then more *N*-ethylmethylamine (0.03 mL, 0.04 mmol) was added. After 2.5 h, the mixture was concentrated and the residue was purified by chromatography on silica gel [MeOH−DCM (25:1) to (2 N NH_3 in MeOH)−DCM (10:1)] to afford the title compound (331 mg) that was taken directly to the next step. MS (ESI pos ion) m/z: calcd for $C_{16}H_{21}N_3O_3$, 303.2; found, 304.1 (M + H). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.11 (t, J = 7.1 Hz, 3 H), 2.30 (s, 3 H), 2.57 (q, J = 7.1 Hz, 2 H), 3.48 (s, 3 H), 3.85 (s, 3 H), 3.98 (s, 2 H), 7.29−7.33 (m, 2 H), 7.37−7.43 (m, 1 H), 7.47−7.53 (m, 2 H).

(B) 5-((Ethyl(methyl)amino)methyl)-1-methyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxylic Acid. Methyl 5-((ethyl-(methyl)amino)methyl)-1-methyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carboxylate (331 mg, 1.09 mmol) was dissolved in MeOH (6 mL). Aqueous NaOH (1 N, 0.6 mL) and solid NaOH (96 mg, 2.42 mmol) were added. The flask was fitted with a reflux condenser and placed in a preheated oil bath (90 °C) and stirred for 1.5 h. The mixture was allowed to cool to rt, partially concentrated, and treated with HCl (concd) to lower the pH to ~5. The mixture was concentrated, triturated with MeOH−DCM (1:1), and filtered. The filtrate was concentrated, and the residue was dried under high vacuum to afford the title compound (366.5 mg) that was taken to the next step. MS (ESI pos ion) m/z: calcd for $C_{15}H_{19}N_3O_3$, 289.1; found, 290.1 (M + H).

*(C) 5-((Ethyl(methyl)amino)methyl)-N-(5-(7-methoxyquinolin-4-yloxy)pyridin-2-yl)-1-methyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxamide (**26c**).* The general procedure for amide coupling between 1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carboxylic acid and anilines was followed to prepare the title compound (42 mg, 7% over 3 steps from the methyl ester). MS (ESI pos ion) m/z: calcd for $C_{31}H_{30}FN_5O_4$, 555.2; found, 555.8 (M + 1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.15 (t, J = 7.0 Hz, 3 H), 2.37 (s, 3 H), 2.63 (q, J = 6.8 Hz, 2 H), 3.58 (s, 3 H), 3.98 (s, 3 H), 4.22 (s, 2 H), 6.41 (d, J = 5.1 Hz, 1 H), 7.15−7.19 (m, 1 H), 7.21−7.33 (m, 2 H), 7.36−7.43 (m, 3 H), 7.47−7.54 (m, 1 H), 7.55−7.61 (m, 2 H), 7.92 (d, J = 11.9 Hz, 1 H), 8.28 (d, J = 9.2 Hz, 1 H), 8.59 (d, J = 4.9 Hz, 1 H), 11.06 (s, 1 H).

***N*-(3-Fluoro-4-(7-methoxyquinolin-4-yloxy)phenyl)-1-methyl-3-oxo-2-phenyl-5-(pyrrolidin-1-ylmethyl)-2,3-dihydro-1*H*-pyrazole-4-carboxamide (26d).** *(A) Methyl 1-Methyl-3-oxo-2-phenyl-5-(pyrrolidin-1-ylmethyl)-2,3-dihydro-1H-pyrazole-4-carboxylate (**25d**).* Methyl 5-(bromomethyl)-1-methyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carboxylate (1.266 g, 3.89 mmol) was dissolved in DCM (30 mL), and pyrrolidine (0.40 mL, 4.8 mmol) was added via syringe. The mixture was stirred under N_2 at rt. After 20 min, more pyrrolidine (0.090 mL, 1.1 mmol) was added, and stirring was continued for 3.5 h. The mixture was concentrated, and the residue was purified by chromatography on silica gel [MeOH−DCM (1:50 to 1:25),(2 N NH_3 in MeOH)−DCM (1:15)] to give the title compound (1.182 g, 67%). MS (ESI pos ion) m/z: calcd for $C_{17}H_{21}N_3O_3$, 315.2; found, 316.1 (M + H). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.81 (dt, J = 6.5, 3.1 Hz, 4 H), 2.65 (t, J = 6.0 Hz, 4 H), 3.48 (s, 3 H), 3.86 (s, 3 H), 4.12 (s, 2 H), 7.32 (d, J = 7.4 Hz, 2 H), 7.38−7.44 (m, 1 H), 7.48−7.54 (m, 2 H).

(B) 1-Methyl-3-oxo-2-phenyl-5-(pyrrolidin-1-ylmethyl)-2,3-dihydro-1H-pyrazole-4-carboxylic Acid. Methyl 1-methyl-3-oxo-2-phenyl-5-(pyrrolidin-1-ylmethyl)-2,3-dihydro-1*H*-pyrazole-4-carboxylate (1.182 g, 3.7 mmol) was dissolved in MeOH (17 mL). Aqueous

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NaOH (1.0 M, 4.2 mL, 4.2 mmol) and solid NaOH (282 mg, 7.05 mmol) were added. The mixture was stirred at rt for 3 h and then stirred at 90 °C for 1 h. The mixture was then cooled to rt and treated with a solution of HCl (10%) to lower the pH to ~2. The mixture was concentrated, treated with MeOH−DCM (1:1), and filtered. The filtrate was concentrated to give the title compound (1.342 g, 93%). MS (ESI pos ion) m/z: calcd for $C_{16}H_{19}N_3O_3$, 301.1; found, 302.1 (M + H). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.17−2.23 (m, 4 H), 3.45−3.55 (m, 4 H), 3.83 (s, 3 H), 4.75 (s, 2 H), 7.44−7.49 (m, 2 H), 7.51−7.61 (m, 3 H).

*(C) N-(3-Fluoro-4-(7-methoxyquinolin-4-yloxy)phenyl)-1-methyl-3-oxo-2-phenyl-5-(pyrrolidin-1-ylmethyl)-2,3-dihydro-1H-pyrazole-4-carboxamide (**26d**).* The general procedure for amide coupling between 1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carboxylic acid and anilines was followed to prepare the title compound (81 mg, 8%). MS (ESI pos ion) m/z: calcd for $C_{32}H_{30}FN_5O_4$, 567.2; found, 568.1 (M + H). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.84 (br s, 4 H), 2.72 (br s, 4 H), 3.58 (s, 3 H), 3.98 (s, 3 H), 4.28−4.40 (m, 2 H), 6.41 (d, J = 5.3 Hz, 1 H), 7.10−7.20 (m, 1 H), 7.20−7.34 (m, 2 H), 7.36−7.44 (m, 3 H), 7.47−7.54 (m, 1 H), 7.55−7.65 (m, 2 H), 7.93 (d, J = 13.1 Hz, 1 H), 8.28 (d, J = 9.0 Hz, 1 H), 8.60 (d, J = 5.1 Hz, 1 H), 11.06 (s, 1 H).

***N*-(5-(7-Methoxyquinolin-4-yloxy)pyridin-2-yl)-1-methyl-3-oxo-2-phenyl-5-(pyrrolidin-1-ylmethyl)-2,3-dihydro-1*H*-pyrazole-4-carboxamide (27).** The general procedure for amide coupling between 1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carboxylic acid and anilines was followed to prepare the title compound (90 mg, 8%). MS (ESI pos ion) m/z: calcd for $C_{31}H_{30}N_6O_4$, 550.2; found, 551.1 (M + H). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.84 (br s, 4 H), 2.73 (br s, 4 H), 3.57 (s, 3 H), 3.98 (s, 3 H), 4.35 (s, 2 H), 6.43 (d, J = 5.1 Hz, 1 H), 7.24 (d, J = 9.0 Hz, 1 H), 7.36−7.63 (m, 7 H), 8.22−8.28 (m., 2 H), 8.37 (d, J = 9.00 Hz, 1 H), 8.61 (d, J = 5.3 Hz, 1 H), 11.44 (s, 1 H).

5-(2-Aminopropan-2-yl)-*N*-(3-fluoro-4-(7-methoxyquinolin-4-yloxy)phenyl)-1-methyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carboxamide (35a). *(A) tert-Butyl 2-Methyl-1-oxo-1-(2-phenylhydrazinyl)propan-2-ylcarbamate (**29a**).* The title compound was prepared from 2-(*tert*-butoxycarbonylamino)-2-methylpropanoic acid **28a** (5.26 g, 25.90 mmol) according to the procedure described for **29b** (5.92 g, 78%). MS (ESI pos ion) m/z: calcd for $C_{15}H_{23}N_3O_3$, 293.2; found, 316.1 (M + Na). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.49 (s, 9 H), 1.57 (s, 6 H), 4.87 (br s, 1 H), 6.04 (d, J = 4.3 Hz, 1 H), 6.89 (d, J = 7.6 Hz, 3 H), 7.23 (t, J = 7.9 Hz, 2 H), 8.48 (br s, 1 H).

*(B) Benzyl 2-(2-(tert-Butoxycarbonylamino)-2-methylpropanoyl)-1-phenylhydrazinecarboxylate (**30a**).* The title compound was prepared from *tert*-butyl 2-methyl-1-oxo-1-(2-phenylhydrazinyl)-propan-2-ylcarbamate (5.88 g, 20.0 mmol) according to the procedure described for **30b** (7.540 g, 81%). MS (ESI pos ion) m/z: calcd for $C_{23}H_{29}N_3O_5$, 427.2; found, 450.0 (M + Na). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.24 (br s, 6 H), 1.36 (s, 9 H), 5.13 (s, 2 H), 7.04−7.11 (m, 2 H), 7.26 (t, J = 7.6 Hz, 2 H), 7.30−7.39 (m, 6 H), 7.52 (br s, 1 H), 10.47 (s, 1 H).

*(C) Benzyl 2-(2-(tert-Butoxycarbonylamino)-2-methylpropanoyl)-2-methyl-1-phenylhydrazinecarboxylate (**31a**).* The title compound was prepared from benzyl 2-(2-(*tert*-butoxycarbonylamino)-2-methylpropanoyl)-1-phenylhydrazinecarboxylate (4.033 g, 9.43 mmol) according to the procedure described for **31b** and was used directly in the next step. MS (ESI pos ion) m/z: calcd for $C_{24}H_{31}N_3O_5$, 441.2; found, 342.1 (M-Boc + H). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.37 (s, 15 H), 3.28 (s, 3 H), 5.14 (s, 2 H), 7.10−7.14 (m, 1 H), 7.21−7.43 (m, 8 H), 7.47−7.57 (br s, 1 H), 7.62 (s, 1 H).

*(D) tert-Butyl 2-Methyl-1-(1-methyl-2-phenylhydrazinyl)-1-oxopropan-2-ylcarbamate (**32a**).* The title compound was prepared according to the procedure described for **32b** to give 3.306 g (86% over 2 steps). MS (ESI pos ion) m/z: calcd for $C_{16}H_{25}N_3O_3$, 307.2; found, 252.1 (M-C_4H_8 + H).

*(E) 5-(2-(tert-Butoxycarbonyl)propan-2-yl)-1-methyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxylic Acid (**34a**).* The title compound was prepared according to the procedure described for **34b** from *tert*-butyl 2-methyl-1-(1-methyl-2-phenylhydrazinyl)-1-oxopropan-2-ylcarbamate (2.50 g, 8.1 mmol) to give 1.53 g (27% over 2 steps). MS (ESI pos ion) m/z: calcd for $C_{19}H_{25}N_3O_5$, 375.2; found, 376.1 (M + H). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40 (s, 9 H), 1.89 (s, 6 H), 3.67 (s, 3 H), 6.84 (br s, 1 H), 7.37−7.41 (m, 2 H), 7.46−7.51 (m, 1 H), 7.54−7.60 (m, 2 H).

*(F) 5-(2-Aminopropan-2-yl)-N-(3-fluoro-4-(7-methoxyquinolin-4-yloxy)phenyl)-1-methyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxamide (**35a**).* The title compound was prepared according to the general procedure for amide coupling between 1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carboxylic acid and anilines, followed by the removal of the Boc group (28 mg, 8% over 2 steps). MS (ESI pos ion) m/z: calcd for $C_{30}H_{28}FN_5O_4$, 541.2; found, 542.1 (M + H). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.87 (s, 6 H), 3.59 (s, 3 H), 3.98 (s, 3 H), 6.42 (dd, J = 5.3, 0.8 Hz, 1 H), 7.18−7.27 (m, 2 H), 7.34 (d, J = 10.0 Hz, 1 H), 7.40−7.53 (m, 4 H), 7.55−7.61 (m, 2 H), 7.92 (dd, J = 12.3, 2.4 Hz, 1 H), 8.28 (d, J = 9.2 Hz, 1 H), 8.59 (d, J = 5.3 Hz, 1 H), 11.95 (s, 1 H).

(*S*)-*N*-(3-Fluoro-4-(7-methoxyquinolin-4-yloxy)phenyl)-1-methyl-3-oxo-2-phenyl-5-(pyrrolidin-2-yl)-2,3-dihydro-1*H*-pyrazole-4-carboxamide (35b). *(A) (S)-tert-Butyl 2-(2-Phenylhydrazinecarbonyl)pyrrolidine-1-carboxylate (**29b**).* To a mixture of (*S*)-1-(*tert*-butoxycarbonyl)pyrrolidine-2-carboxylic acid (**28b**, 6.021 g, 27.97 mmol) and 1-hydroxybenzotriazole (5.156 g, 38.16 mmol) in DCM (100 mL) was added EDCI-HCl (6.462 g, 33.71 mmol), Et_3N (4.70 mL, 33.7 mmol), and 1-phenylhydrazine (3.40 mL, 34.5 mmol). The mixture was stirred at rt under N_2 for 3 h and then was treated with H_2O (100 mL) and HCl (1 N, 75 mL). The organic phase was separated, and the aqueous phase was filtered and the solid was washed with H_2O and DCM. The layers of the filtrate were separated, and the combined organic phases were washed with HCl (1 N, 3 × 50 mL), saturated Na_2CO_3 (75 mL), and brine (75 mL). The organic phase was dried over Na_2SO_4, filtered, concentrated, and dried under high vacuum to afford the title compound (8.50 g, 100%). MS (ESI pos ion) m/z: calcd for $C_{16}H_{23}N_3O_3$, 305.2; found, 250.1 (M − C_4H_8 + H). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.52 (s, 9 H), 1.88−2.08 (m, 3 H), 2.35−2.50 (m, 1 H), 3.30−3.60 (m, 2 H), 4.39 (br s, 1 H), 6.07 (d, J = 3.3 Hz, 1 H), 6.84 (d, J = 7.8 Hz, 2 H), 6.85−6.95 (m, 1 H), 7.23 (t, J = 7.6 Hz, 2 H), 8.76 (br s, 1 H).

*(B) (S)-tert-Butyl 2-(2-(Benzyloxycarbonyl)-2-phenylhydrazinecarbonyl)pyrrolidine-1-carboxylate (**30b**).* To a solution of (*S*)-*tert*-butyl 2-(2-phenylhydrazinecarbonyl)pyrrolidine-1-carboxylate (8.50 g, 27.8 mmol) in THF (150 mL) was added aqueous NaOH (5.0 N, 14.0 mL, 70 mmol) and benzyl chloroformate (5.0 mL, 35 mmol). After the mixture was stirred at rt overnight, more NaOH (5 N, 13 mL, 65 mmol) and benzyl chloroformate (8.0 mL, 56 mmol) were added. After another 30 min, H_2O (200 mL) was added, and the layers were separated. The organic phase was dried over Na_2SO_4, filtered, and concentrated. The residue was washed repeatedly with hexanes and then dried under high vacuum. The material was purified by chromatography on silica gel using MeOH−DCM (0−2.5%) as eluent to afford the title compound (5.31 g, 26%). MS (ESI pos ion) m/z: calcd for $C_{24}H_{29}N_3O_5$, 439.2; found, 462.1 (M + Na).

*(C) (S)-tert-Butyl 2-(2-(benzyloxycarbonyl)-1-methyl-2-phenylhydrazinecarbonyl)pyrrolidine-1-carboxylate (**31b**).* To a solution of (*S*)-*tert*-butyl 2-(2-(benzyloxycarbonyl)-2-phenylhydrazinecarbonyl)pyrrolidine-1-carboxylate (5.31 g, 12.1 mmol) in DMF (50 mL), cooled in an ice−water bath under N_2, was added NaH (683 mg, 60% in mineral oil). After 20 min, more DMF (40 mL) was added, and the reaction was allowed to warm to rt and stirred for 1 h. More DMF (10 mL) was added, followed by MeI (0.81 mL, 13 mmol). The resulting homogeneous mixture was stirred at rt for 15 min and then was poured into ice and allowed to warm to rt overnight. The aqueous phase was extracted with DCM, and the combined organic extracts were washed with H_2O (4 × 200 mL) and brine (100 mL), dried over Na_2SO_4, filtered, and concentrated under high vacuum to afford the title compound that was taken on to the next step. MS (ESI pos ion) m/z: calcd for $C_{25}H_{31}N_3O_5$, 453.2; found, 354.1 (M-Boc + H).

*(D) (S)-tert-Butyl 2-(1-Methyl-2-phenylhydrazinecarbonyl)-pyrrolidine-1-carboxylate (**32b**).* A mixture of (*S*)-*tert*-butyl 2-(2-(benzyloxycarbonyl)-1-methyl-2-phenylhydrazinecarbonyl)-pyrrolidine-1-carboxylate (5.275 g, 11.63 mmol) and Pd/C (5%, 505 mg) in MeOH (100 mL) was evacuated and backfilled with H_2 (balloon). The mixture was stirred at rt for 2 h and filtered through a pad of Celite. The filtrate was concentrated, and the residue was dried under high vacuum to afford the tile compound (3.890 g, 83% over 2 steps). MS (ESI pos ion) *m*/*z*: calcd for $C_{17}H_{25}N_3O_3$, 319.2; found, 220.1 (M-Boc + H).

*(E) (S)-5-(1-(tert-Butoxycarbonyl)pyrrolidin-2-yl)-1-methyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxylic Acid (**34b**).* To a solution of (*S*)-*tert*-butyl 2-(1-methyl-2-phenylhydrazinecarbonyl)-pyrrolidine-1-carboxylate (3.890 g, 12.18 mmol) and DMAP (2.059 g, 16.85 mmol) in DCM (100 mL), cooled under N_2 in an ice water bath, was added ethyl malonoyl chloride (1.85 mL, 14.7 mmol). After 1 h at rt, more DMAP (889 mg, 7.29 mol) and ethyl malonylchloride (0.70 mL, 5.6 mmol) were added. After 30 min, the mixture was treated with H_2O (100 mL). The aqueous phase was extracted with DCM. The combined organic phases were dried over Na_2SO_4, filtered, concentrated, and purified by chromatography on silica gel with MeOH−DCM (0−3.5%). The purified material was dissolved in EtOH (54 mL), and sodium ethoxide (1.94 g, 28.5 mmol) was added. The mixture was stirred at rt under N_2 for 2.5 h and then heated at 90 °C−100 °C for 18 h. The mixture was allowed to cool to rt and then was diluted with H_2O (25 mL) and partially concentrated. The residue was washed repeatedly with DCM. The DCM extracts were combined and washed with NaOH (1 N, 15 mL). The aqueous phases were combined, and the pH was adjusted to ∼4. The aqueous phase was concentrated and extracted with MeOH−DCM (1:3). The combined extracts were concentrated, and the residue was dried under high vacuum to afford the title compound (1.117 g, 21% over 2 steps). MS (ESI pos ion) *m*/*z*: calcd for $C_{20}H_{25}N_3O_5$, 387.2; found, 388.1 (M + H).

*(F) (S)-N-(3-Fluoro-4-(7-methoxyquinolin-4-yloxy)phenyl)-1-methyl-3-oxo-2-phenyl-5-(pyrrolidin-2-yl)-2,3-dihydro-1H-pyrazole-4-carboxamide (**35b**).* The general procedure for amide coupling between 1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carboxylic acid and anilines was followed to prepare the Boc-protected derivative (*S*)-*tert*-butyl 2-(4-((3-fluoro-4-(7-methoxyquinolin-4-yloxy)phenyl)carbamoyl)-1-methyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-5-yl)pyrrolidine-1-carboxylate. MS (ESI pos ion) *m*/*z*: calcd for $C_{36}H_{36}FN_5O_6$, 653.3; found, 654.1 (M + H). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.37−1.51 (m, 9 H), 2.00−2.15 (m, 4 H), 2.68 (br s, 2 H), 3.43 (s, 3 H), 3.48−3.56 (m, 1 H), 4.08 (s, 3 H), 6.76 (d, *J* = 6.6 Hz, 1 H), 7.18−7.25 (m, 1 H), 7.31−7.38 (m, 3 H), 7.45 (dd, *J* = 9.4, 2.4 Hz, 1 H), 7.46−7.63 (m, 3 H), 7.86 (d, *J* = 2.4 Hz, 1 H), 8.04 (dd, *J* = 12.5, 2.4 Hz, 1 H), 8.43 (d, *J* = 9.4 Hz, 1 H), 8.77 (d, *J* = 6.5 Hz, 1 H), 11.15 (s, 1 H).

(*S*)-*tert*-Butyl 2-(4-((3-fluoro-4-(7-methoxyquinolin-4-yloxy)-phenyl)carbamoyl)-1-methyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-5-yl)pyrrolidine-1-carboxylate (0.82 g, 1.3 mmol) was dissolved in DCM and TFA (0.77 mL, 10 mmol) was added. After 23 h, the mixture was treated with NH_3 in MeOH (2 N) and then concentrated. The residue was filtered through a silica gel plug [MeOH−DCM (2−10%); (2 N NH_3 in MeOH)−DCM (5%)]. The fractions with the desired product were collected, concentrated, and purified on HPLC (10−95% MeCN/H_2O with 0.1% TFA) to afford the title compound (72 mg, 11% over 2 steps). MS (ESI pos ion) *m*/*z*: calcd for $C_{31}H_{28}FN_5O_4$, 553.2; found, 554.1 (M + H). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.81−2.11 (m, 3 H), 2.42 (dtd, *J* = 12.0, 7.9,4.0 Hz, 1 H), 3.05−3.12 (m, 1 H), 3.19−3.26 (m, 1 H), 3.66 (s, 3 H), 3.97 (s, 3 H), 5.38 (t, *J* = 8.6 Hz, 1 H), 6.40 (dd, *J* = 5.3, 0.8 Hz, 1 H), 7.12−7.20 (m, 1 H), 7.22 (dd, *J* = 9.1, 2.4 Hz, 1 H), 7.27−7.31 (m, 1 H), 7.35−7.43 (m, 3 H), 7.46−7.53 (m, 1 H), 7.54−7.62 (m, 2 H), 7.91 (dd, *J* = 12.4, 2.4 Hz, 1 H), 8.27 (d, *J* = 9.2 Hz, 1 H), 8.59 (d, *J* = 5.1 Hz, 1 H), 11.22 (s, 1 H).

(*S*)-*N*-(3-Fluoro-4-(7-methoxyquinolin-4-yloxy)phenyl)-1-methyl-3-oxo-2-phenyl-5-(pyrrolidin-2-yl)-2,3-dihydro-1*H*-pyrazole-4-carboxamide (36). The Boc-protected derivative (*S*)-*tert*-butyl 2-(4-((5-(7-methoxyquinolin-4-yloxy)pyridin-2-yl)carbamoyl)-1-methyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-5-yl)pyrrolidine-1-carboxylate was prepared according to the general procedure for amide coupling between 1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carboxylic acid and anilines. MS (ESI pos ion) *m*/*z*: calcd for $C_{35}H_{36}N_6O_6$, 636.3; found, 637.2 (M + H). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36−1.53 (m, 9 H), 2.02−2.16 (m, 4 H), 2.65−2.73 (m, 2 H), 3.43 (s, 3 H), 3.45−3.52 (m, 1 H), 4.08 (s, 3 H), 6.76 (d, *J* = 6.6 Hz, 1 H), 7.36 (d, *J* = 7.2 Hz, 2 H), 7.47 (dd, *J* = 9.3, 2.2 Hz, 1 H), 7.51−7.64 (m, 4 H), 7.85 (d, *J* = 2.4 Hz, 1 H), 8.31 (d, *J* = 2.7 Hz, 1 H), 8.42 (d, *J* = 9.4 Hz, 1 H), 8.49 (d, *J* = 8.4 Hz, 1 H), 8.81 (d, *J* = 6.3 Hz, 1 H), 11.49 (s, 1 H).

The intermediate from previous step was dissolved in DCM (8 mL), and TFA (0.60 mL, 7.8 mmol) was added. The mixture was stirred at rt overnight. More TFA (0.55 mL) was added, and stirring was continued for 3 h. The reaction mixture was treated with a solution of NH_3 in MeOH (2 N) and stirred for 1 h. The mixture was concentrated, and the residue was purified on a silica gel column [(2 N NH_3 in MeOH)−DCM (5−10%)] to afford the title compound (175 mg, 28% over 2 steps). MS (ESI pos ion) *m*/*z*: calcd for $C_{30}H_{28}N_6O_4$, 536.2; found, 537.1 (M + H). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.02−2.28 (m, 3 H), 2.48 (qd, *J* = 7.8, 3.5 Hz, 1 H), 3.30−3.39 (m, 1 H), 3.42−3.51 (m, 1 H), 3.63 (s, 3 H), 3.98 (s, 3 H), 5.28−5.32 (m, 1 H), 6.44 (d, *J* = 5.3 Hz, 1 H), 7.24 (dd, *J* = 9.3, 2.4 Hz, 1 H), 7.37−7.44 (m, 3 H), 7.48−7.60 (m, 4 H), 8.21−8.28 (m, 3 H), 8.62 (d, *J* = 5.3 Hz, 1 H), 11.70 (s, 1 H).

(±)-*N*-(3-Fluoro-4-(7-methoxyquinolin-4-yloxy)phenyl)-1-methyl-3-oxo-2-phenyl-5-(tetrahydrofuran-2-yl)-2,3-dihydro-1*H*-pyrazole-4-carboxamide (42a). *(A) (±)-Methyl 3-Oxo-3-(tetrahydrofuran-2-yl)propanoate (**38a**).* In a 100 mL round-bottomed flask under N_2 was mixed tetrahydro-2-furoic acid (2.0 mL, 20.7 mmol), CDI (4.02 g, 24.8 mmol), and THF (50 mL). The mixture was stirred at rt for 1.5 h before magnesium chloride (1.97 g, 20.7 mmol) and methyl potassium malonate (3.23 g, 20.7 mmol) were added. After stirring at rt overnight, the reaction mixture was carefully neutralized with HCl (2 N) (exothermic, gas evolution). The aqueous phase was extracted with DCM (3×). The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude mixture was purified by chromatography on silica gel with DCM−MeOH (100:0 to 90:10) to afford the title compound (3.29 g, 92.4% yield) as colorless oil. MS (ESI pos ion) calcd for $C_8H_{12}O_4$, 172.1; found, 173.1 (M + H).

*(B) (±)-1-Methyl-2-phenyl-5-(tetrahydrofuran-2-yl)-1H-pyrazol-3(2H)-one (**39a**).* A mixture of methyl 3-oxo-3-(tetrahydrofuran-2-yl)-propanoate (1973 mg, 11460 μmol) and 1-methyl-2-phenylhydrazine (700 mg, 5730 μmol) in PhMe (2 mL) in a 25 mL sealed tube under N_2 were stirred at rt for 2 d. After 48 h, the reaction mixture was directly purified by chromatography on silica gel with MeOH/EtOAc (10:90) to afford the title compound (255 mg, 18.2%) as a white solid. MS (ESI pos ion) *m*/*z* calcd for $C_{14}H_{16}N_2O_2$, 244.1; found, 245.1 (M + H).

*(C) (±)-1-Methyl-3-oxo-2-phenyl-5-(tetrahydrofuran-2-yl)-2,3-dihydro-1H-pyrazole-4-carbaldehyde (**40a**).* In a 10 mL round-bottomed flask under N_2 was added $POCl_3$ (389 μL, 4175 μmol) to DMF (2021 μL, 26096 μmol) at 0 °C. After 45 min, the Vilsmeier reagent was transferred via cannula to solid 1-methyl-2-phenyl-5-(tetrahydrofuran-2-yl)-1,2-dihydropyrazol-3-one (255 mg, 1044 μmol) and the mixture was stirred at rt for 48 h. The reaction mixture was poured into a mixture of ice and NaOH (2 N). The aqueous phase was extracted with DCM (5×), and the organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the aldehyde. MS (ESI pos ion) *m*/*z* calcd for $C_{15}H_{16}N_2O_3$, 272.1; found, 273.1 (M + H).

*(D) (±)-1-Methyl-3-oxo-2-phenyl-5-(tetrahydrofuran-2-yl)-2,3-dihydro-1H-pyrazole-4-carboxylic (**41a**).* In a 100 -mL round-bottomed flask cooled to 0 °C was added 1-methyl-3-oxo-2-phenyl-5-(tetrahydrofuran-2-yl)-2,3-dihydro-1*H*-pyrazole-4-carbaldehyde (284 mg, 1043 μmol), *t*-BuOH (5 mL), and then 2-methyl-2-butene (2210 μL, 20859 μmol). A solution of sodium chlorite (377 mg, 4172 μmol) in H_2O (4 mL) was added dropwise followed by slow addition of KH_2PO_4

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(1135 mg, 8344 μmol) in H_2O (4 mL). The biphasic mixture was warmed to rt and stirred vigorously for 48 h to give, after acidic workup, the title compound. MS (ESI pos ion) m/z calcd for $C_{15}H_{16}N_2O_4$, 288.1; found, 289.1(M + H).

*(E) (±)-N-(3-Fluoro-4-(7-methoxyquinolin-4-yloxy)phenyl)-1-methyl-3-oxo-2-phenyl-5-(tetrahydrofuran-2-yl)-2,3-dihydro-1H-pyrazole-4-carboxamide (**42a**).* The title compound was prepared using 3-fluoro-4-(7-methoxyquinolin-4-yloxy)aniline according to the general procedure for amide coupling between 1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carboxylic acid and anilines to give a white solid (325 mg, 86%). MS (ESI pos ion) m/z calcd for $C_{31}H_{27}FN_4O_5$, 554.2; found, 555.2 (M + H). ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.01−2.16 (m, 3 H), 2.42−2.48 (m, 1 H), 3.50 (s, 3 H), 3.85−3.92 (m, 1 H), 3.95 (s, 3 H), 4.05−4.13 (m, 1 H), 5.94−6.03 (m, 1 H), 6.49 (d, J = 5.3 Hz, 1 H), 7.31 (dd, J = 9.2, 2.5 Hz, 1 H), 7.33−7.38 (m, 1 H), 7.40−7.45 (m, 2 H), 7.49 (d, J = 7.2 Hz, 2 H), 7.53−7.59 (m, 1 H), 7.59−7.66 (m, 2 H), 7.99 (dd, J = 13.0, 2.3 Hz, 1 H), 8.24 (d, J = 9.1 Hz, 1 H), 8.62 (d, J = 5.2 Hz, 1 H), 11.11 (s, 1 H).

(±)-*N*-(3-Fluoro-4-(7-methoxyquinolin-4-yloxy)phenyl)-1-methyl-3-oxo-2-phenyl-5-(tetrahydrofuran-3-yl)-2,3-dihydro-1*H*-pyrazole-4-carboxamide (42b). (A) 1-Methyl-3-oxo-2-phenyl-5-(tetrahydrofuran-2-yl)-2,3-dihydro-1*H*-pyrazole-4-carboxylic acid (**41b**) was prepared according to the procedure for the preparation of **41a**.

(B) The title compound was prepared using using 3-fluoro-4-(7-methoxyquinolin-4-yloxy)aniline according to the general procedure for amide coupling between 1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carboxylic acid and anilines to give a white solid (492 mg, 70%). MS (ESI pos ion) m/z calcd for $C_{31}H_{27}FN_4O_5$, 554.2; found, 555.2 (M + H). ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.26−2.40 (m, 2 H), 3.47 (s, 3 H), 3.77 (q, J = 7.8 Hz, 1 H), 3.94 (s, 3 H), 3.96−4.01 (m, 1 H), 4.13 (t, J = 7.5 Hz, 1 H), 4.19 (td, J = 8.0, 4.0 Hz, 1 H), 4.55−4.66 (m, 1 H), 6.48 (d, J = 5.2 Hz, 1 H), 7.31 (dd, J = 9.2, 2.3 Hz, 1 H), 7.33−7.38 (m, 1 H), 7.40−7.46 (m, 2 H), 7.49 (d, J = 7.8 Hz, 2 H), 7.52−7.57 (m, 1 H), 7.58−7.65 (m, 2 H), 7.99 (dd, J = 13.1, 2.0 Hz, 1 H), 8.23 (d, J = 9.2 Hz, 1 H), 8.61 (d, J = 5.2 Hz, 1 H), 11.34 (s, 1 H).

***N*-(3-Fluoro-4-(7-methoxyquinolin-4-yloxy)phenyl)-1-methyl-3-oxo-2-phenyl-5-(tetrahydro-2*H*-pyran-4-yl)-2,3-dihydro-1*H*-pyrazole-4-carboxamide (42c).** *(A) Tetrahydro-2H-pyran-4-carboxylic Acid (**37c**).* To a 100 mL round-bottomed flask was added methyl tetrahydro-2*H*-pyran-4-carboxylate (10 mL, 69 mmol) and MeOH (25 mL, 618 mmol). The mixture was chilled to −10 °C in a dry ice/acetone bath and allowed to stir for 10 min. KOH (12 g, 208 mmol) was added, and the mixture was allowed to stir at −10 °C for 5 h under inert atmosphere. The ice bath was removed, and the mixture was allowed to slowly warm to rt. After 20 min of stirring, the mixture was concentrated in vacuo. The residue was diluted with H_2O and DCM, and the mixture was cooled in an ice bath. The chilled mixture was treated HCl (concd) until pH ∼ 2−3. The aqueous layer was extracted with DCM (3 × 50 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated in vacuo to give the title compound (7.40 g, 57 mmol, 82%) as white solid. MS (ESI pos ion) m/z calcd for $C_6H_{10}O_3$, 130.1; found, 131.2 (M + H). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.73−1.93 (m, 4 H), 2.53−2.64 (m, 1 H), 3.40−3.52 (m, 2 H), 3.99 (dt, J = 11.7, 3.6 Hz, 2 H), 5.30 (s, 1 H).

*(B) Methyl 3-Oxo-3-(tetrahydro-2H-pyran-4-yl) Propanoate (**38c**).* The title compound was prepared from tetrahydro-2*H*-pyran-4-carboxylic acid (3.905 g, 30 mmol) according to the procedure for the preparation of **38a** to give the product as tan oil (2.80 g). MS (ESI pos ion) m/z calcd for $C_9H_{14}O_4$, 186.2; found, 187.1(M + H). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.62−1.85 (m, 5 H), 2.66−2.77 (m, 1 H), 3.43 (td, J = 11.5, 2.6 Hz, 2 H), 3.53 (s, 2 H), 3.74 (s, 3 H), 4.00 (ddd, J = 11.5, 3.9, 2.8 Hz, 2 H).

*(C) 1-Methyl-2-phenyl-5-(tetrahydro-2H-pyran-4-yl)-1,2-dihydropyrazol-3-one (**39c**).* To a 250 mL round-bottomed flask was added ethyl 3-oxo-3-(tetrahydro-2*H*-pyran-4-yl)propanoate (1.8 g, 9.1 mmol), HOAc (0.52 mL, 9.1 mmol), H_2O (0.70 mL, 121 mmol), and pyridine (0.73 mL, 9.1 mmol). After 5 min, 1-methyl-2-phenylhydrazine (0.740 g, 6.1 mmol) was added. The mixture was placed in a preheated (105 °C) oil bath and stirred for 2 h. The reaction mixture was allowed to cool to rt and then was diluted with H_2O, saturated $NaHCO_3$, and DCM. The aqueous layer was extracted with DCM−MeOH (10:2, 3 × 24 mL), and the combined extracts were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude mixture was purified by by chromatography on a prepacked amino-propyl silica-gel column (40 g) with MeOH−DCM (1−5%) as eluent to provide the title compound (0.430 g, 1.7 mmol, 27%) as tan solid. MS (ESI pos ion) m/z calcd for $C_{15}H_{18}N_2O_2$, 258.3; found, 259.1 (M + H).

*(D) 1-Methyl-3-oxo-2-phenyl-5-(tetrahydro-2H-pyran-4-yl)-2,3-dihydro-1H-pyrazole-4-carbaldehyde (**40c**).* The title compound was prepared according to the procedure for the preparation of **40a** to give, starting with 1-methyl-2-phenyl-5-(tetrahydro-2*H*-pyran-4-yl)-1,2-dihydropyrazol-3-one (0.421 g, 1.6 mmol), the final compound as tan oil (0.380 g, 81%). MS (ESI pos ion) m/z calcd for $C_{16}H_{18}N_2O_3$, 286.3; found, 287.1 (M + H).

*(E) 1-Methyl-3-oxo-2-phenyl-5-(tetrahydro-2H-pyran-4-yl)-2,3-dihydro-1H-pyrazole-4-carboxylic Acid (**41c**).* Starting with 1-methyl-3-oxo-2-phenyl-5-(tetrahydro-2*H*-pyran-4-yl)-2,3-dihydro-1*H*-pyrazole-4-carbaldehyde (0.380 g, 1.3 mmol), the title compound was prepared using the procedure similar to that for the preparation of **41a** to give a light-yellow oil (0.400 g, 98%). To prevent decomposition, this material was carried into the next step of the synthesis without further purification. MS (ESI pos ion) m/z calcd for $C_{16}H_{18}N_2O_4$, 302.3; found, 303.1(M + H).

*(F) N-(3-Fluoro-4-(7-methoxyquinolin-4-yloxy)phenyl)-1-methyl-3-oxo-2-phenyl-5-(tetrahydro-2H-pyran-4-yl)-2,3-dihydro-1H-pyrazole-4-carboxamide (**42c**).* Starting with 3-fluoro-4-(7-methoxyquinolin-4-yloxy)aniline and 1-methyl-3-oxo-2-phenyl-5-(tetrahydro-2*H*-pyran-4-yl)-2,3-dihydro-1*H*-pyrazole-4-carboxylic acid (0.200 g, 0.66 mmol), the title compound was prepared using the general procedure for amide coupling between 1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carboxylic acid and anilines to give a tan solid (0.072 g, 19%). MS (ESI pos ion) m/z calcd for $C_{32}H_{29}FN_4O_5$, 568.5; found, 569.2 (M + H). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.83 (d, J = 11.0 Hz, 2 H), 2.33 (qd, J = 12.6, 4.4 Hz, 2 H), 3.49 (s, 3 H), 3.63 (t, J = 11.0 Hz, 2 H), 3.96 (s, 3 H), 4.15 (dd, J = 11.4, 3.8 Hz, 2 H), 4.47−4.60 (m, 1 H), 5.29 (s, 1 H), 6.40 (dd, J = 5.2, 0.8 Hz, 1 H), 7.14−7.42 (m, 4 H), 7.46−7.60 (m, 3 H), 7.92 (dd, J = 12.5, 2.3 Hz, 1 H), 8.27 (d, J = 9.2 Hz, 1 H), 8.59 (d, J = 5.3 Hz, 1 H), 11.25 (s, 1 H).

***N*-(5-(7-Methoxyquinolin-4-yloxy)pyridin-2-yl)-1-methyl-3-oxo-2-phenyl-5-(tetrahydro-2*H*-pyran-4-yl)-2,3-dihydro-1*H*-pyrazole-4-carboxamide (43c).** Starting with 5-(7-methoxyquinolin-4-yloxy)pyridin-2-amine and 1-methyl-3-oxo-2-phenyl-5-(tetrahydro-2*H*-pyran-4-yl)-2,3-dihydro-1*H*-pyrazole-4-carboxylic acid (0.200 g, 0.66 mmol), the title compound was prepared using the general procedure for amide coupling between 1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carboxylic acid and anilines to give a colorless solid (0.050 g, 14%). MS (ESI pos ion) m/z calcd for $C_{31}H_{29}N_5O_5$, 551.5; found, 552.2 (M + H). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.76 (d, J = 10.7 Hz, 2 H), 2.19−2.35 (m, 2 H), 3.42 (s, 3 H), 3.50−3.60 (m, 2 H), 3.89 (s, 3 H), 4.07 (dd, J = 11.6, 3.8 Hz, 2 H), 4.37−4.49 (m, 1 H), 5.22 (s, 1 H), 6.34 (d, J = 5.3 Hz, 1 H), 7.15 (dd, J = 9.2, 2.5 Hz, 1 H), 7.28−7.50 (m, 5 H), 8.15 (d, J = 6.1 Hz, 1 H), 8.17 (s, 1 H), 8.29 (d, J = 9.1 Hz, 1 H), 8.52 (d, J = 5.3 Hz, 1 H), 11.55 (s, 1 H).

***N*-(5-(7-Methoxyquinolin-4-yloxy)pyridin-2-yl)-1-methyl-3-oxo-2-phenyl-5-(pyridin-4-yl)-2,3-dihydro-1*H*-pyrazole-4-carboxamide (43d).** *(A) 1-Methyl-2-phenyl-5-(pyridin-4-yl)-1,2-dihydropyrazol-3-one (**39d**).* The title compound was prepared from ethyl isonicotinoylacetate (3.01 g, 16 mmol) according to the procedure for the preparation of **39c** to give the product (3.31 g). MS (ESI pos ion) calcd for $C_{15}H_{13}N_3O$, 251.1; found, 252.1 (M + H). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.04 (s, 3 H), 5.98 (s, 1 H), 7.40−7.60 (m, 7 H), 8.80 (d, J = 6.1 Hz, 2 H).

*(B) 1-Methyl-3-oxo-2-phenyl-5-(pyridin-4-yl)-2,3-dihydro-1H-pyrazole-4-carbaldehyde (**40d**).* Prepared according to the procedure for the preparation of **40a**, from 1-methyl-2-phenyl-5-(pyridin-4-yl)-1,2-dihydropyrazol-3-one (3.31 g, 13 mmol) to yield the title compound that was taken to the next step without further purification. MS (ESI pos ion) m/z: calcd for $C_{16}H_{13}N_3O_2$, 279.1; found, 280.1 (M + H).

*(C) 1-Methyl-3-oxo-2-phenyl-5-(pyridin-4-yl)-2,3-dihydro-1H-pyrazole-4-carboxylic Acid (**41d**).* The title compound was prepared using the procedure similar to that for the preparation of **41a** (1.98 g, 52% over 2 steps). MS (ESI pos ion) *m/z*: calcd for $C_{16}H_{13}N_3O_3$, 295.1; found, 296.1 (M + H). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.18 (s, 3 H), 7.30−7.49 (m, 7 H), 8.69 (d, *J* = 6.0 Hz, 2 H).

*(D) N-(5-(7-Methoxyquinolin-4-yloxy)pyridin-2-yl)-1-methyl-3-oxo-2-phenyl-5-(pyridin-4-yl)-2,3-dihydro-1H-pyrazole-4-carboxamide (**43d**).* Starting with 5-(7-methoxyquinolin-4-yloxy)pyridin-2-amine and 1-methyl-3-oxo-2-phenyl-5-(pyridin-4-yl)-2,3-dihydro-1*H*-pyrazole-4-carboxylic acid, the title compound was prepared using the general procedure for amide coupling between 1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carboxylic acid and anilines (285 mg, 45%). MS (ESI pos ion) *m/z*: calcd for $C_{31}H_{24}N_6O_4$, 544.2; found, 545.1 (M + H). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.20 (s, 3 H), 3.98 (s, 3 H), 6.41 (d, *J* = 5.3 Hz, 1 H), 7.23 (d, *J* = 9.2 Hz, 1 H), 7.39−7.67 (m, 9 H), 8.21−8.27 (m, 3 H), 8.60 (d, *J* = 5.1 Hz, 1 H), 8.89 (d, *J* = 5.3 Hz, 2 H), 11.33 (s, 1 H).

N-(5-(7-Methoxyquinolin-4-yloxy)pyridin-2-yl)-1-methyl-3-oxo-2-phenyl-5-(pyridin-2-yl)-2,3-dihydro-1*H*-pyrazole-4-carboxamide (43e). *(A) 1-Methyl-2-phenyl-5-(pyridin-2-yl)-1H-pyrazol-3(2H)-one (**39e**).* The title compound was prepared from ethyl picolinoylacetate (0.924 g, 4.8 mmol) according to the procedure for the preparation of **39c** to give the product as a tan solid (0.455 g, ∼70% pure at 254 nm). MS (ESI pos ion) *m/z* calcd for $C_{15}H_{13}N_3O$, 251.1; found, 252.1 (M + H). ^{1}H NMR (300 MHz, CD_3OD) δ 3.37 (s, 3 H), 7.36−7.45 (m, 2 H), 7.50−7.58 (m, 2 H), 7.87 (dd, *J* = 8.6, 1.0 Hz, 2 H), 7.93 (td, *J* = 7.7, 1.8 Hz, 2 H), 8.10 (d, *J* = 8.0 Hz, 1 H), 8.61 (d, *J* = 3.4 Hz, 1 H).

*(B) 1-Methyl-3-oxo-2-phenyl-5-(pyridin-2-yl)-2,3-dihydro-1H-pyrazole-4-carbaldehyde (**40e**).* Prepared according to the procedure for the preparation of **40a**, from 1-methyl-2-phenyl-5-(pyridin-2-yl)-1*H*-pyrazol-3(2*H*)-one (0.40 g, 1.6 mmol), to yield the title compound as a dark-brown oil (0.429 g). MS (ESI pos ion) *m/z* calcd for $C_{16}H_{13}N_3O_2$, 279.2; found, 280.1 (M + H). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.88 (s, 3 H), 2.95 (s, 3 H), 3.39−3.45 (m, 3 H), 7.42−7.60 (m, 4 H), 7.83−7.96 (m, 2 H), 8.02 (s, 1 H), 8.78 (d, *J* = 4.7 Hz, 1 H), 9.91 (s, 1 H).

*(C) 1-Methyl-3-oxo-2-phenyl-5-(pyridin-2-yl)-2,3-dihydro-1H-pyrazole-4-carboxylic Acid (**41e**).* Starting with 1-methyl-3-oxo-2-phenyl-5-(pyridin-2-yl)-2,3-dihydro-1*H*-pyrazole-4-carbaldehyde (0.429 g, 1.5 mmol), the title compound was prepared using the procedure similar to that for the preparation of **41a** to yield a tan oil (0.390 g). MS (ESI pos ion) *m/z* calcd for $C_{16}H_{13}N_3O_3$, 295.2; found, 296.1 (M + H).

*(D) N-(5-(7-Methoxyquinolin-4-yloxy)pyridin-2-yl)-1-methyl-3-oxo-2-phenyl-5-(pyridin-2-yl)-2,3-dihydro-1H-pyrazole-4-carboxamide (**43e**).* Starting with 5-(7-methoxyquinolin-4-yloxy)pyridin-2-amine and 1-methyl-3-oxo-2-phenyl-5-(pyridin-2-yl)-2,3-dihydro-1*H*-pyrazole-4-carboxylic acid (0.40 g, 1.4 mmol), the title compound was prepared using the general procedure for amide coupling between 1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carboxylic acid and anilines to give a tan solid (0.15 g, 20%). MS (ESI pos ion) *m/z* calcd for $C_{31}H_{24}N_6O_4$, 544.5; found, 545.2 (M + H). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.12 (s, 1 H), 3.24 (s, 3 H), 3.88 (s, 3 H), 6.32 (d, *J* = 5.3 Hz, 1 H), 7.13 (dd, *J* = 9.1, 2.4 Hz, 1 H), 7.20 (s, 1 H), 7.31−7.53 (m, 8 H), 7.80−7.90 (m, 2 H), 8.10−8.23 (m, 3 H), 8.50 (d, *J* = 5.3 Hz, 1 H), 8.72 (d, *J* = 4.8 Hz, 1 H), 11.39 (s, 1 H).

N-(5-(7-Methoxyquinolin-4-yloxy)pyridin-2-yl)-1-methyl-3-oxo-2-phenyl-5-(pyridin-3-yl)-2,3-dihydro-1*H*-pyrazole-4-carboxamide (43f). *(A) 1-Methyl-2-phenyl-5-(pyridin-3-yl)-1,2-dihydropyrazol-3-one (**39f**).* Starting with methyl nicotinoylacetate (1.3 g, 7.3 mmol), the title compound was prepared using a similar procedure for the preparation of **39a** to yield a tan solid (0.72 g, 39%). MS (ESI pos ion) *m/z* calcd for $C_{15}H_{13}N_3O$, 251.1; found, 252.1 (M + H). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.02 (s, 3 H), 5.90 (s, 1 H), 7.26 (s, 2 H), 7.28−7.37 (m, 1 H), 7.45−7.58 (m, 3 H), 7.88 (dt, *J* = 7.9, 2.0 Hz, 1 H), 8.76 (dd, *J* = 4.8, 1.6 Hz, 1 H), 8.84 (d, *J* = 1.9 Hz, 1 H).

*(B) 1-Methyl-3-oxo-2-phenyl-5-(pyridin-3-yl)-2,3-dihydro-1H-pyrazole-4-carbaldehyde (**40f**).* The title compound was prepared using a similar procedure for the preparation of **40a** to yield a brown oil. MS (ESI pos ion) *m/z* calcd for $C_{16}H_{13}N_3O_2$, 279.2; found, 280.1 (M + H).

*(C) 1-Methyl-3-oxo-2-phenyl-5-(pyridin-3-yl)-2,3-dihydro-1H-pyrazole-4-carboxylic Acid (**41f**).* The title compound was prepared using a similar procedure for the preparation of **41a** to yield a tan oil. MS (ESI pos ion) calcd for $C_{16}H_{13}N_3O_3$, 295.2; found, 296.1 (M + H).

*(D) N-(5-(7-Methoxyquinolin-4-yloxy)pyridin-2-yl)-1-methyl-3-oxo-2-phenyl-5-(pyridin-3-yl)-2,3-dihydro-1H-pyrazole-4-carboxamide (**43f**).* Starting with 5-(7-methoxyquinolin-4-yloxy)pyridin-2-amine and 1-methyl-3-oxo-2-phenyl-5-(pyridin-3-yl)-2,3-dihydro-1*H*-pyrazole-4-carboxylic acid (0.230 g, 0.78 mmol), the title compound was prepared using the general procedure for amide coupling between 1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carboxylic acid and anilines to give a light-yellow solid (0.080 g, 19%). MS (ESI pos ion) *m/z* calcd for $C_{31}H_{24}N_6O_4$, 544.5; found, 545.2 (M + H). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.42 (s, 3 H), 3.89 (s, 3 H) 4.37−4.49 (m, 1 H), 5.22 (s, 1 H), 6.34 (d, *J* = 5.3 Hz, 1 H), 7.15 (dd, *J* = 9.2, 2.5 Hz, 1 H), 7.20 (s, 2 H), 7.28−7.50 (m, 7 H), 8.15 (d, *J* = 6.1 Hz, 1 H), 8.17 (s, 1 H), 8.29 (d, *J* = 9.1 Hz, 1 H), 8.52 (d, *J* = 5.3 Hz, 1 H), 11.55 (s, 1 H).

N-(5-(7-Methoxyquinolin-4-yloxy)pyridin-2-yl)-1-methyl-3-oxo-2-phenyl-5-(pyrazin-2-yl)-2,3-dihydro-1*H*-pyrazole-4-carboxamide (43g). *(A) Methyl 3-oxo-3-(pyrazin-2-yl)propanoate (**38g**).* The title compound was prepared from 2-pyrazinecarboxylic acid (1.00 g, 8.06 mmol) according to the procedure for the preparation of **38a** to give the product as a pale-yellow crystalline solid (1.28 g, 88.2%). MS (ESI pos ion) *m/z* calcd for $C_8H_8N_2O_3$, 180.2; found, 181.1 (M + H). ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.63 (s, 3 H), 4.21 (s, 2 H), 8.79−8.84 (m, 1 H), 8.94 (d, *J* = 2.5 Hz, 1 H), 9.16 (d, *J* = 1.4 Hz, 1 H).

*(B) 1-Methyl-2-phenyl-5-(pyrazin-2-yl)-1,2-dihydropyrazol-3-one (**39g**).* The title compound was prepared from methyl 3-oxo-3-(pyrazin-2-yl)propanoate (0.865 g, 4.8 mmol) according to the procedure for the preparation of **39c** to give the product as a yellowish−brown solid (0.378 g, 31%). MS (ESI pos ion) *m/z* calcd for $C_{14}H_{12}N_4O$, 252.3; found, 253.1 (M + H). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.32 (s, 3 H), 6.19 (s, 1 H), 7.33−7.40 (m, 1 H), 7.49−7.59 (m, 4 H), 8.67−8.71 (m, 1 H), 8.72−8.75 (m, 1 H), 8.96−9.00 (m, 1 H).

*(C) 1-Methyl-3-oxo-2-phenyl-5-(pyrazin-2-yl)-2,3-dihydro-1H-pyrazole-4-carbaldehyde (**40g**).* Prepared according to the procedure for the preparation of **40a**, from 1-methyl-2-phenyl-5-(pyrazin-2-yl)-1,2-dihydropyrazol-3-one (0.263 g, 1.0 mmol), to yield the title compound as an orange solid (0.289 g, 99%). MS (ESI pos ion) *m/z* calcd for $C_{15}H_{12}N_4O_2$, 280.3; found, 281.1 (M + H). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.43 (s, 3 H), 7.42−7.63 (m, 5 H), 8.76 (s, 2 H), 9.17 (s, 1 H), 9.96 (s, 1 H).

*(D) 1-Methyl-3-oxo-2-phenyl-5-(pyrazin-2-yl)-2,3-dihydro-1H-pyrazole-4-carboxylic Acid (**41g**).* Starting with 1-methyl-3-oxo-2-phenyl-5-(pyrazin-2-yl)-2,3-dihydro-1*H*-pyrazole-4-carbaldehyde (0.390 g, 1.4 mmol), the title compound was prepared using the procedure similar to that for the preparation of **41a** to yield an off-white solid (0.300 g, 73%). MS (ESI pos ion) *m/z* calcd for $C_{15}H_{12}N_4O_3$, 296.3; found, 297.1 (M + H). ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.27 (s, 3 H), 7.52−7.59 (m, 3 H), 7.59−7.67 (m, 2 H), 8.82−8.86 (m, 1 H), 8.86−8.89 (m, 1 H), 9.03−9.07 (m, 1 H).

*(E) N-(5-(7-Methoxyquinolin-4-yloxy)pyridin-2-yl)-1-methyl-3-oxo-2-phenyl-5-(pyrazin-2-yl)-2,3-dihydro-1H-pyrazole-4-carboxamide (**43g**).* A mixture of 1-methyl-3-oxo-2-phenyl-5-(pyrazin-2-yl)-2,3-dihydro-1*H*-pyrazole-4-carboxylic acid (0.100 g, 0.34 mmol), 5-(7-methoxyquinolin-4-yloxy)pyridin-2-amine (0.090 g, 0.34 mmol), EDCI-HCl (0.097 g, 0.51 mmol), and HOAt (0.046 g, 0.34 mmol) was suspended in DMF (1.7 mL). ^{i}Pr$_2$NEt (0.21 mL, 1.2 mmol) was added, and the reaction mixture was stirred at rt for 2 d and then at 50 °C overnight. The reaction mixture was diluted with EtOAc and H_2O. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under vacuum. The crude material was purified by chromatography on silica gel eluting with MeOH−DCM (2−5%) to yield the title compound (0.046 g, 25%) as a light-orange solid. MS

(ESI pos ion) m/z calcd for $C_{30}H_{23}N_7O_4$, 545.5; found, 546.2 (M + H). ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.30 (s, 3 H), 3.94 (s, 3 H), 6.52 (d, J = 5.3 Hz, 1 H), 7.30 (dd, J = 9.1, 2.4 Hz, 1 H), 7.41 (d, J = 2.4 Hz, 1 H), 7.57−7.70 (m, 5 H), 7.75 (dd, J = 9.0, 2.9 Hz, 1 H), 8.18−8.25 (m, 2 H), 8.35 (d, J = 2.6 Hz, 1 H), 8.61 (d, J = 5.2 Hz, 1 H), 8.85 (d, J = 2.5 Hz, 1 H), 8.87−8.91 (m, 1 H), 9.10−9.13 (m, 1 H), 11.29 (s, 1 H).

***N*-(5-(7-Methoxyquinolin-4-yloxy)pyridin-2-yl)-1-methyl-5-(5-methylisoxazol-3-yl)-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carboxamide (43h).** *(A) Methyl 3-(5-Methylisoxazol-3-yl)-3-oxopropanoate (**38h**).* The title compound was prepared using a similar procedure for the preparation of **38a** to yield a white solid (3.25 g, 90%). MS (ESI pos ion) m/z calcd for $C_8H_9NO_4$,: 183.2; found, 184.1 (M + H). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.49 (s, 3 H), 3.82 (s, 3 H), 5.90 (s, 1 H), 6.28−6.32 (m, 1 H), 12.10 (s, 1 H).

*(B) 1-Methyl-5-(5-methylisoxazol-3-yl)-2-phenyl-1,2-dihydropyrazol-3-one (**39h**).* The title compound was prepared using a similar procedure for the preparation of **39a** to yield a light-yellow crystalline solid (1.71 g, 39%). MS (ESI pos ion) m/z calcd for $C_{14}H_{13}N_3O_2$, 255.3; found, 256.0 (M + H). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.54 (s, 3 H), 3.38 (s, 3 H), 5.96 (s, 1 H), 6.29 (s, 1 H), 7.32−7.40 (m, 1 H), 7.49−7.53 (m, 4 H).

*(C) 1-Methyl-5-(5-Methylisoxazol-3-yl)-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carbaldehyde(**40h**).* The title compound was prepared using a similar procedure for the preparation of **40a** to yield a pale-orange oil (1.33 g, 74%). MS (ESI pos ion) m/z calcd for $C_{15}H_{13}N_3O_3$, 283.3; found, 284.0 (M + H). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.58 (s, 3 H), 3.58 (s, 3 H), 6.79 (s, 1 H), 7.39−7.47 (m, 2 H), 7.47−7.54 (m, 1 H), 7.54−7.61 (m, 2 H), 9.96 (s, 1 H).

*(D) 1-Methyl-5-(5-methylisoxazol-3-yl)-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxylic Acid (**41h**).* The title compound was prepared using a similar procedure for the preparation of **41a** to yield a pale-yellow solid (1.04 g, 74.0%). MS (ESI pos ion) m/z calcd for $C_{15}H_{13}N_3O_4$, 299.3; found, 300.0 (M + H). ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.55 (s, 3 H), 3.34 (s, 3 H), 6.75 (s, 1 H), 7.51−7.69 (m, 5 H), 12.43 (bs, 1 H).

*(E) N-(5-(7-Methoxyquinolin-4-yloxy)pyridin-2-yl)-1-methyl-5-(5-methylisoxazol-3-yl)-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxamide (**43h**).* The title compound was prepared using a similar procedure for the preparation of 43 g to yield a brown−yellow solid (0.065 g, 24%). MS (ESI pos ion) m/z calcd for $C_{30}H_{24}N_6O_5$, 548.5; found, 549.2 (M + H). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.59 (s, 3 H), 3.49 (s, 3 H), 3.98 (s, 3 H), 6.44 (d, J = 5.2 Hz, 1 H), 6.74 (s, 1 H), 7.22−7.26 (m, 1 H), 7.43−7.55 (m, 5 H), 7.56−7.63 (m, 2 H), 8.21−8.28 (m, 2 H), 8.32 (d, J = 9.0 Hz, 1 H), 8.61 (d, J = 5.3 Hz, 1 H), 11.46 (s, 1 H).

***N*-(5-(7-Methoxyquinolin-4-yloxy)pyridin-2-yl)-1-methyl-5-(2-methylthiazol-4-yl)-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carboxamide (43i).** *(A) Methyl 3-(2-Methylthiazol-4-yl)-3-oxopropanoate (**38i**).* The title compound was prepared using a similar procedure for the preparation of **38a** to yield an off-white crystalline solid (3.13 g, 90%). MS (ESI pos ion) m/z calcd for $C_8H_9NO_3S$, 199.2; found, 200.1 (M + H). ^{1}H NMR indicated that the sample was an approximate 3:1 mixture of the diketo form and the enol form of the product. The diketo-form: ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 2.75 (s, 3 H), 3.76 (s, 3 H), 4.10 (s, 2 H), 8.09 (s, 1 H). The enol-form: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.74 (s, 3 H), 3.81 (s, 3 H), 6.06 (s, 1 H), 7.73 (s, 1 H), 12.09 (s, 1 H).

*(B) 1-Methyl-5-(2-methylthiazol-4-yl)-2-phenyl-1,2-dihydropyrazol-3-one (**39i**).* The title compound was prepared using a similar procedure for the preparation of **39a** to yield a pale-orange foam (2.38 g, 62%). MS (ESI pos ion) m/z calcd for $C_{14}H_{13}N_3OS$, 271.3; found, 272.0 (M + H). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.82 (s, 3 H), 3.29 (s, 3 H), 5.94 (s, 1 H), 7.29−7.36 (m, 1 H), 7.46−7.52 (m, 2 H), 7.52−7.58 (m, 3 H).

*(C) 1-Methyl-5-(2-methylthiazol-4-yl)-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carbaldehyde (**40i**).* The title compound was prepared using a similar procedure for the preparation of **40a** to yield a light-yellow solid (2.44 g, 97%). MS (ESI pos ion) m/z calcd for $C_{15}H_{13}N_3O_2S$, 299.3; found, 300.0 (M + H). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.81 (s, 3 H), 3.62 (s, 3 H), 7.42−7.49 (m, 3 H), 7.52−7.59 (m, 2 H), 8.76 (s, 1 H), 9.95 (s, 1 H).

*(D) 1-Methyl-5-(2-methylthiazol-4-yl)-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxylic Acid (**41i**).* The title compound was prepared using a similar procedure for the preparation of **41a** to yield a pale-yellow solid (2.31 g, 90%). MS (ESI pos ion) m/z calcd for $C_{15}H_{13}N_3O_3S$, 315.3; found, 316.0 (M + H). ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.76 (s, 3 H), 3.43 (s, 3 H), 7.52−7.60 (m, 3 H), 7.60−7.66 (m, 2 H), 8.45 (s, 1 H), 12.79 (s, 1 H).

*(E) N-(5-(7-Methoxyquinolin-4-yloxy)pyridin-2-yl)-1-methyl-5-(2-methylthiazol-4-yl)-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxamide (**43i**).* The title compound was prepared using a similar procedure for the preparation of **43g** to yield a white solid (0.027 g, 10%). MS (ESI pos ion) m/z calcd for $C_{30}H_{24}N_6O_4S$, 564.6; found, 565.1 (M + H). ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.77 (s, 3 H), 3.34 (s, 3 H), 3.94 (s, 3 H), 6.53 (d, J = 5.2 Hz, 1 H), 7.30 (dd, J = 9.1, 2.4 Hz, 1 H), 7.42 (d, J = 2.4 Hz, 1 H), 7.53−7.61 (m, 3 H), 7.61−7.68 (m, 2 H), 7.77 (dd, J = 9.2, 2.8 Hz, 1 H), 8.22 (d, J = 9.1 Hz, 1 H), 8.29 (d, J = 9.1 Hz, 1 H), 8.32−8.37 (m, 2 H), 8.62 (d, J = 5.2 Hz, 1 H), 11.51 (s, 1 H).

1-Ethyl-*N*-(3-fluoro-4-(7-methoxyquinolin-4-yloxy)phenyl)-5-methyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carboxamide (48a). *(A) 1-Ethyl-5-methyl-2-phenyl-1H-pyrazol-3(2H)-one (**45a**).* A mixture of ethyl 4-methylbenzenesulfonate (1.26 g, 6 mmol) and 1-ethyl-5-methyl-2-phenyl-1*H*-pyrazol-3(2*H*)-one (1.00 g, 5.74 mmol) was heated at 160 °C for 16 h. The mixture was allowed to cool to rt and partitioned between DCM (80 mL) and NaOH (1 N, 10 mL). After 30 min, the mixture was diluted with H_2O (40 mL). The organic phase was separated, washed with brine (50 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by chromatography on silica gel with MeOH/EtOAc (0 to 10%) to afford the desired product as light-yellow oil (1 g, 86%). MS (ESI pos ion) m/z calcd for $C_{12}H_{14}N_2O$, 202.1; found, 203.1(M + H). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86 (t, J = 6.9 Hz, 3 H), 2.23 (s, 3 H), 3.56 (q, J = 7.0 Hz, 2 H), 5.42 (s, 1 H), 7.22−7.33 (m, 1 H), 7.35−7.42 (m, 14 H), 7.42−7.52 (m, 14 H).

*(B) 1-Ethyl-5-methyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carbaldehyde (**46a**).* To a solution of DMF (0.76 mL, 9.9 mmol) in a 50 mL round-bottomed flask cooled to 0 °C was added $POCl_3$ (0.69 mL, 7.4 mmol). After 30 min, the mixture was transferred to a 50 mL round-bottomed flask containing 1-ethyl-5-methyl-2-phenyl-1,2-dihydropyrazol-3-one (1.00 g, 4.9 mmol). The mixture was heated at 84 °C for 3 h and allowed to cool to rt. The mixture was poured into a mixture of ice, and the pH of the mixture was adjusted to ∼11 with NaOH (2 N). The mixture was then extracted with $CHCl_3$ (100 mL) twice. The combined organic phases were washed with brine (80 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by chromatography on silica gel with EtOAc/hexanes (50 to 100%) to the desired product as a white solid (0.95 g, 83%). MS (ESI pos ion) m/z calcd for $C_{13}H_{14}N_2O_2$, 230.1; found, 231.1 (M + H). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.09 (t, J = 7.1 Hz, 3 H), 2.66 (s, 3 H), 3.79 (q, J = 7.1 Hz, 2 H), 7.32 (dd, J = 8.2, 1.0 Hz, 2 H), 7.39−7.47 (m, 1 H), 7.48−7.57 (m, 2 H), 7.57−7.58 (m, 1 H), 9.89 (s, 1 H).

*(C) 1-Ethyl-5-methyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxylic Acid (**47a**).* To a mixture of 1-ethyl-5-methyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carbaldehyde (5.0 g, 22 mmol) in ^{t}BuOH (82 mL, 869 mmol) was added 2-methyl-2-butene (23 mL, 217 mmol) at 0 °C, followed by sodium chlorite (5.9 g, 65 mmol) in H_2O (25 mL). A solution of KH_2PO_4 (15 g, 109 mmol) in H_2O (25 mL) was added, and the mixture was allowed to warm to rt. After 18 h, the reaction mixture was extracted with EtOAc (2 × 100 mL). The organic phase was washed with brine (80 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was washed with small amount of EtOAc/hexanes (20%) to give the desired product as light-yellow solid (4.8 g, 90%). MS (ESI pos ion) m/z calcd for $C_{13}H_{14}N_2O_3$, 246.0; found, 247.0 (M + H). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.08 (t, J = 7.2 Hz, 3 H), 2.71 (s, 3 H), 3.86 (q, J = 7.0 Hz, 2 H), 7.30−7.41 (m, 2 H), 7.41−7.66 (m, 3 H).

*(D) 1-Ethyl-N-(3-fluoro-4-(7-methoxyquinolin-4-yloxy)phenyl)-5-methyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxamide (**48a**).* The general procedure for amide coupling between 1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carboxylic acid and anilines was followed to prepare the title compound as white solid (0.50 g, 80%). MS (ESI pos ion) *m*/*z* calcd for $C_{29}H_{25}FN_4O_4$, 512.2; found, 513.1 (M + H). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.99−1.16 (m, 3 H), 2.81 (s, 3 H), 3.84 (q, *J* = 7.0 Hz, 2 H), 3.97 (s, 3 H), 6.42 (d, *J* = 5.3 Hz, 1 H), 7.13−7.63 (m, 9 H), 7.84−8.09 (m, 1 H), 8.27 (d, *J* = 9.0 Hz, 1 H), 8.59 (d, *J* = 5.3 Hz, 1 H), 10.91 (s, 1 H).

1-Ethyl-*N*-(5-(7-methoxyquinolin-4-yloxy)pyridin-2-yl)-5-methyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carboxamide (49a). The title compound was prepared similarly as **48a** (isolated after HPLC purification as the TFA salt, 0.30 g, 50%). MS (ESI pos ion) *m*/*z* calcd for $C_{28}H_{25}N_5O_4$, 495.2; found, 496.1 (M + H). ^{1}H NMR (300 MHz, CD_3OD) δ 1.08 (t, *J* = 7.1 Hz, 3 H), 2.80 (s, 3 H), 3.94 (q, *J* = 6.9 Hz, 2 H), 4.07 (s, 3 H), 6.98 (d, *J* = 6.8 Hz, 1 H), 7.40−7.65 (m, 7 H), 7.81 (dd, *J* = 9.0, 2.8 Hz, 1 H), 8.30 (d, *J* = 2.6 Hz, 1 H), 8.44 (d, *J* = 9.2 Hz, 1 H), 8.52 (d, *J* = 9.4 Hz, 1 H), 8.79 (d, *J* = 6.8 Hz, 1 H).

N-(3-Fluoro-4-(7-methoxyquinolin-4-yloxy)phenyl)-5-methyl-3-oxo-2-phenyl-1-propyl-2,3-dihydro-1H-pyrazole-4-carboxamide (48b). *(A) 5-Methyl-2-phenyl-1-propyl-1H-pyrazol-3(2H)-one (**45b**).* A mixture of 1-phenyl-3-methyl-5-pyrazolone (10.0 g, 57 mmol) and 1-iodopropane (8.9 mL, 92 mmol) was heated in an oil bath at 110 °C overnight under inert atmosphere. The reaction mixture was allowed to cool to rt and was diluted with saturated $NaHCO_3$ and DCM. After 30 min, the mixture was treated with NaOH (5 N, 50 mL) while stirring. The aqueous layer was extracted with DCM (3 × 100 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude material was recrystallized from warm EtOAc/hexanes to give a green crystalline solid as the desired product (3.2 g, 26%). MS (ESI pos ion)*m*/*z* calcd for $C_{13}H_{16}N_2O$, 216.1; found, 217.1(M + H). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.75 (t, *J* = 7.4 Hz, 3 H), 1.35 (m, 2 H), 2.25 (s, 3 H), 3.39−3.57 (m, 2 H), 5.38 (s, 1 H), 7.25−7.33 (m, 1 H), 7.33−7.41 (m, 2 H), 7.41−7.52 (m, 2 H).

*(B) 5-Methyl-3-oxo-2-phenyl-1-propyl-2,3-dihydro-1H-pyrazole-4-carbaldehyde (**46b**).* The same procedure that was used to prepare **46a** was followed to prepare the aldehyde (2.0 g, 63%) that was carried directly to the next step. MS (ESI pos ion) *m*/*z* calcd for $C_{14}H_{16}N_2O_2$, 244.1; found, 245.1 (M + H).

*(C) 5-Methyl-3-oxo-2-phenyl-1-propyl-2,3-dihydro-1H-pyrazole-4-carboxylic Acid (**47b**).* Method A. The same procedure that was used to prepare **47a** was followed to prepare the title compound. The crude product was recrystallized from DCM/hexanes to give the pure product as a tan colored crystalline solid. Method B. A mixture of 1-allyl-5-methyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carboxylic acid (0.40 g, 1.5 mmol, prepared from allylation) and Pd/C (10%, 0.16 g) in EtOAc (50 mL) was stirred under H_2 (balloon) for 3 h. The mixture was filtered though a pad of Celite, and the filtrate was concentrated in vacuo. The residue was washed with EtOAc to give a white solid as the desired product (0.37 g, 92%). MS (ESI pos ion) *m*/*z* calcd for $C_{14}H_{16}N_2O_3$, 260.1; found, 261.1 (M + H). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.79 (t, *J* = 6.8 Hz, 3 H), 1.49 (d, *J* = 6.7 Hz, 2 H), 2.72 (bs, 3 H), 3.77 (t, *J* = 6.6 Hz, 2 H), 7.34 (d, *J* = 6.9 Hz, 2 H), 7.55 (d, *J* = 6.9 Hz, 3 H), 12.10 (s, 1 H).

*(D) N-(3-Fluoro-4-(7-methoxyquinolin-4-yloxy)phenyl)-5-methyl-3-oxo-2-phenyl-1-propyl-2,3-dihydro-1H-pyrazole-4-carboxamide (**48b**).* The general procedure for amide coupling between 1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carboxylic acid and anilines was followed to prepare the title compound as white solid (0.65 g, 80%). MS (ESI pos ion) *m*/*z* calcd for $C_{30}H_{27}FN_4O_4$, 526.2; found, 527.1 (M + H). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.80 (t, *J* = 7.4 Hz, 3 H), 1.40−1.57 (m, 2 H), 2.81 (s, 3 H), 3.76 (t, *J* = 7.2 Hz, 2 H), 3.96 (s, 3 H), 6.42 (d, *J* = 5.3 Hz, 1 H), 7.17 (t, *J* = 8.7 Hz, 1 H), 7.23 (dd, *J* = 9.2, 2.4 Hz, 1 H), 7.25−7.33 (m, 1 H), 7.36 (d, *J* = 8.0 Hz, 2 H), 7.42 (d, *J* = 1.8 Hz, 1 H), 7.47 (t, *J* = 7.4 Hz, 1 H), 7.51−7.61 (m, 2 H), 7.92 (dd, *J* = 12.2, 1.7 Hz, 1 H), 8.27 (d, *J* = 9.0 Hz, 1 H), 8.59 (d, *J* = 5.3 Hz, 1 H), 10.90 (s, 1 H).

N-(5-(7-Methoxyquinolin-4-yloxy)pyridin-2-yl)-5-methyl-3-oxo-2-phenyl-1-propyl-2,3-dihydro-1H-pyrazole-4-carboxamide (50b). The same procedure that was used to prepare **48b** was followed to prepare the title compound as light-yellow solid (0.18 g, 86%). MS (ESI pos ion) *m*/*z* calcd for $C_{29}H_{27}N_5O_4$, 509.2; found, 510.2 (M + H). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.80 (t, *J* = 7.4 Hz, 3 H), 1.40−1.58 (m, 2 H), 2.81 (s, 3 H), 3.76 (t, *J* = 7.2 Hz, 2 H), 3.98 (s, 3 H), 6.46 (d, *J* = 5.5 Hz, 1 H), 7.22−7.26 (m, 1 H), 7.37 (d, *J* = 8.0 Hz, 2 H), 7.43−7.47 (m, 2 H), 7.47−7.59 (m, 3 H), 8.20−8.30 (m, 2 H), 8.38 (d, *J* = 9.0 Hz, 1 H), 8.61 (d, *J* = 5.5 Hz, 1 H), 11.29 (s, 1 H).

N-(3-Fluoro-4-(7-methoxyquinolin-4-yloxy)phenyl)-5-methyl-1-(2-methylallyl)-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxamide (48c). *(A) 5-Methyl-1-(2-methylallyl)-2-phenyl-1H-pyrazol-3(2H)-one (**45c**).* A mixture of 5-methyl-2-phenyl-1*H*-pyrazol-3(2*H*)-one (18.0 g, 103 mmol) and 2-(bromomethyl)-prop-1-ene (14 g, 103 mmol) was heated at 120 °C for 16 h. The reaction mixture was allowed to cool to rt and partitioned between $CHCl_3$ (400 mL) and NaOH (0.5 N, 100 mL). After 30 min, the organic phase was separated and washed with $NaHCO_3$ (saturated, 100 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by chromatography on silica gel with EtOAc/hexanes (50 to 100%) to afford the desired product (6.6 g, 28%). MS (ESI pos ion) *m*/*z* calcd for $C_{14}H_{16}N_2O$, 228.1; found, 229.1 (M + H). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.52 (s, 3 H), 2.25 (s, 3 H), 4.05 (s, 2 H), 4.51 (s, 1 H), 4.79 (s, 1 H), 5.37 (s, 1 H), 7.25−7.36 (m, 4 H), 7.40−7.50 (m, 2 H).

*(B) 5-Methyl-1-(2-methylallyl)-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carbaldehyde (**46c**).* The same procedure that was used to prepare **46a** was followed to prepare the title compound as yellow solid (5.13 g, 89.6%). MS (ESI pos ion) *m*/*z* calcd for $C_{15}H_{16}N_2O_2$, 256.1; found, 257.1 (M + H). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.56 (s, 3 H), 2.63 (d, *J* = 1.2 Hz, 3 H), 4.20 (s, 2 H), 4.50 (s, 1 H), 4.92 (s, 1 H), 7.13−7.35 (m, 2 H), 7.38−7.59 (m, 3 H), 9.93 (d, *J* = 1.4 Hz, 1 H).

*(C) 5-Methyl-1-(2-methylallyl)-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxylic Acid (**47c**).* The same procedure that was used to prepare **47a** was followed to prepare the title compound as white solid (4.0 g, 93%). MS (ESI pos ion) *m*/*z* calcd for $C_{15}H_{16}N_2O_3$, 272.1; found, 273.1 (M + H). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.56 (s, 3 H), 2.68 (s, 3 H), 4.26 (s, 2 H), 4.45 (s, 1 H), 4.93 (s, 1 H), 7.29−7.37 (m, 2 H), 7.46−7.58 (m, 3 H), 12.12 (bs, 1 H).

*(D) N-(3-Fluoro-4-(7-methoxyquinolin-4-yloxy)phenyl)-5-methyl-1-(2-methylallyl)-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxamide (**48c**).* The general procedure for amide coupling between 1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carboxylic acid and anilines was followed to prepare the title compound as light-yellow solid (0.90 g, 91%). MS (ESI pos ion) *m*/*z* calcd for $C_{31}H_{27}FN_4O_4$, 538.2; found, 539.2 (M + H). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.58 (s, 3 H), 2.74−2.81 (s, 3 H), 3.97 (s, 3 H), 4.27 (s, 2 H), 4.50 (s, 1 H), 4.92 (s, 1 H), 6.42 (d, *J* = 5.3 Hz, 1 H), 7.13−7.25 (m, 2 H), 7.28−7.37 (m, 3 H), 7.40−7.60 (m, 5 H), 7.92 (dd, *J* = 12.5, 2.4 Hz, 1 H), 8.27 (d, *J* = 9.2 Hz, 1 H), 8.60 (d, *J* = 5.3 Hz, 1 H), 10.93 (s, 1 H).

N-(3-Fluoro-4-((7-methoxyquinolin-4-yl)oxy)phenyl)-1-isobutyl-5-methyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxamide (48d). *(A) 1-Isobutyl-5-methyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxylic Acid (**47d**).* A mixture of 5-methyl-1-(2-methylallyl)-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carboxylic acid (**47c**, 0.20 g, 0.73 mmol) and Pd/C (10%, 0.016 g) in EtOAc (60 mL) was stirred under H_2 (balloon) for 3 h. The mixture was filtered though a pad of Celite, and the filtrate was concentrated in vacuo to give the product as yellow solid (0.15 g, 74%). MS (ESI pos ion) *m*/*z* calcd for $C_{15}H_{18}N_2O_3$, 274.1; found, 275.1 (M + H). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.76 (d, *J* = 6.6 Hz, 6 H), 1.76−1.85 (m, 1 H), 2.71 (s, 3 H), 3.63 (d, *J* = 7.6 Hz, 2 H), 7.31 (d, *J* = 7.2 Hz, 2 H), 7.47−7.59 (m, 3 H).

*(B) N-(3-Fluoro-4-((7-methoxyquinolin-4-yl)oxy)phenyl)-1-isobutyl-5-methyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxamide (**48d**).* The general procedure for amide coupling between 1, 5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carboxylic acid

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and anilines was followed to prepare the title compound as white solid (0.067 g, 10%). MS (ESI pos ion) m/z calcd for $C_{31}H_{29}FN_4O_5$, 540.2; found, 541.2 (M + H). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.78 (d, J = 6.6 Hz, 6 H), 1.85 (dt, J = 13.9, 6.9 Hz, 1 H), 2.82 (s, 3 H), 3.64 (d, J = 7.6 Hz, 2 H), 3.97 (s, 3 H), 6.41 (d, J = 5.1 Hz, 1 H), 7.11−7.25 (m, 2 H), 7.27−7.37 (m, 3 H), 7.41 (d, J = 2.4 Hz, 1 H), 7.44−7.51 (m, 1 H), 7.52−7.60 (m, 2 H), 7.92 (dd, J = 12.3, 2.4 Hz, 1 H), 8.27 (d, J = 9.2 Hz, 1 H), 8.59 (d, J = 5.3 Hz, 1 H), 10.90 (s, 1 H).

_N_-(3-Fluoro-4-(7-methoxyquinolin-4-yloxy)phenyl)-1-(2-hydroxypropyl)-5-methyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carboxamide (53) Method A. *(A) 1-(2,3-Dihydroxy-2-methylpropyl)-N-(3-fluoro-4-(7-methoxyquinolin-4-yloxy)phenyl)-5-methyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxamide (**51**).* To a solution of *N*-(3-fluoro-4-(7-methoxyquinolin-4-yloxy)phenyl)-5-methyl-1-(2-methylallyl)-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carboxamide (0.90 g, 1.7 mmol) in ^{t}BuOH/H_2O (9:1, 20 mL) was added 4-methylmorpholine *N*-oxide (0.59 g, 5.0 mmol), followed by a solution of OsO_4 (0.098 M/toluene, 3.4 mL, 0.33 mmol) at rt. After16 h, the solution was diluted with H_2O (10 mL) and EtOAc (40 mL). The organic phase was separated and washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was washed with 50% EtOAc/hexanes to give the desired product as white solid (0.95 g, 99%). MS (ESI pos ion) m/z calcd for $C_{31}H_{29}FN_4O_6$, 572.2; found, 573.2 (M + H). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.07 (s, 3 H), 2.89 (s, 3 H), 3.34 (s, 2 H), 3.86 (d, J = 15.6 Hz, 1 H), 3.96 (s, 4 H), 4.09−4.21 (m, 1 H), 6.42 (d, J = 5.3 Hz, 1 H), 7.10−7.35 (m, 5 H), 7.36−7.48 (m, 2 H), 7.49−7.59 (m, 2 H), 7.90 (d, J = 12.5 Hz, 1 H), 8.27 (d, J = 9.2 Hz, 1 H), 8.56 (d, J = 5.3 Hz, 1 H), 10.85 (s, 1 H).

*(B) N-(3-Fluoro-4-(7-methoxyquinolin-4-yloxy)phenyl)-5-methyl-3-oxo-1-(2-oxopropyl)-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxamide (**52**).* To a solution of 1-(2,3-dihydroxy-2-methylpropyl)-*N*-(3-fluoro-4-(7-methoxyquinolin-4-yloxy)phenyl)-5-methyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carboxamide (0.95 g, 1.7 mmol) in ^{t}BuOH/H_2O (9:1, 20 mL) was added a solution of sodium periodate (1.1 g, 5.0 mmol) in H_2O (20 mL) at rt. The mixture was stirred for 4 h and was diluted with H_2O (20 mL). The mixture was extracted with EtOAc (80 mL) and the organic phase was washed with saturated Na_2SO_3 (30 mL) followed by brine. The organic phase was dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was washed with MeOH (5 mL) to give the desired product as white solid (0.80 g, 89%). MS (ESI pos ion) m/z calcd for $C_{30}H_{25}FN_4O_5$, 540.1; found, 541.2 (M + H). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.07 (s, 3 H), 2.69 (s, 3 H), 3.97 (s, 3 H), 4.52 (s, 2 H), 6.44 (d, J = 5.3 Hz, 1 H), 7.11−7.35 (m, 5 H), 7.40−7.62 (m, 4 H), 7.92 (dd, J = 12.4, 2.4 Hz, 1 H), 8.28 (d, J = 9.2 Hz, 1 H), 8.60 (d, J = 5.3 Hz, 1 H), 10.86 (s, 1 H).

*(C) N-(3-Fluoro-4-(7-methoxyquinolin-4-yloxy)phenyl)-1-(2-hydroxypropyl)-5-methyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxamide (**53**).* To a solution of *N*-(3-fluoro-4-(7-methoxyquinolin-4-yloxy)phenyl)-5-methyl-3-oxo-1-(2-oxopropyl)-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carboxamide (0.15 g, 0.28 mmol) in MeOH (15 mL) was added $NaBH_4$ (0.021 g, 0.55 mmol) in portions. The mixture was stirred at rt for 2 h and was then quenched with a solution of NaH_2PO_4 (1 M, 20 mL). The mixture was extracted with EtOAc (50 mL). The organic phase was washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was washed with small amount of EtOAc−ether mixture to give the desired product as light-yellow solid (0.14 g, 93%). 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 (400 MHz, $CDCl_3$) δ 1.09 (d, J = 5.9 Hz, 3 H), 2.85 (s, 3 H), 3.61−3.74 (m, 1 H), 3.79−3.94 (m, 2 H), 3.97 (s, 3 H), 6.48 (d, J = 5.5 Hz, 1 H), 7.12−7.22 (m, 1 H), 7.24−7.34 (m, 4 H), 7.38−7.49 (m, 2 H), 7.49−7.58 (m, 2 H), 7.93 (dd, J = 12.4, 2.2 Hz, 1 H), 8.30 (d, J = 9.2 Hz, 1 H), 8.53 (d, J = 5.5 Hz, 1 H), 10.90 (s, 1 H).

_N_-(3-Fluoro-4-(7-methoxyquinolin-4-yloxy)phenyl)-1-(2-hydroxypropyl)-5-methyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carboxamide (53−58a) Method B. Alternatively, the title compound was prepared from racemic **57a** and aniline **9d** through amide coupling.

(_R_)-_N_-(3-Fluoro-4-(7-methoxyquinolin-4-yloxy)phenyl)-1-(2-hydroxypropyl)-5-methyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carboxamide ((_R_)-58a). *(A) (R)-Benzyl 1-(2-Hydroxypropyl)-5-methyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxylate ((R)-**56a**).*[32] To a stirred suspension of benzyl 5-methyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carboxylate (15.0 g, 49 mmol) in dry ACN (100 mL) at 0 °C was added magnesium perchlorate (33 g, 146 mmol) in 3 portions over 1 min. The suspension was allowed to warm to rt over 10 min and was returned to 0 °C. (*R*)-(+)-propylene oxide (17 mL, 243 mmol) was added and the reaction mixture was head at 37 °C for 2 h. The mixture was concentrated to a thick syrup under vacuum and was taken in $CHCl_3$ (100 mL). The mixture was chilled to 10 °C and quenched with ice-cold H_2O (200 mL). After being stirred for 1 h, the biphasic system was separated and the aqueous was extracted with $CHCl_3$ (2 × 50 mL). The combined organics were washed with saturated NH_4Cl, dried over $MgSO_4$, filtered, and concentrated. The resulting foam was dissolved in hot MeOH (15−20 mL) and chilled at 4 °C overnight. The mother liquor was separated, and the solid was dried under vacuum to give (*R*)-benzyl 1-(2-hydroxypropyl)-5-methyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carboxylate (14.6 g, 82% yield) as a light-tan crystals.

*(B) (R)-1-(2-Hydroxypropyl)-5-methyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxylic Acid (**57a**).* A solution of (*R*)-benzyl 1-(2-hydroxypropyl)-5-methyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carboxylate (14.4 g, 39.3 mmol) in MeOH (200 mL) was sparged with Ar for 20 min. To this mixture was added Pd/C (10%, 2.09 g). The mixture was stirred overnight under H_2 (balloon). The reaction mixture was filtered through a bed of Celite and evaporated to a solid. This solid was recrystallized from a minimal amount of boiling MeOH. The crystals, readily formed after 1 h at rt, were collected by filtration and was washed with cold MeOH (2 × 10 mL) and ether (20 mL) to give a white solid (4.1 g). MS (ESI pos ion) m/z: calcd for $C_{14}H_{16}N_2O_4$, 276.3; found, 277.1 (M + H). ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.88 (d, J = 6.3 Hz, 3 H), 2.65 (s, 3 H), 3.37 (bs, 1 H), 3.61−3.70 (m, 1 H), 3.78−3.93 (m, 1 H), 7.42 (d, J = 7.4 Hz, 2 H), 7.46−7.65 (m, 3 H).

*(C) (R)-N-(3-Fluoro-4-(7-methoxyquinolin-4-yloxy)phenyl)-1-(2-hydroxypropyl)-5-methyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxamide ((R)-**58a**).* To a stirring solution of (*R*)-1-(2-hydroxypropyl)-5-methyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carboxylic acid (3.0 g, 10.8 mmol) and ^{i}Pr$_2$NEt (1.9 mL, 10.8 mmol) in DMF (10 mL) was added HATU (4.2 g, 10.9 mmol). The mixture was stirred at rt for 20 min before 3-fluoro-4-(7-methoxyquinolin-4-yloxy)benzenamine (3.1 g, 10.9 mmol) was added. The dark solution was heated at 40 °C overnight. The reaction mixture was diluted with MeOH/$CHCl_3$ (1:9, 200 mL) and aqueous $NaHCO_3$ (5%, 150 mL). The aqueous layer was extracted twice with $CHCl_3$/MeOH (9:1; 50 mL). The combined organics were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The resulting oil was azeotroped with toluene until a solid formed. The solid was recrystallized with a minimal amount of MeOH (15−20 mL). After 2 h at rt, the solid was collected by filtration and washed twice with cold MeOH (10 mL) to give (*R*)-*N*-(3-fluoro-4-(7-methoxyquinolin-4-yloxy)phenyl)-1-(2-hydroxypropyl)-5-methyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carboxamide (3.35 g, 57% yield) as a white solid. MS (ESI pos ion) m/z: calcd for $C_{30}H_{27}FN_4O_5$, 542.5; found, 543.2 (M + H). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.10 (d, J = 6.1 Hz, 3 H), 2.85 (s, 3 H), 3.66 (dd, J = 14.7, 2.4 Hz, 1 H), 3.78−3.93 (m, 2 H), 3.95 (s, 3 H), 6.42 (d, J = 4.9 Hz, 1 H), 7.14−7.31 (m, 6 H), 7.37 (d, J = 2.4 Hz, 1 H), 7.39−7.46 (m, 1 H), 7.46−7.55 (m, 2 H), 7.94 (dd, J = 12.5, 2.4 Hz, 1 H), 8.29 (d, J = 9.0 Hz, 1 H), 8.51 (d, J = 5.3 Hz, 1 H), 10.88 (s, 1 H).

(_S_)-_N_-(3-Fluoro-4-(7-methoxyquinolin-4-yloxy)phenyl)-1-(2-hydroxypropyl)-5-methyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carboxamide ((_S_)-58a). *(A) (S)-Benzyl 1-(2-Hydroxypropyl)-5-methyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxylate ((S)-**56a**).* To a 250 mL round-bottomed flask was added benzyl 5-methyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carboxylate (9.2 g, 30.0 mmol) and ACN (60 mL). The solution was cooled in an ice bath, and magnesium perchlorate (27 g, 120 mmol) was added in 3 portions. Then (*S*)-2-methyloxirane (8.7 g, 150 mmol) was added, and the reaction mixture was heated at

35 °C in an oil bath for 5 h. The reaction mixture was concentrated, dissolved in $CHCl_3$, washed with H_2O, dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by chromatography on silica gel eluting with MeOH/$CHCl_3$ (0 to 2%) to give (*S*)-benzyl 1-(2-hydroxypropyl)-5-methyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carboxylate (8.7 g, 79% yield) as a solid.

*(B) The Next Two Steps Were Carried Out Similar to That for the Preparation of (R)-**58a**.* MS (ESI pos ion) *m/z*: calcd for $C_{30}H_{27}FN_4O_5$, 542.5; found, 543.2 (M + H). ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.90 (d, *J* = 6.1 Hz, 3 H), 2.76 (s, 3 H), 3.55−3.70 (m, 2 H), 3.88 (dd, *J* = 15.1, 8.6 Hz, 1 H), 3.94 (s, 3 H), 5.07 (d, *J* = 5.3 Hz, 1 H), 6.49 (d, *J* = 5.1 Hz, 1 H), 7.26−7.38 (m, 2 H), 7.38−7.47 (m, 3 H), 7.47−7.54 (m, 1 H), 7.54−7.64 (m, 2 H), 7.98 (dd, *J* = 13.1, 2.4 Hz, 1 H), 8.23 (d, *J* = 9.2 Hz, 1 H), 8.62 (d, *J* = 5.3 Hz, 1 H), 10.99 (s, 1 H). Anal. Calcd for: C, 66.41; H, 5.02; N, 10.33. Found: C, 65.39; H, 5.03; N, 10.21.

1-(2-Hydroxypropyl)-*N*-(5-(7-methoxyquinolin-4-yloxy)-pyridin-2-yl)-5-methyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carboxamide (59a). Prepared from racemic **57a** and aniline **9d** through amide coupling. MS (ESI pos ion) *m/z*: calcd for $C_{29}H_{27}N_5O_5$, 525.2; found, 526.2 (M + H). ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.86−0.93 (m, 3 H), 2.77 (s, 3 H), 3.56−3.69 (m, 2 H), 3.88 (dd, *J* = 15.2, 8.9 Hz, 1 H), 3.94 (s, 3 H), 5.08 (d, *J* = 5.3 Hz, 1 H), 6.54 (d, *J* = 5.3 Hz, 1 H), 7.30 (dd, *J* = 9.1, 2.4 Hz, 1 H), 7.39−7.45 (m, 3 H), 7.47−7.55 (m, 1 H), 7.55−7.64 (m, 2 H), 7.80 (dd, *J* = 9.0, 2.9 Hz, 1 H), 8.22 (d, *J* = 9.0 Hz, 1 H), 8.32 (d, *J* = 2.7 Hz, 1 H), 8.36 (d, *J* = 9.0 Hz, 1 H), 8.62 (d, *J* = 5.3 Hz, 1 H), 11.27 (s, 1 H).

***N*-(3-Fluoro-4-(7-methoxyquinolin-4-yloxy)phenyl)-1-(2-hydroxyethyl)-5-methyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carboxamide (58b).** *(A) 1-(2-Hydroxyethyl)-5-methyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxylic Acid (**57b**).* A mixture of benzyl 1-(2-hydroxyethyl)-5-methyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carboxylate (**56b**, 0.73 g, 2.1 mmol) and Pd/C (10%, 0.22 g) in EtOAc (40 mL) was stirred under H_2 (balloon) for 3 h. The mixture was filtered though a pad of Celite, and the filtrate was concentrated in vacuo. The residue was washed with MeOH to give the desired product as white solid (0.45 g, 83%). MS (ESI pos ion) *m/z* calcd for $C_{13}H_{14}N_2O_4$, 262.1; found, 263.1 (M + H). ^{1}H NMR (300 MHz, CD_3OD) δ 2.72 (s, 3 H), 3.48 (t, *J* = 5.1 Hz, 2 H), 4.01 (t, *J* = 5.2 Hz, 2 H), 7.37−7.49 (m, 2 H), 7.52−7.67 (m, 3 H).

*(B) N-(3-Fluoro-4-(7-methoxyquinolin-4-yloxy)phenyl)-1-(2-hydroxyethyl)-5-methyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxamide (**58b**).* The general procedure for amide coupling between 1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carboxylic acid and anilines was followed to prepare the title compound, starting with 3-fluoro-4-(7-methoxyquinolin-4-yloxy)benzenamine-HCl salt (0.26 g, 0.92 mmol) and 1-(2-hydroxyethyl)-5-methyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carboxylic acid (0.40 g, 1.5 mmol), as white solid (0.43 g, 89%). MS (ESI pos ion) *m/z* calcd for $C_{29}H_{25}FN_4O_5$, 528.2; found, 529.2 (M + H). ^{1}H NMR (300 MHz, CD_3OD) δ 2.84 (s, 3 H), 3.52 (t, *J* = 5.1 Hz, 2 H), 3.99 (s, 3 H), 4.03 (t, *J* = 5.2 Hz, 2 H), 6.51 (dd, *J* = 5.37, 1.0 Hz, 1 H), 7.24−7.41 (m, 4 H), 7.43−7.51 (m, 2 H), 7.51−7.68 (m, 3 H), 7.89−8.00 (m, 1 H), 8.30 (d, *J* = 9.2 Hz, 1 H), 8.55 (d, *J* = 5.3 Hz, 1 H).

1-(2-Hydroxyethyl)-*N*-(5-(7-methoxyquinolin-4-yloxy)-pyridin-2-yl)-5-methyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carboxamide (59b). The general procedure for amide coupling between 1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carboxylic acid and anilines was followed to prepare the title compound, starting with 1-(2-hydroxyethyl)-5-methyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carboxylic acid (0.30 g, 1.1 mmol) and 5-(7-methoxyquinolin-4-yloxy)pyridin-2-amine (0.31 g, 1.1 mmol), as white solid (TFA salt) (0.20 g, 34%). MS (ESI pos ion) *m/z* calcd for $C_{28}H_{25}N_5O_5$, 511.2.2; found, 512.2 (M + H). ^{1}H NMR (300 MHz, CD_3OD) δ 2.84 (s, 3 H), 3.43−3.58 (m, 2 H), 4.03 (t, *J* = 4.4 Hz, 2 H), 4.08 (s, 3 H), 7.00 (d, *J* = 6.6 Hz, 1 H), 7.38−7.68 (m, 8 H), 7.83 (d, *J* = 9.0 Hz, 1 H), 8.33 (bs, 1 H), 8.47 (d, *J* = 9.0 Hz, 1 H), 8.55 (d, *J* = 9.4 Hz, 1 H), 8.81 (d, *J* = 6.8 Hz, 1 H).

(*S*)-*N*-(3-Fluoro-4-(7-methoxyquinolin-4-yloxy)phenyl)-1-(2-hydroxybutyl)-5-methyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carboxamide (58c). The general procedure for amide coupling between 1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carboxylic acid and anilines was followed to prepare the title compound. MS (ESI pos ion) *m/z*: calcd for $C_{31}H_{29}FN_4O_5$, 556.2; found, 556.6 (M + H). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.83 (t, *J* = 7.3 Hz, 3 H), 1.27−1.43 (m, 2 H), 1.60−1.82 (m, 1 H), 2.85 (s, 3 H), 3.56−3.66 (m, 1 H), 3.70 (dd, *J* = 1.6 Hz, 1 H), 3.79−3.90 (m, 1 H), 3.95 (s, 3 H),6.42 (d, *J* = 5.3 Hz, 3 H), 7.11−7.31 (m, 6 H), 7.36 (d, *J* = 2.2 Hz, 1 H), 7.39−7.53 (m, 3 H), 7.95 (dd, *J* = 12.5, 2.0 Hz, 1 H), 8.30 (d, *J* = 9.2 Hz, 1 H), 8.50 (d, *J* = 5.3 Hz, 1 H), 10.90 (s, 1 H).

***N*-(3-Fluoro-4-(7-methoxyquinolin-4-yloxy)phenyl)-1-(2-hydroxy-3-methylbutyl)-5-methyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carboxamide (58d).** The general procedure for amide coupling between 1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carboxylic acid and anilines was followed to prepare the title compound. MS (ESI pos ion) *m/z*: calcd for $C_{32}H_{31}FN_4O_5$, 570.2; found, 571.6 (M + H). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.73 (d, *J* = 6.8 Hz, 3 H), 0.79 (d, *J* = 6.8 Hz, 3 H), 1.45−1.70 (m, 3H), 2.85 (s, 3 H), 3.39−3.48 (m, 1 H), 3.72−3.80 (m, 1 H), 3.83−3.92 (m, 1 H), 3.96 (s, 3 H), 6.38−6.44 (m, 1 H), 7.13−7.24 (m, 2 H), 7.28−7.33 (m, 2 H), 7.40 (d, *J* = 2.4 Hz, 1 H), 7.42−7.49 (m, 1 H), 7.49−7.58 (m, 2 H), 7.92 (dd, *J* = 12.4, 2.4 Hz, 1 H), 8.28 (d, *J* = 9.0 Hz, 1 H), 8.56 (d, *J* = 5.3 Hz, 1 H), 10.89 (s, 1 H).

Synthesis of **58e** and **59e** were described previously.[9]

1-(2-Aminoethyl)-*N*-(3-fluoro-4-(7-methoxyquinolin-4-yloxy)phenyl)-5-methyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carboxamide (61). *(A) 1-(2-(1,3-Dioxoisoindolin-2-yl)-ethyl)-N-(3-fluoro-4-(7-methoxyquinolin-4-yloxy)phenyl)-5-methyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxamide (**60**).* To a solution of *N*-(3-fluoro-4-(7-methoxyquinolin-4-yloxy)phenyl)-1-(2-hydroxyethyl)-5-methyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carboxamide (0.20 g, 0.38 mmol) and phthalimide (0.11 g, 0.76 mmol) in DCM (10 mL) was added Ph_3P (0.15 g, 0.57 mmol), followed by diethyl azodicarboxylate (0.089 mL, 0.57 mmol) via a syringe. The mixture was stirred at rt for 16 h. The solution was concentrated in vacuo, and the residue was purified by chromatography on silica gel with MeOH/EtOAc (0 to 10%) to give the desired product as light-yellow solid (0.22 g, 88%). MS (ESI pos ion) *m/z* calcd for $C_{37}H_{28}FN_5O_6$, 657.2; found, 658.2 (M + H). ^{1}H NMR (300 MHz, CD_3OD) δ 2.61 (s, 3 H), 3.67 (t, *J* = 5.5 Hz, 2 H), 3.89 (s, 3 H), 4.20 (t, *J* = 5.5 Hz, 2 H), 6.41 (dd, *J* = 5.4, 1.0 Hz, 1 H), 7.15−7.31 (m, 6 H), 7.35−7.46 (m, 3 H), 7.70−7.85 (m, 5 H), 8.20 (d, *J* = 9.0 Hz, 1 H), 8.45 (d, *J* = 5.5 Hz, 1 H).

*(B) 1-(2-Aminoethyl)-N-(3-fluoro-4-(7-methoxyquinolin-4-yloxy)-phenyl)-5-methyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxamide (**61**).* To a solution of 1-(2-(1,3-dioxoisoindolin-2-yl)ethyl)-*N*-(3-fluoro-4-(7-methoxyquinolin-4-yloxy)phenyl)-5-methyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carboxamide (0.20 g, 0.30 mmol) in EtOH/H_2O (1:1, 20 mL) was added H_2N_2 (0.049 g, 1.5 mmol). The mixture was heated at 50 °C for 8 h and allowed to cool to rt. The mixture was diluted with $NaHCO_3$ (saturated, 20 mL) and EtOAc (60 mL). The organic phase was separated and washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was washed with hexanes/EtOAc (20%) to give desired product as light-yellow solid (0.13 g, 81%). MS (ESI pos ion) *m/z* calcd for $C_{29}H_{26}FN_5O_4$, 527.1; found, 528.1 (M + H). ^{1}H NMR (300 MHz, CD_3OD) δ 2.67 (t, *J* = 6.7 Hz, 3 H), 2.82 (s, 3 H), 3.86−4.04 (m, 6 H), 6.49 (dd, *J* = 5.5, 0.94 Hz, 1 H), 7.21−7.40 (m, 4 H), 7.40−7.50 (m, 2 H), 7.52−7.69 (m, 3 H), 7.89−8.00 (m, 1 H), 8.29 (d, *J* = 9.2 Hz, 1 H), 8.53 (d, *J* = 5.5 Hz, 1 H).

1-(2-Methoxyethyl)-*N*-(5-(7-methoxyquinolin-4-yloxy)-pyridin-2-yl)-5-methyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carboxamide (63). *(A) Benzyl 1-(2-Methoxyethyl)-5-methyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxylate (**62a**).* To a solution of benzyl 1-(2-hydroxyethyl)-5-methyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carboxylate (5.0 g, 14 mmol) in DCM (50 mL) was added a solution of fluoroboric acid (50%, 14 mL, 284 mmol). A solution of trimethylsilyl

diazomethane in hexanes (2.0 M, 32 mL, 284 mmol) was added to the mixture dropwise over 30 min. The reaction mixture was allowed to warm to rt and stirred for 1 h. The mixture was diluted with DCM (50 mL) and H_2O (50 mL). The organic phase was separated and was washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by chromatography on silica gel [EtOAc/hexanes (50 to 100%; then MeOH/EtOAc (2%)] to give the desired product as white solid (0.10 g, 2% yield). MS (ESI pos ion) *m/z* calcd for $C_{21}H_{22}N_2O_4$, 366.2; found, 367.2 (M + H). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.66 (s, 3 H), 3.20 (s, 3 H), 3.30 (t, J = 5.0 Hz, 2 H), 3.90 (t, J = 4.9 Hz, 2 H), 5.33 (s, 2 H), 7.22−7.40 (m, 6 H), 7.42−7.57 (m, 4 H).

*(B) 1-(2-Methoxyethyl)-5-methyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxylic Acid (**62b**).* To a solution of benzyl 1-(2-methoxyethyl)-5-methyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carboxylate (0.80 g, 2.2 mmol) in EtOAc (50 mL) was added Pd/C (10%, 0.023 g). The mixture was stirred under H_2 (balloon) for 6 h. The catalyst was removed by filtration through a pad of Celite. The filtrate was concentrated in vacuo to give the desired product as a white solid (0.60 g, 99%). MS (ESI pos ion) *m/z* calcd for $C_{14}H_{16}N_2O_4$, 276.2; found, 277.1 (M + H). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.73 (s, 3 H), 3.23 (s, 3 H), 3.31 (t, J = 4.9 Hz, 2 H), 3.98 (t, J = 4.9 Hz, 2 H), 7.34 (d, J = 7.4 Hz, 2 H), 7.42−7.61 (m, 3 H), 12.10 (bs, 1H).

*(C) 1-(2-Methoxyethyl)-N-(5-(7-methoxyquinolin-4-yloxy)pyridin-2-yl)-5-methyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxamide (**63**).* The general procedure for amide coupling between 1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carboxylic acid and anilines was followed to prepare the title compound, starting with 5-(7-methoxyquinolin-4-yloxy)pyridin-2-amine (0.10 g, 0.4 mmol) and 1-(2-methoxyethyl)-5-methyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carboxylic acid (0.1 g, 0.4 mmol), as white solid (TFA slat) (0.08 g, 42%). MS (ESI pos ion) *m/z* calcd for $C_{29}H_{27}N_5O_5$, 525.2; found, 526.2 (M + H). ^{1}H NMR (300 MHz, CD_3OD) δ 2.81 (s, 3 H), 3.26 (s, 3 H), 3.38 (t, J = 4.9 Hz, 2 H), 4.05−4.15 (m, 5 H), 7.00 (d, J = 6.8 Hz, 1 H), 7.39−7.67 (m, 7 H), 7.84 (dd, J = 9.2, 2.8 Hz, 1 H), 8.34 (d, J = 2.5 Hz, 1 H), 8.49 (d, J = 9.0 Hz, 1 H), 8.56 (d, J = 9.4 Hz, 1 H), 8.81 (d, J = 6.8 Hz, 1 H).

1-(3-Amino-2-hydroxypropyl)-*N*-(3-fluoro-4-((7-methoxyquinolin-4-yl)oxy)phenyl)-5-methyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carboxamide (67). *(A) Benzyl 1-(3-Azido-2-hydroxypropyl)-5-methyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxylate (**65a**).* A suspension of benzyl 1-(3-chloro-2-hydroxypropyl)-5-methyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carboxylate (2.0 g, 5.00 mmol) and NaN_3 (0.97 g, 15 mmol) were heated at 90 °C in DMF (15 mL) and H_2O (5 mL) for 18 h. The reaction was diluted with $CHCl_3$ (100 mL) and saturated NH_4Cl (10 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford title compound as white solid. MS (ESI pos ion) *m/z*: calcd for $C_{21}H_{21}N_5O_4$, 407.2; found, 408.2 (M + H).

*(B) Benzyl 1-(3-Amino-2-hydroxypropyl)-5-methyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxylate (**65b**).* To a stirred solution of benzyl 1-(3-azido-2-hydroxypropyl)-5-methyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carboxylate (1.80 g, 4.42 mmol) in dry MeOH (2 mL) was added ^{i}Pr$_2$NEt$_2$ (3.8 mL, 22.1 mmol) and propane-1,3-dithiol (2.2 mL, 22.1 mmol). After 48 h, the mixture was concentrated under reduced pressure. The residue was purified by chromatography on silica gel [(2 N NH_3 in MeOH)−DCM (2−10%)] to afford the title compound (1.35 g, 80% yield) as white foam. MS (ESI pos ion) *m/z*: calcd for $C_{21}H_{23}N_3O_4$, 381.2; found, 382.2 (M + H). ^{1}H NMR (400 MHz, CDCl3) δ 2.40−2.28 (m, 1 H), 2.52−2.42 (m, 1 H), 2.68 (s, 3 H), 3.58−3.42 (m, 1 H), 3.75−3.64 (m, 1 H), 3.87−3.75 (m, 1 H), 5.25 (s, 2 H), 7.52−7.36 (m, 5 H), 7.35−7.28 (m, 5 H).

*(C) Benzyl 1-(3-(tert-Butoxycarbonyl)-2-hydroxypropyl)-5-methyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxylate (**66a**).* To a stirred solution of benzyl 1-(3-amino-2-hydroxypropyl)-5-methyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carboxylate (167 mg, 0.44 mmol) in DCM (1 mL) was added Boc_2O (1 M/THF, 0.44 mL, 0.44 mmol). After 18 h at 23 °C, the mixture was diluted with $CHCl_3$ (15 mL) and washed with saturated NH_4Cl (5 mL). The separated organic was dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford the title compound as white solid (200 mg, 95% yield). MS (ESI pos ion) *m/z*: calcd exact mass for $C_{26}H_{31}N_3O_6$, 481.2; found, 482.3 (M + H).

*(D) 1-(3-((tert-Butoxycarbonyl)amino)-2-hydroxypropyl)-5-methyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxylic acid (**66b**).* A stirred solution of benzyl 1-(3-(*tert*-butoxycarbonyl)-2-hydroxypropyl)-5-methyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carboxylate (160 mg, 332 μmol) in MeOH (15 mL) was sparged with Ar for 10 min. To this mixture was added Pd/C (10%, 35 mg), and the mixture was stirred under H_2 (balloon) for 1 h. The reaction mixture was filtered through a bed of Celite and concentrated to give a solid. MS (ESI pos ion) *m/z*: calcd for $C_{19}H_{25}N_3O_6$: 391.2; found: 392.2 (M + H).

*(E) 1-(3-Amino-2-hydroxypropyl)-N-(3-fluoro-4-((7-methoxyquinolin-4-yl)oxy)phenyl)-5-methyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxamide (**67**).* To a stirred solution of 1-(3-(*tert*-butoxycarbonyl)-2-hydroxypropyl)-5-methyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carboxylic acid (90 mg, 230 μmol) and ^{i}Pr$_2$NEt (40 μL, 230 μmol) in DMF (1 mL) was added HATU (87 mg, 230 μmol). The mixture was stirred at rt for 20 min before 3-fluoro-4-(7-methoxyquinolin-4-yloxy)benzenamine (65 mg, 230 μmol) was added. After overnight, the reaction mixture was partitioned between DCM and aqueous $NaHCO_3$ (5%). The aqueous layer was extracted with DCM (2 × 5 mL), and the combined organics were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The crude material was purified by chromatography on silica gel eluting with MeOH−DCM (0−4%). The resulting film was exposed to TFA (1 mL) in DCM (1 mL) for 15 min. The mixture was washed with NaOH (1 M) and purified by chromatography on silica gel [MeOH−DCM (5%), then 3−10% of (2 M NH_3 in MeOH)−DCM (3−10%)] to afford 1-(3-amino-2-hydroxypropyl)-*N*-(3-fluoro-4-(7-methoxyquinolin-4-yloxy)phenyl)-5-methyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carboxamide as fluffy white powder (40 mg, 31% yd). MS (ESI pos ion) *m/z*: calcd for $C_{30}H_{28}FN_5O_5$, 557.2; found, 558.3 (M + H). ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.28 (dd, J = 5.4, 2.6 Hz, 2 H), 2.69 (s, 3 H), 3.87 (s, 5 H), 4.94−5.15 (m, 1 H), 6.42 (d, J = 5.1 Hz, 1 H), 7.19−7.31 (m, 2 H), 7.31−7.40 (m, 4 H), 7.43 (s, 1 H), 7.51 (d, J = 7.6 Hz, 2 H), 7.90 (d, J = 2.4 Hz, 1 H), 8.16 (d, J = 9.0 Hz, 1 H), 8.55 (d, J = 5.3 Hz, 1 H), 10.93 (s, 1 H)

***N*-(3-Fluoro-4-(7-methoxyquinolin-4-yloxy)phenyl)-5-methyl-3-oxo-1-((2-oxooxazolidin-5-yl)methyl)-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carboxamide (69).** *(A) Benzyl 5-Methyl-3-oxo-1-((2-oxooxazolidin-5-yl)methyl)-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxylate (**68a**).* To a stirred suspension of benzyl 1-(3-amino-2-hydroxypropyl)-5-methyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carboxylate (345 mg, 0.91 mmol) in 1,4-dioxane (2 mL) was added disuccinimidyl carbonate (232 mg, 0.91 mmol). The mixture was stirred for 30 min at 23 °C. To this solution was added DBU (327 μL, 2.2 mmol), and stirring was continued for an additional 1 h at 23 °C. The reaction mixture was diluted with DCM (25 mL) and washed with HCl (1 N, 10 mL). The separated organic phase was dried over $MgSO_4$, filtered, concentrated under reduced pressure. The residue was purified by chromatography on silica gel eluting with MeOH−DCM (1−4%) to afford the title compound as white solid (310 mg, 84%). MS (ESI pos ion) *m/z*: calcd for $C_{22}H_{21}N_3O_5$, 407.2; found, 408.2 (M + H). ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.61 (s, 3 H), 3.04 (dd, J = 5.6, 9.3 Hz, 1 H), 3.40 (t, J = 9.0 Hz, 1 H), 3.89 (dd, J = 2.7, 16.0 Hz, 1 H), 4.23 (dd, J = 9.1, 15.9 Hz, 1 H), 4.57 (ddt, J = 2.9, 5.5, 8.8 Hz, 1 H), 5.23 (s, 2 H), 7.49−7.25 (m, 8 H), 7.58−7.48 (m, 2 H), 7.63 (s, 1 H).

*(B) 5-Methyl-3-oxo-1-((2-oxooxazolidin-5-yl)methyl)-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxylic Acid (**68b**).* A stirred suspension of benzyl 5-methyl-3-oxo-1-((2-oxooxazolidin-5-yl)methyl)-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carboxylate (150 mg, 0.37 mmol) in MeOH (10 mL) was sparged with Ar for 20 min. To this

suspension was added Pd/C (10%, 5 mg). After18 h at 23 °C under H_2 (balloon), the reaction was filtered through a bed of Celite and concentrated under reduced pressure to afford title compound as white solid in quantitative yield. MS (ESI pos ion) *m/z*: calcd for $C_{15}H_{15}N_3O_5$, 317.1; found, 318.1 (M + H). ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.63 (s, 3 H), 3.04 (dd, *J* = 5.5, 9.2 Hz, 1 H), 3.44−3.37 (m, 1 H), 3.97 (dd, *J* = 2.7, 16.0 Hz, 1 H), 4.25 (dd, *J* = 9.2, 16.0 Hz, 1 H), 4.62−4.51 (m, 1 H), 7.40 (d, *J* = 7.2 Hz, 2 H), 7.52−7.46 (m, 1 H), 7.60−7.54 (m, 2 H), 7.64 (s, 1 H).

*(C) N-(3-Fluoro-4-(7-methoxyquinolin-4-yloxy)phenyl)-5-methyl-3-oxo-1-((2-oxooxazolidin-5-yl)methyl)-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxamide (**69**).* A solution of 5-methyl-3-oxo-1-((2-oxooxazolidin-5-yl)methyl)-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carboxylic acid (80 mg, 252 μmol), ^{i}Pr$_2$NEt2 (44 μL, 252 μmol), and HATU (96 mg, 252 μmol) in DMF (1 mL) was stirred for 20 min at 23 °C before 3-fluoro-4-(7-methoxyquinolin-4-yloxy)benzenamine was added. After 18 h at 40 °C, the reaction was diluted with DCM (15 mL) and washed with 5% $NaHCO_3$ (50 mL). The separated aqueous layer was extracted with DCM (2 × 5 mL), and the combined organics were dried over $MgSO_4$, filtered, concentrated under reduced pressure, and purified by chromatography on silica gel eluting with MeOH−DCM (1−5%) to afford title compound as colorless film which was subsequently lyophilized from 50% ACN/H_2O (2 mL) to provide amorphous white powder (100 mg, 68%). MS (ESI pos ion) *m/z*: calcd for $C_{31}H_{26}FN_5O_6$, 583.2; found, 584.2 (M + H). ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.07 (dd, *J* = 9.4, 5.5 Hz, 1 H), 3.43 (t, *J* = 9.1 Hz, 1 H), 3.90−4.07 (m, 4 H), 4.30 (dd, *J* = 16.0, 9.2 Hz, 1 H), 4.52−4.67 (m, 1 H), 6.50 (d, *J* = 5.3 Hz, 1 H), 7.28−7.48 (m, 6 H), 7.48−7.53 (m, 1 H), 7.54−7.68 (m, 3 H), 7.99 (dd, *J* = 13.0, 2.2 Hz, 1 H), 8.24 (d, *J* = 9.0 Hz, 1 H), 8.63 (d, *J* = 5.1 Hz, 1 H), 10.90 (s, 1 H).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Biological assays, standard deviations, and X-ray crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

Accession Codes

The cocrystal structure data for VEGFR-2 + **1** and c-Met + (*R*)-**58a** have been deposited in the Protein Data Bank with PDB codes 3U6J and 3U6I, respectively.

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Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS USED

ATP, adenosine-5′-triphosphate; EGFR, epidermal growth factor receptor; EDCI, 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide); HATU, 2-(7-aza-1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate; HGF, hepatocyte growth factor; HOAt, (1-hydroxy-7-azabenzotriazole); IGF-1R, insulin-like growth factor receptor 1; RTK, receptor tyrosine kinase; SAR, structure−activity relationship; VEGFR-2, vascular endothelial growth factor receptor 2

■ REFERENCES

(1) (a) Bottaro, D. P.; Rubin, J. S.; Faletto, D. L.; Chan, A. M.; Kmiecik, T. E.; Vande Woude, G. F.; Aaronson, S. A. Identification of the hepatocyte growth factor receptor as the c-met proto-oncogene product. *Science* **1991**, *251*, 802−4. (b) Naldini, L.; Weidner, K. M.; Vigna, E.; Gaudino, G.; Bardelli, A.; Ponzetto, C.; Narsimhan, R. P.; Hartmann, G.; Zarnegar, R.; Michalopoulos, G. K. Scatter factor and hepatocyte growth factor are indistinguishable ligands for the MET receptor. *EMBO J.* **1991**, *10*, 2867−78.

(2) Longati, P.; Bardelli, A.; Ponzetto, C.; Naldini, L.; Comoglio, P. M. Tyrosines 1234−1235 are critical for activation of the tyrosine kinase encoded by the MET protoocogene (HGF receptor). *Oncogene* **1994**, *9*, 49−57.

(3) (a) Nakamura, T.; Mizuno, S.; Matsumoto, K.; Sawa, Y.; Matsuda, H.; Nakamura, T. Myocardial protection from ischemia/reperfusion injury by endogenous and exogenous HGF. *J. Clin. Invest.* **2000**, *106*, 1511−1519. (b) Huh, C. G.; Factor, V. W.; Sanchez, A.; Uchida, K.; Commer, E. A.; Thorgeirsson, S. S. Hepatocyte growth factor/c-met signaling pathway is required for efficient liver regeneration and repair. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 4477−4482.

(4) For reviews, see, (a) Sattler, M.; Salgia, R. c-Met and hepatocyte growth factor: potential as novel targets in cancer therapy. *Curr. Oncol. Rep.* **2007**, *9*, 102−108. (b) Mazzone, M.; Comoglio, P. M. The Met pathway: master switch and drug target in cancer progression. *FASEB J.* **2006**, *20*, 1611−1621. (c) Matsumoto, K.; Nakamura, T. NK4 (HGF-antagonist/angiogenesis inhibitor) in cancer biology and therapeutics. *Cancer Sci.* **2003**, *94*, 321−327. (d) Birchmeier, C.; Birchmeier, W.; Gherardi, E.; Vande Woude, G. F. Met, metastasis, motility and more. *Nature Rev. Mol. Cell Biol.* **2003**, *4*, 915−925. and references cited therein. (e) Trusolino, L.; Comoglio, P. M. Scatter-factor and semaphorin receptors: cell signaling for invasive growth. *Nature Rev. Cancer* **2002**, *2*, 289−300.

(5) (a) 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*, 1−25. (b) Dussault, I.; Kaplan-Lefko, P.; Jun, T.; Coxon, A.; Burgess, T. L. HGF- and c-Met-targeted drugs: hopes, challenges and their future in cancer therapy. *Drugs Future* **2006**, *31*, 819−825. (c) Abidoye, O.; Murukurthy, N.; Salgia, R. Review of clinic trials: agents targeting c-Met. *Rev. Recent Clin. Trials* **2007**, *2*, 143−147. (d) 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.

(6) (a) Cui, J. J. Inhibitors targeting hepatocyte growth factor receptor and their potential therapeutic applications. *Expert Opin. Ther. Pat.* **2007**, *17*, 1035−1045. (b) Porter, J. Small molecule c-Met kinase inhibitors: a review of recent patents. *Expert Opin. Ther. Pat.* **2010**, *20*, 159−177.

(7) Schroeder, G. M.; An, Y.; Cai, Z.-W.; Chen, X.-T.; Clark, C.; Cornelius, L. A. M.; Dai, J.; Gullo-Brown, J.; Gupta, A.; Henley, B.; Hunt, J. T.; Jeyaseelan, R.; Kamath, A.; Kim, K.; Lippy, J.; Lombardo, L. J.; Manne, V.; Oppenheimer, S.; Sack, J. S.; Schmidt, R. J.; Shen, G.; Stefanski, K.; Tokarski, J. S.; Trainor, G. L.; Wautlet, B. S.; Wei, D.; Williams, D. K.; Zhang, Y.; Zhang, Y.; Fargnoli, J.; Borzilleri, R. M. 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.

(8) Norman, M. H.; Liu, L.; Lee, M.; Xi, N.; Fellows, I.; D'Angelo, N.; Dominguez, C.; Rex, R.; Bellon, S. F.; Kim, T.-S.; Dussault, I. Structure-based design of novel class II c-Met inhibitors: 1. Identification of pyrazolone-based derivatives. *J. Med. Chem.* **2012**, DOI 10.1021/jm201330u.

(9) For the work leading to a clinical candidate based on pyrazolones, see, Liu, L.; Siegmund, A.; Xi, N.; Kaplan-Lefko, P.; Rex, K.; Chen, A.; Lin, J.; Moriguchi, J.; Berry, L.; Huang, L.; Teffera, Y.; Yang, Y.; Zhang,

Y.; Bellon, S. F.; Lee, M.; Shimaanovich, R.; Bak, A.; Dominguez, C.; Norman, M.; Harmange, J. C.; Dussault, I.; Kim, T.-S. Discovery of 1-(2-hydroxy-2-methylpropyl)-*N*-(5-(7-methoxyquinolin-4-yloxy)-pyridin-2-yl)-5-methyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carboxamide (AMG 458): a potent, selective, and orally bioavailable c-Met Inhibitor. *J. Med. Chem.* **2008**, *51*, 3688−3691.

(10) Dussault, I.; Bellon, S. F. From concept to reality: the long road to c-Met and RON receptor tyrosine kinase inhibitors for the treatment of cancer. *Anti-Cancer Agents Med. Chem.* **2009**, *9*, 221−229.

(11) Ronsin, C.; Muscatelli, F.; Mattei, M. G.; Breathnach, R. A novel putative receptor protein tyrosine kinase of the met family. *Oncogene* **1993**, *8*, 1195−1202.

(12) Complete kinase selectivity profile of compound **1** is available in the Supporting Information.

(13) (a) Baka, S.; Clamp, A. R.; Jayson, G. C. A review of the latest clinical compounds to inhibit VEGF in pathological angiogenesis. *Expert Opin. Ther. Targets* **2006**, *10*, 867−876. (b) Gasparini, G.; Longo, R.; Toi, M.; Ferrara, N. Angiogenic inhibitors: a new therapeutic strategy in oncology. *Nature Clin. Pract. Oncol.* **2005**, *2*, 562−577.

(14) (a) Rochester, M. A.; Riedemann, J.; Hellawell, G. O.; Brewster, S. F.; Macaulay, V. M. Silencing of the IGF-1R gene enhances sensitivity to DNA-damaging agents in both PTEN wild-type and mutant human prostate cancer. *Cancer Gene Ther.* **2005**, *12*, 90−100. (b) Baserga, R. The insulin-like growth factor-1 receptor as a target for cancer therapy. *Expert. Opin. Ther. Targets* **2005**, *9*, 753−768. (c) Miller, B. S.; Yee, D. Type I insulin-like growth factor receptor as a therapeutic target in cancer. *Cancer Res.* **2005**, *65*, 10123−10127. (d) Ueda, S.; Hatsuse1, K.; Tsuda, H.; Ogata, S.; Kawarabayashi, N.; Takigawa, T.; Einama, T.; Morita, D.; Fukatsu1, K.; Sugiura, Y.; Matsubara, O.; Mochizuki, H. Potential crosstalk between insulin-like growth factor receptor type 1 and epidermal growth factor receptor in progression and metastasis of pancreatic cancer. *Mod. Pathol.* **2006**, *19*, 788−796.

(15) A previously described hierarchical molecular modeling method was used for generating the docked models: Lee, M. R.; Sun, Y. Improving Docking Accuracy through Molecular Mechanics Generalized Born Optimization and Scoring. *J. Chem. Theory Comput.* **2007**, *3*, 1106.

(16) (a) Unpublished results. Published DFG-out X-ray structures of c-Met inhibitors include: (b) 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.; An, Y.; Sack, J. S.; Tokarski, J. S.; Darienzo, C.; Kamath, A.; Marathe, P.; Zhang, Y.; Lippy, J.; Jeyaseelan, R.; Wautlet, B.; Henley, B.; Gullo-Brown, J.; Manne, V.; Hunt, J. T.; Fargnoli, J.; Borzilleri, R. M. Discovery of pyrrolopyridine-pyridone based inhibitors of Met kinase: synthesis, X-ray crystallographic analysis, and biological Activities. *J. Med. Chem.* **2008**, *51*, 5330−5341. (c) Qian, F.; Engst, S.; Yamaguchi, K.; Yu, P.; Won, K.-A.; Mock, L.; Lou, T.; Tan, J.; Li, C.; Tam, D.; Lougheed, J.; Yakes, F. M.; Bentzien, F.; Xu, W.; Zaks, T.; Wooster, R.; Greshock, J.; Holy, A. H. Inhibition of tumor cell growth, invasion, and metastasis by EXEL-2880 (XL880, GSK1363089), a novel inhibitor of HGF and VEGF receptor tyrosine kinases. *Cancer Res.* **2009**, *69*, 8009−8016.

(17) Lin, A. J.; Loo, T. L. Synthesis and antitumor activity of halogen-substituted 4-(3,3-dimethyl-1-triazeno)quinolines. *J. Med. Chem.* **2002**, *21*, 268−272.

(18) Samizu, K.; Hisamichi, H.; Matsuhisa, A.; Kinoyama, I.; Hayakawa, M.; Taniguchi, N.; Ideyama, Y.; Kuromitsu, S.; Yahiro, K.; Okada, M. Preparation of 3-quinoline-2(1*H*)-ylideneindolin-2-one derivatives as vascular endothelial growth factor (VEGF) inhibitors. Patent WO 2002/094809A1, 2002.

(19) Herbert, J. M. Negishi-type coupling of bromoarenes with dimethylzinc. *Tetrahedron Lett.* **2004**, *45*, 817−819.

(20) Molander, G. A.; Rivero, M. R. Suzuki Cross-coupling reactions of potassium alkenyltrifluoroborates. *Org. Lett.* **2002**, *4*, 107−109.

(21) Kubo, K.; Shimizu, T.; Ohyama, S.-I.; Murooka, H.; Iwai, A.; Nakamura, K.; Hasegawa, K.; Kobayashi, Y.; Takahashi, N.; Takahashi, K.; Kato, S.; Izawa, T.; Isoe, T. Novel potent orally active selective VEGFR-2 tyrosine kinase inhibitors: synthesis, structure−activity relationships, and antitumor activities of *N*-phenyl-*N*′-{4-(4-quinolyloxy)phenyl}ureas. *J. Med. Chem.* **2005**, *48*, 1359−1366.

(22) Bannen, L. C.; Chan, D. S.-m.; Chen, J.; Dalrymple, L. E.; Forsyth, T. P.; Huynh, T. P.; Jammalamadaka, V.; Khoury, R. G.; Leahy, J. W.; Mac, M. B.; Mann, G.; Mann, L. W.; Nuss, J. M.; Parks, J. J.; Takeuchi, C. S.; Wang, Y.; Xu, W. Preparation of quinolines and quinazolines as inhibitors of c-Met and other tyrosine kinases and therapeutic uses against proliferative diseases. Patent WO 2005/030140, 2005.

(23) Kung, P. P.; Funk, L.; Meng, J.; Alton, G.; Padrique, E.; Mroczkowski, B. Structure activity relationships of quinoline-containing c-Met inhibitors. *Eur. J. Med. Chem.* **2008**, *43*, 1321−1329.

(24) Lauer, W. M.; Arnold, R. T.; Tiffany, B.; Tinker, J. Synthesis of some chloromethoxyquinolines. *J. Am. Chem. Soc.* **1946**, *68*, 1268−1269.

(25) Nara, S. J.; Jha, M.; Brinkhorst, J.; Zemanek, T. J.; Pratt, D. A. A simple Cu-catalyzed coupling approach to substituted 3-pyridinol and 5-opyrimidinol antioxidants. *J. Org. Chem.* **2008**, *73*, 9326−9333.

(26) (a) Ledrut, J.; Combes, G. Reaction of *N*-bromosuccinamide with pyrazolones. *Comptes Rendus* **1950**, *231*, 1513−1515. (b) de Graef, H.; Ledrut, J.; Combes, G. Prazolone series. XI. Reaction of *N*-halo imides with antipyrine and derivatives. *Bull. Soc. Chim. Belges* **1952**, *61*, 331−351. (c) Ito, I.; Oda, N. Synthesis of pyrazolone derivatives. XI. Synthesis of 6-substituted 1,2,6,7-tetrahydro-3*H*-pyrazolo[4,3-*c*]pyridine. *Chem. Pharm. Bull.* **1966**, *14*, 297−298 and references cited therein.

(27) Bodendorf, K.; Mildner, J.; Lehmann, T. Über Antipyrinaldehyd und Antipyrinsaure. *Eur. J. Org. Chem.* **1949**, *563*, 1−11.

(28) Brooks, D. W.; Lu, L. D.-L.; Masamune, S. C-Acylation under virtually neutral conditions. *Angew. Chem. Int Ed.* **1979**, *18*, 72−74.

(29) Barluenga, J.; Merino, I.; Viña, S.; Palacios, F. Regioselective synthesis of 1-alkyl-1-phenylhydrazines, 2-alkyl-1-phenylhydrazines, and 1,2-dialkyl-1-phenylhydrazines. *Synthesis* **1990**, 398−400.

(30) Rockley, J. E.; Summers, L. A. Structures of 5-Methyl-4-((arylamino)methylene)-2,4-dihydro-3*H*-pyrazol-3-ones. *Aust. J. Chem.* **1981**, *34*, 1117−1124.

(31) Bal, B. S.; Childers, W. E. Jr.; Pinnick, H. W. *Tetrahedron* **1981**, *37*, 2091−2096.

(32) Siegmund, A.; Retz, D.; Xi, N.; Dominguez, C.; Burli, R.; Liu, L. Selective *β*-hydroxyethylation at the N-1 position of a pyrazolone: synthesis of benzyl 1-(*β*-hydroxyethyl)-5-methyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carboxylate. *Synlett* **2008**, 1005−1008.

(33) For selected papers, see, (a) Bridges, A. J.; Zhou, H.; Cody, D. R.; Rewcastle, G. W.; McMichael, A.; Showalter, H. D. H.; Fry, D. W.; Kraker, A. J.; Denny, W. A. Tyrosine kinase inhibitors: unusually steep structure−activity relationship for analogs of 4-(3-bromoanilino)-6,7-dimethoxyquinazoline (PD 153035), a potent inhibitor of the epidermal growth factor receptor. *J. Med. Chem.* **1996**, *39*, 267−76. (b) Wissner, A.; Berger, D. M.; Boschelli, D. H.; Floyd, M. B. Jr.; Greenberger, L. M.; Gruber, B. C.; Johnson, B. D.; Mamuya, N.; Nilakantan, R.; Reich, M. F.; Shen, R.; Tsou, H.-R.; Upeslacis, E.; Wang, Y. F.; Wu, B.; Ye, F.; Zhang, N. 4-Anilino-6,7-dialkoxyquinoline-3-carbonitrile inhibitors of epidermal growth factor receptor kinase and their bioisosteric relationship to the 4-anilino-6,7-dialkoxyquinazoline inhibitors. *J. Med. Chem.* **2000**, *43*, 3244−3256. (c) Scott, D. A.; Balliet, C. L.; Cook, D. J.; Davis, A. M.; Gero, T. W.; Omer, C. A.; Poondru, S.; Theoclitou, M.-E.; Tyurin, B.; Zinda, M. J. Identification of 3-amido-4-anilinoquinolines as potent and selective inhibitors of CSF-1R kinase. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 697−700. (d) Cincinelli, R.; Cassinelli, G.; Dallavalle, S.; Lanzi, C.; Merlini, L.; Botta, M.; Tuccinardi, T.; Martinelli, A.; Penco, S.; Zunino, F. Synthesis, modeling, and RET protein kinase inhibitory activity of 3- and 4-substituted b-Carbolin-1-ones. *J. Med. Chem.* **2008**, *51*, 7777−7787. (e) Kim, K.-H.; Wissner, A.; Floyd, M. B. Jr.; Fraser, H. L.; Wang, Y. D.; Dushin, R. G.; Hu, Y.; Olland, A.; Guo, B.; Arndt, K. Benzo[*c*][2,7]naphthyridines as inhibitors of PDK-1. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 5225−5228.

(34) Flowers-Geary, L.; Harvey, R. G.; Penning, T. M. Cytotoxicity of polycyclic aromatic hydrocarbon *o*-quinones in rats and human hepatoma cells. *Chem. Res. Toxicol.* **1993**, *6*, 252−260.
(35) In a related system where the N(1) was substituted with a 2-hydroxy propyl group, removing the 7-methoxyl group resulted in 12-fold loss of potency relative to the 6.7-dimethoxyl analogue.
(36) Evans, D. C.; Watt, A. P.; Nicoll-Griffith, D. A.; Baillie, T. A. Drug−protein adducts: an industry prespective on minimizing the potential for drug bioactivation in drug discovery and development. *Chem. Res. Toxicol.* **2004**, *17*, 3−16.
(37) (a) Nelson, S. D. Metabolic activation and drug toxicity. *J. Med. Chem.* **1982**, *25*, 753−765. (b) This strategy was recently applied to an acylthiourea series: Kung, P.-P.; Funk, L.; Meng, J.; Alton, G.; Padrique, E.; Mroczkowski, B. Structure−activity relationships of quinoline-containing c-Met inhibitors. *Eur. J. Med. Chem.* **2008**, *43*, 1321−1329.
(38) Zhang, Y.; Kaplan-Lefko, P. J.; Rex, K.; Yang, Y.; Moriguchi, J.; Osgood, T.; Mattson, B.; Coxon, A.; Reese, M.; Kim, T.-S.; Lin, J.; Chen, A.; Burgess, T. L.; Dussault, I. Identification of a novel Recepteur d'Origine Nantais/c-Met small molecule kinase inhibitor with antitumor activity in vivo. *Cancer Res.* **2008**, *68*, 6680−6687.
(39) Part of the synthesis and characterization of compounds have been described in: Kim, T.-S.; Bauer, D.; Bellon, S.; Boezio, A.; Booker, S.; Choquette, D.; D'Amico, D. C.; D'Angelo, N.; Dominguez, C.; Fellows, I. M.; Germain, J.; Graceffa, R.; Harmange, J.-C.; Hirai, S.; La, D.; Lee, M.; Liu, L.; Norman, M. H.; Potashman, M.; Rovet, P.; Siegmund, A. C.; Xi, N.; Yang, K. (Amgen Inc) . Patent WO 2006/116713A1, 2006.
(40) Kubo, K.; Shimizu, T.; Ohyama, S.-I.; Murooka, H.; Iwai, A.; Nakamura, K.; Hasegawa, K.; Kobayashi, Y.; Takahashi, N.; Takahashi, K.; Kato, S.; Izawa, T.; Isoe, T. Novel potent orally active selective VEGFR-2 tyrosine kinase inhibitors: synthesis, structure−activity relationships, and antitumor activities of *N*-phenyl-*N*′-{4-(4-quinolyloxy)phenyl}ureas. *J. Med. Chem.* **2005**, *48*, 1359−1366.