Discovery of a Potent, Selective, and Orally Bioavailable c-Met Inhibitor: 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)

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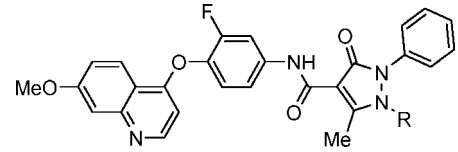
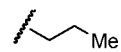
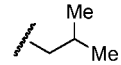
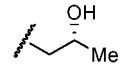
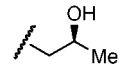
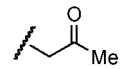
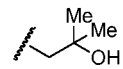
Abstract: Deregulation of the receptor tyrosine kinase c-Met has been implicated in human cancers. Pyrazolones with N-1 bearing a pendent hydroxyalkyl side chain showed selective inhibition of c-Met over VEGFR2. However, studies revealed the generation of active, nonselective metabolites. Blocking this metabolic hot spot led to the discovery of **17** (AMG 458). When dosed orally, **17** significantly inhibited tumor growth in the NIH3T3/TPR-Met and U-87 MG xenograft models with no adverse effect on body weight.

c-Met is a receptor tyrosine kinase that is activated by its ligand, hepatocyte growth factor/scatter factor (HGF/SF).[1] Upon activation, the intracellular C-terminal docking domain recruits and subsequently activates a wide range of downstream signaling molecules that contribute to the survival, proliferation, migration, and invasion of cells.[2] Transient activation of c-Met by HGF through a paracrine mechanism is important during embryogenesis and tissue repair. However, overexpression of HGF and/or c-Met or activating mutations of c-Met have been linked to human cancers.

Among various approaches that target the c-Met/HGF signaling pathway,[3] inhibiting the c-Met kinase activity with small molecules has the potential of blocking the ligand-dependent and ligand-independent activation of c-Met. Most studies involving c-Met inhibitors have been limited to in vitro experiments because of the poor pharmacokinetic properties of these agents.[4] Recently, a dual c-Met/ALK (anaplastic lymphoma kinase) inhibitor exhibited antitumor effects in xenograft models expressing activated c-Met.[5] Herein, we describe the discovery of a novel c-Met inhibitor that has on-target antitumor activity in xenograft models and exhibits favorable pharmacokinetic profiles in several animal species.[6]

Table 1. c-Met and VEGFR2 Activities of Substituted Pyrazolones



	R	c-Met Ki[a] (nM)	PC3 IC_{50}[b] (nM)	VEGFR2 Ki[a] (nM)	Huvec IC_{50}[c] (nM)
1		1.0	37	24	52
2		1.0	49	460	143
3		8.0	204	999	329
4		1.0	24	396	236
5		1.1	23	386	208
6		1.3	48	2	86
7		2.7	50	1160	921

[a] Inhibitory constant for the kinase activities (substrate: gastrin). [b] IC_{50} (ip) value for HGF-mediated c-Met phosphorylation in PC3 cells. [c] IC_{50} (ip) value for VEGFR2-mediated survival of human umbilical vein endothelial cells. See Table S1 for details.

During the course of searching for c-Met inhibitors, we established that strong c-Met inhibition could be achieved with pyrazolone **1** (Table 1).[7] Compound **1** was also a potent inhibitor of VEGFR2[a] with an affinity of 24 nM (K_i) and cellular potency of 52 nM (IC_{50} in Huvec). VEGFR2 is involved in tumor angiogensis that has been targeted with much success.[8] To specifically evaluate the effect of c-Met inhibiton on tumor growth, we sought to improve the selectivity of **1** against VEGFR2. Structural modifications revealed that replacing the methyl group at the N-1 position by a propyl group (**2**) significantly improved the selectivity, while branching of the *N*-propyl group (**3**) resulted in lower activity. However, introduction of a secondary hydroxyl group afforded similar enzymatic and cellular activities to **2**. In addition, good selectivity over VEGFR2 was maintained for both enantiomers (**4**, **5**). Encouraged by these results, along with the fact that **2** was prone to P450-mediated hydroxylations at the *N*-propyl side chain, we decided to evaluate these alcohols in vivo.

Both **4** and **5** were reasonably stable in human, rat, and mouse liver microsomes (Cl_{int}: HLM < 55, RLM < 60, MLM < 45 (μL/min)/mg). In rat, they exhibited low clearance (CL < 200 (mL/h)/kg; $t_{1/2}$ = 1.9−2.6 h) and good oral bioavailability (F > 50%). To assess the pharmacological activity of **4**, inhibition

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[a] Abbreviations: VEGFR2, vascular endothelial growth factor receptor 2; AUC, area under the curve; HATU, 2-(1*H*-7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate methanaminium.

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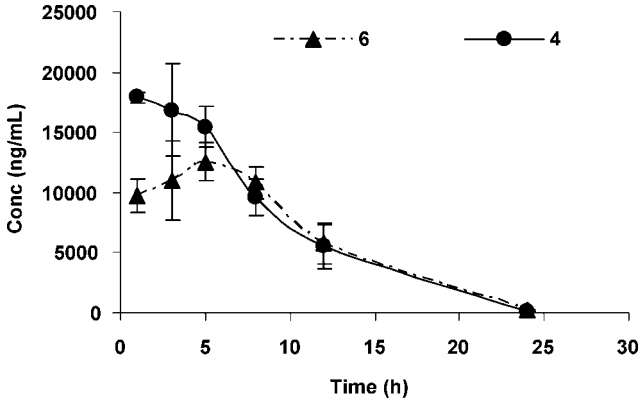
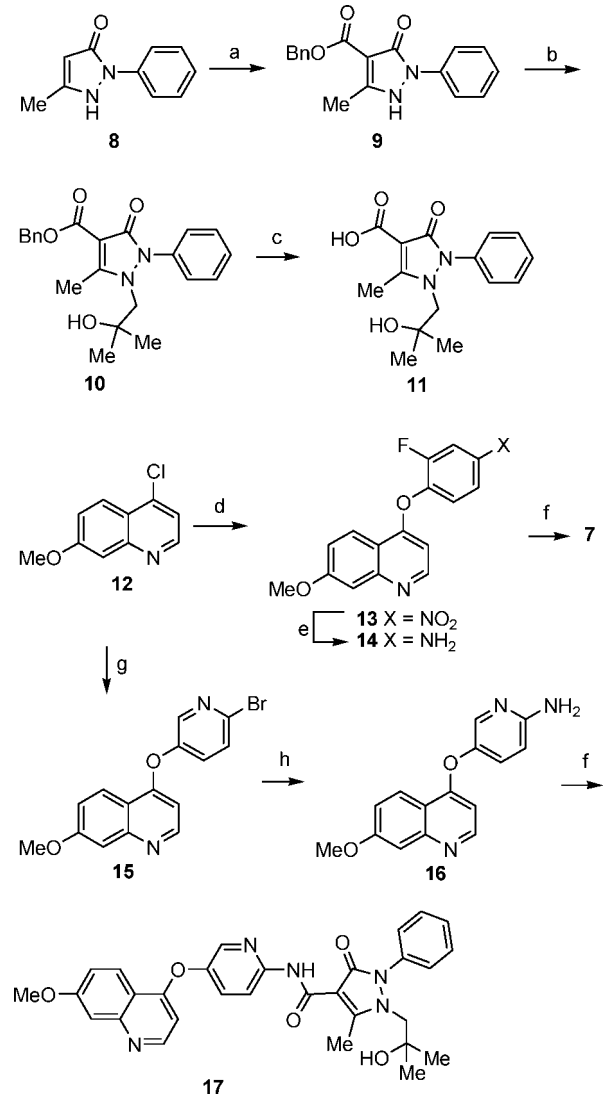


Figure 1. Concentration−time profiles of **4** and **6** in Balb/c mice following oral administration of **4** (30 mg/kg).

of HGF-mediated c-Met phosphorylation in the mouse liver was measured after oral administration. At 30 mg/kg, **4** inhibited HGF-mediated c-Met phosphorylation by 98% at 6 h postdose. However, detailed analysis of plasma samples from mice dosed with **4** revealed the presence of significant amounts of ketone **6**. As shown in Figure 1, **4** was rapidly converted to the corresponding ketone, resulting in similar overall exposure for the alcohol and the ketone [AUC(**6**)/AUC(**4**) = 0.87]. These findings immediately raised several concerns. (1) Ketone **6** is a potent c-Met inhibitor (K_i = 1.3 nM; IC_{50}(PC3) = 48 nM), and it would likely exhibit c-Met inhibition in vivo. Therefore, the presence of **6** would complicate the interpretation of the pharmacodynamic (vide supra) and any efficacy studies with **4**. (2) Ketone **6** is also a potent VEGFR2 inhibitor (K_i = 2; IC_{50}(Huvec) = 86 nM, Table 1). It is conceivable that this antiangiogenic activity would contribute to the tumor growth inhibition by **4** or **6** in future studies. For the purpose of evaluating the effect of c-Met inhibitors on tumor growth, we felt it would be desirable to test more selective compounds. (3) When incubated in liver microsomes, the oxidation of **4** to **6** proceeded with different rates across species: while ketone **6** was the major metabolite in rat and mouse liver microsomes, it was a minor metabolite in dog, monkey, and human liver microsomes. Such cross-species variation in the formation of an active metabolite such as **6** would render human dose predictions, based on mouse efficacy studies of **4**, difficult. The stereoisomer **5** did not provide any advantage, as it showed a metabolic profile similar to that of **4**, indicating that the extent of ketone formation was insensitive to the stereogenic nature of the hydroxyl group.

To circumvent the formation of ketone **6**, we decided to replace the secondary hydroxyl group in **4** or **5** with a tertiary hydroxyl group.[9] The synthesis of alcohol **7** is depicted in Scheme 1. The installation of the requisite methylhydroxyethyl group at the N-1 position of the pyrazolone was achieved using the recently described selective alkylation of pyrazolone **9** with oxiranes in the presence of Lewis acid catalysts.[10] Commercially available 5-methyl-2-phenyl-1,2-dihydropyrazol-3-one **8** was converted to benzyl ester **9** according to the procedure of Lopez et al.[11] Treatment of **9** with excess 1,1-dimethyloxirane in the presence of Me_3Al led to the formation of alcohol **10** that was converted to acid **11** in good overall yield. Concurrently, 7-methoxy-4-chloroquinoline **12**[12] was coupled with 2-fluoro-4-nitrophenol and the resulting aryl ether **13** was hydrogenated to give aniline **14**. Finally, amide coupling between **11** and **14** in the presence of HATU afforded the desired tertiary alcohol **7** (Scheme 1).

Scheme 1[a]



[a] Conditions: (a) $ClCO_2Bn$, $Ca(OH)_2$, dioxane, 79%; (b) 1,1-dimethyloxirane, $AlMe_3$, chlorobenzene, 42%; (c) H_2, Pd/C (10%), MeOH, 98%; (d) 2-fluoro-4-nitrophenol, chlorobenzene, 140 °C, 91%; (e) H_2, Pd/C (10%), EtOH, 57%; (f) **11**, HATU, (^{i}Pr$_2$)EtN, DMF, 60 °C, 68% (**7**), 70% (**17**); (g) 6-bromopyridin-3-ol, chlorobenzene, 97%; (h) $LiN(SiMe_3)_2$, $Pd_2(dba)_3$, 2-(dicyclohexylphosphino)biphenyl, dioxane, 65 °C, 78%.

Despite the low cellular activity of the isopropyl derivative **3**, the tertiary alcohol **7** inhibited c-Met phosphorylation in PC3 cells with an IC_{50} of 50 nM. Additionally, **7** was more selective against VEGFR2 when compared to **4** or **5** (Table 1). In our early SAR studies, we found that replacing the central fluorophenyl ring with a pyridyl ring could be advantageous.[7a] Such modification was expected to improve the physicochemical properties (predicted change of log *D* at pH 6.5 is from 4.4 to 3.0) and mitigate the potential side effects associated with quinone-imine formation.[13] Therefore, in a similar manner, quinoline **12** was converted to the biaryl ether **15**. Amination under Buchwald's conditions[14] led to **16**, which was then coupled with acid **11** to give **17** (Scheme 1). Compound **17** showed potent inhibition of c-Met at the enzyme and at the cellular levels (K_i = 1.2, IC_{50} = 60 nM; Table 2). Furthermore, it was active against several c-Met mutants that have been identified in cancer patients.[15] Compound **17** also showed greater selectivity against VEGFR2 than **7**. When tested against a panel

Table 2. Enzyme and Cell Activities of **17**

wild type and mutant enzymes (K_i, nM)[a]								cell (IC_{50}, nM)		
human c-Met	mouse c-Met	V1092I	D1228H	M1250T	H1094R	Y1230H	VEGFR2	PC3[b]	CT26[c]	Huvec[d]
1.2	2.0	1.1	2.2	4.1	0.5	4.5	4100	60	120	690

[a] Inhibitory constant for the kinase activities (substrate: gastrin, $n > 2$). [b] IC_{50} values for HGF-mediated c-Met phosphorylation in PC3 cells (human, $n > 4$). [c] IC_{50} values for HGF-mediated c-Met phosphorylation in CT26 cells (mouse, $n > 4$). [d] IC_{50} value for VEGFR2-mediated survival of human umbilical vein endothelial cells ($n > 2$).

Table 3. Preclinical Pharmacokinetic Properties of **17** in Animals[a]

	Balb/c mouse	SD rat	beagle dog	cynomolgus monkey
CL ((L/h)/kg)	0.16	0.73	0.34	0.10
V_{ss} (L/kg)	0.31	0.62	0.75	0.56
$t_{1/2}$ (h)	1.3	1.0	2.8	5.7
F (%)	100	100	100	78

[a] iv dose: 1 mg/kg (20% Captisol with pH adjusted to 3.5 using methanesulfonic acid). po dose: 10 mg/kg (2% HPMC and 1% Tween-80 with pH adjusted to 2.2 using HCl). Both were solution formulations with the same drug concentration of 1 mg/mL.

of 55 tyrosine and serine/threonine kinases, **17** was >100-fold selective over 98% and >1000-fold selective over 80% of the panel.[16]

The in vitro potency and selectivity of the pyridyl derivative **17** warranted further evaluation of its pharmacokinetic properties. Compound **17** was metabolically stable in the liver microsomes of mouse, rat, dog, monkey, and human with low intrinsic clearances (Cl_{int}: <5, 62, 8, 8, 18 (μL/min)/mg, respectively). The in vivo pharmacokinetic properties of **17** in several animal species are summarized in Table 3. Compound **17** exhibited low clearances in mouse, dog, and monkey, and low to moderate clearance in rat associated with low volume of distribution at steady state that was less than or close to the total body water of 0.6−0.8 L/kg in the animals tested. Although **17** was rapidly eliminated in mouse and rat with terminal half-lives of less than 2 h, a more sustained exposure was achieved in dog and monkey with half-life ranging from 3 to 6 h. When administered orally, **17** achieved remarkably high bioavailability in all species tested, in agreement with the observed in vitro low metabolic turnover and high permeability.[17]

As a potent inhibitor of mouse c-Met ($K_i = 2.0$, IC_{50}(CT26) = 120 nM; Table 2), **17** was evaluated in the mouse liver pharmacodynamic assay. Oral dosing of **17** inhibited HGF-mediated c-Met phosphorylation in a dose-dependent manner with an approximate ED_{90} of 30 mg/kg and an associated plasma exposure of approximately 15 μM at 6 h (Figure 2A). There was a clear correlation between the inhibition of liver c-Met phosphorylation and the plasma concentration of **17**.

The antitumor effect of **17** as a single agent was then examined in two xenograft models. It was first evaluated in the NIH-3T3/TPR-Met model that was derived from NIH3T3 cells transfected with human TPR-Met, a constitutively active, ligand-independent, oncogenic form of c-Met (TPR-Met).[18] In this model, tumor growth is specifically driven by c-Met activation that is independent of its ligand HGF/SF. When administered orally q.d. or b.i.d., **17** induced dose-dependent tumor growth inhibition with an ED_{50} of ~12 mg/kg and an ED_{90} of ~ 34 mg/kg (Figure 2B). Compound **17** was also evaluated in the U-87 MG human glioblastoma xenograft model in which c-Met is activated via its ligand HGF/SF through an autocrine loop.[19] In this model, oral dosing of **17** inhibited tumor growth with an ED_{50} of ~16 mg/kg and an ED_{90} of ~59 mg/kg (Figure 2C). In both ligand-dependent and independent xenograft models, **17** significantly inhibited tumor growth at 30 and 100 mg/kg q.d. and 30 mg/kg b.i.d. without adverse effect on body weight. These encouraging results combined with favorable pharmacokinetic profiles across species warranted advancement of **17** into preclinical safety studies.

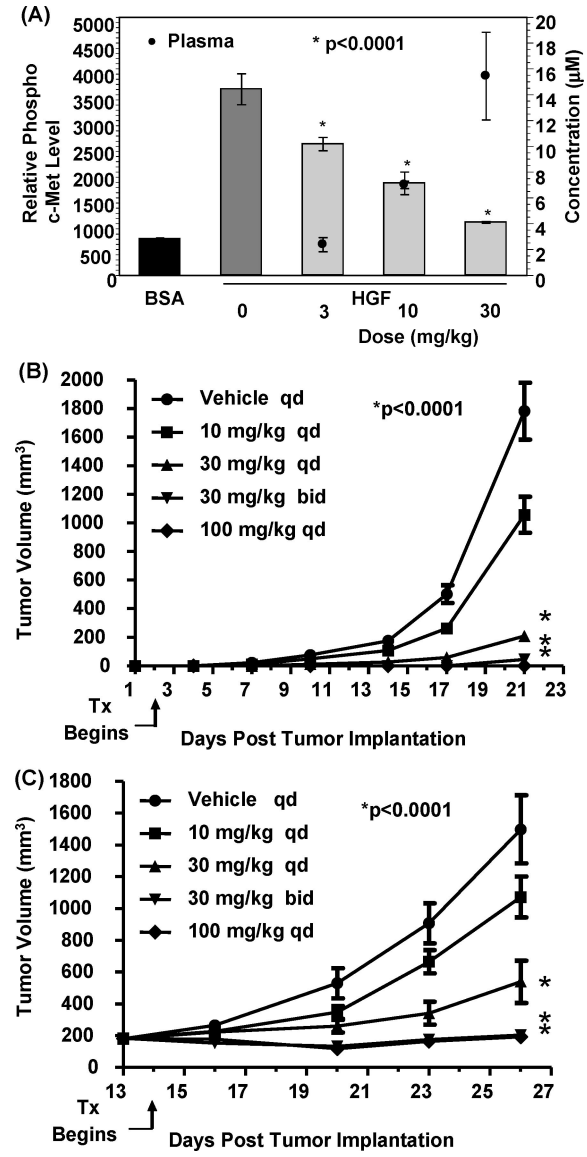


Figure 2. Pharmacology and efficacy studies of **17** administered orally. (A) Inhibition of HGF-mediated c-Met phosphorylation at 6 h in mouse (Balb/c) liver. Terminal plasma concentration of **17** is indicated by the black circles. (B) Tumor growth inhibition in the NIH-3T3/TPR-Met xenograft model in nude mice. The $AUC_{(0-24)}$ at ED_{50} and ED_{90} were 96 and 241 μM·h, respectively. (C) Tumor growth inhibition in the U-87 MG xenograft model in nude mice. The $AUC_{(0-24)}$ values at ED_{50} and ED_{90} were 130 and 482 μM·h, respectively. Arrow denotes the first day of dosing.

In conclusion, we identified *N*-(2-hydroxypropyl)pyrazolones (**4**, **5**) as selective c-Met inhibitors. However, the extensive in vitro and in vivo conversion to significantly less selective ketone **6** posed a potential obstacle in evaluating the selective antitumor effect of **4** and **5** as c-Met inhibitors. The ketone formation was circumvented by replacing the oxidation-prone 2-hydroxypropyl

group with a 2-hydroxy-2-methylpropyl chain. This led to potent, selective, and stable c-Met inhibitors culminating in the identification of **17** (AMG 458). The favorable profile of this molecule justified its safety evaluation in preclinical species as a potential clinical candidate for the treatment of human cancers.

Acknowledgment. We acknowledge Randall Hungate, Teresa Burgess, Angela Coxon, Richard Kendall, and Robert Radinsky for their guidance. We thank Daniel Retz and James Rider for providing compounds **3** and **5**, respectively.

Supporting Information Available: Analytical data and experimental protocols (PK, PD, xenograft, synthesis of **9**−**17**). This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) (a) The discovery and detailed SAR studies of **1** will be reported in a separate publication. *J. Med. Chem.*, to be submitted. (b) For the synthesis and nomenclature of the pyrazolone piece leading to **4** and **5**, see ref 10 (and ref 16 therein).

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(17) Compound **17** had an apparent permeability of 27×10^{-6} cm/s in wild-type LLC-PK1 cells and good permeability in Caco-2 monolayer in both directions (Papp(A-B): 32×10^{-6} cm/s; Papp(B-A)/Papp(A-B): 0.8.

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