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Letter

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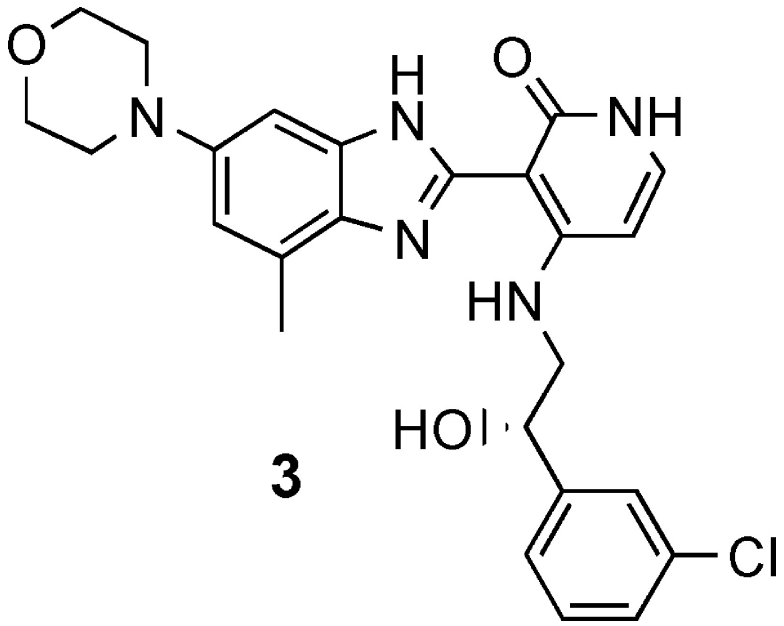

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Letters

Discovery of a 1*H*-Benzoimidazol-2-yl)-1*H*-pyridin-2-one (BMS-536924) Inhibitor of Insulin-like Growth Factor I Receptor Kinase with in Vivo Antitumor Activity

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Abstract: Compound **3** (BMS-536924), a novel small-molecule inhibitor of the insulin-like growth factor receptor kinase with equal potency against the insulin receptor is described. The in vitro and in vivo biological activity of this interesting compound is also reported.

Considerable attention has been focused on understanding the role of insulin-like growth factor I receptor (IGF-1R) signaling in stimulating mitogenesis, transformation to the oncogenic phenotype, and the anti-apoptotic effects observed in malignant cells.[1] Signaling through IGF-1R is initiated upon the binding of the IGF-I ligand to the receptor leading to receptor dimerization, autophosphorylation, and subsequent activation of the downstream substrates Shc, IRS-1, and IRS-2. Signaling through these molecules results in activation of the RAS/Raf/MAPK kinase pathway primarily responsible for mitogenesis and the antiapoptotic PI-3 kinase/Akt pathway.[2,3] The ability of IGF-1R signaling to affect these two major pathways in tumorigenesis has contributed to the wide interest in finding agents to block IGF-1R signaling. From a clinical perspective, epidemiological studies have correlated elevated IGF-I levels with increased risk of developing colon, breast, prostate, and lung tumors,[4−8] highlighting the importance of IGF-1R signaling.

A major challenge in developing small-molecule antagonists of IGF-1R is achieving selectivity over the closely related insulin receptor (IR), which regulates glucose homeostasis and the biosynthesis of glycogen and fat. IGF-1R and IR share an 84% sequence identity in the tyrosine kinase domain but are identical in the ATP-binding cleft and the residues that contact the peptide substrate in the substrate binding site. Sequence differences between IGF-1R and IR occur for the most part on the surface of the enzymes, but a subtle difference has been observed in the hinge region (Thr1053/Arg1054 in IGF-1R vs Ala1080/His1081 in IR).[9] Because of the high homology of the ATP binding site and the substrate binding site, a great deal of interest has been focused on the development of monoclonal antibodies[10] that selectively inhibit the binding of IGF-I/IGF-II to the ligand binding domain of the receptor. Recently, small-molecule pyrrolopyrimidine[11] based antagonists of IGF-1R have been disclosed. These compounds, while lacking in vitro kinase selectivity between IGF-1R and IR, are reported to demonstrate selectivity in a cellular context. In addition to pyrrolopyrimidine inhibitors, selected tryphostin analogues[12] and picropodophyllin[13] have also been reported to have selective IGF-1R inhibitory activity.

Despite the selectivity challenges and encouraged by the growing clinical importance of IGF-1R signaling in tumorigenesis, a research program was initiated to identify small-molecule inhibitors of IGF-1R kinase.

The initial screening effort identified benzimidazole **1** as an ATP-competitive inhibitor of the IGF-1R kinase ($IC_{50} = 3.5\ \mu M$). Cocrystallization of **1** with a truncated IGF-1R containing the kinase domain confirmed that the inhibitor bound in the ATP binding site. A key feature of the binding is the hydrogen bond donor/acceptor/donor triad formed between **1** and Met123 and Glu121. Guided by the crystallographic information (Figure 1), the benzimidazole methyl group and the pyridone ring were explored as potential handles to improve the potency of this chemotype against IGF-1R.

Examination of the binding interactions in the complex of **1** with IGF-1R indicates that substitution of the methyl group or the pyridone ring of **1** would allow access to the open ribose binding pocket. Attempts to

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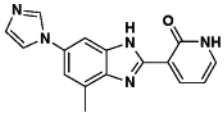

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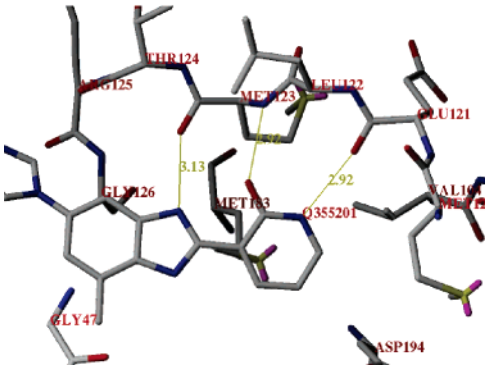
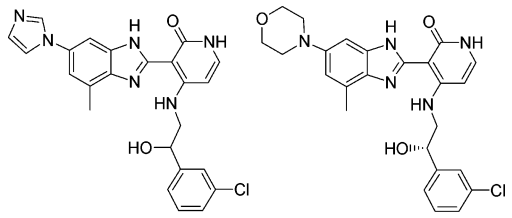


Figure 1. A 1.7 Å resolution X-ray structure of **1** with IGF-1R.

Table 1. In Vitro Profile for Compounds **2** and **3**



2 3

	IC$_{50}$ (μm)	
	2	**3**
IGF-1R	0.180	0.100
CYP1A2	<0.018	34[a]
CYP2C9	<0.018	1.2[a]
CYP2C19	0.026	2.0[a]
CYP2D6	*b*	>40[a]
CYP3A4-BFC	<0.018	0.5[a]
CYP3A4-BzRes	<0.018	5.3

[a] IC$_{50}$ values represent an average of 10 determinations. [b] A value could not be determined because of UV interference.

substitute the methyl group did not improve kinase potency, so attention was redirected toward the pyridone ring. The description of 2-methoxy-3-formyl-4-iodopyridine by Fang et al.[14] suggested that a 4-iodopyridone would provide a useful intermediate for exploring SAR at the 4-position. Using a 1,4 addition/elimination reaction, a structurally diverse set of 4-amino analogues were prepared. Potency improvements were realized for C-4 primary amines with a one or two carbon tether to an aromatic ring system. Additionally, incorporation of a hydroxyl group in the tether improved the in vitro kinase and cell potency. Further refinement with various substituted 2-amino-1-phenylethanols led to the identification of racemate **2** with an IC$_{50}$ of 180 nM for IGF-1R.

The cytochrome P450 inhibition (Cyp) profile of **2** is shown in Table 1. While Cyp inhibition is anticipated for a compound with a pendent imidazole ring, the potency exhibited across all the isozymes is surprising. Replacement of the imidazole ring with various imidazole isosteres was examined. Amidines, imidazolines,

Table 2. Kinase Selectivity and Cellular Activity of **3**

	IC$_{50}$ [a] (nM)
IGF-1R	100
IR	73
FAK	150
Lck	341
CDK2/cyclic E[b]	>1000
Akt1[b]	>5000
MAPK1[b]	>5000
MAPK2[b]	~5000
EGF	1600
Her2	17100
Mek	182
Met	4870
PDGFR[b]	>5000
VEGFR2	1400
IGF-1R Sal[16]	110
RD1(rhabdomyosarcoma)	202
MDA PCa-2b (prostate)	194
Colo205 (colon)	212
Geo (colon)	320
MCF-7 (breast)	460

[a] IC$_{50}$ values were determined with ATP concentration at $^1/_2K_m$ for each kinase. [b] Values were determined from % inhibition at 1 or 5 μM.

and saturated and unsaturated heterocycles were prepared and profiled for kinase and cell potency, CYP inhibition, and oral exposure. The morpholine group represents the optimal balance between P450 inhibition, in vitro potency, and oral exposure.[15] Introduction of the morpholine ring coupled with resolution of the hydroxyl group enantiomers provided (*S*)-**3** (BMS-536924). The difference in potency between the enantiomers was about 8-fold ((*S*)-**3**, 100 nM; (*R*)-**3**, 830nM).

The in vitro kinase selectivity and cellular activity for **3** is presented in Table 2. Cross-reactivity is observed for the insulin receptor with modest activity noted for Mek, Fak, and Lck with very little activity for Akt1, MAPK1/2.

The cellular activity of **3** was investigated using the IGR-1R Sal cell line. This cell line is derived from salivary tumors that develop in transgenic mice that overexpress an IGF-1R/CD8 construct under the MMTV promoter.[16] Passage of the salivary tumor in nude mice provided an IGF-1R driven in vivo model. The CD-8 fusion renders this cell line with a constitutively activated form of the IGF-1R kinase. Compound **3** effectively inhibits proliferation of this cell line in vitro and disrupts Akt and MAPK phosphorylation. Compound **3** blocks cellular proliferation in prostate, breast, and colon tumor cell lines (Table 2) for which there is ample evidence of the involvement of IGF-1R signaling in vitro, in vivo, and clinically.[4−7] Potency against a rhabdomyosarcoma line (RD1) is noteworthy because signaling of IGF-II through the IGF-1R in rhabdomyosarcoma has been shown to be a significant factor driving proliferation and metastasis in this tumor type.[17] The inhibition of Akt phosphorylation strongly correlates with the inhibition of cell growth in vitro and activity in vivo. In contrast, inhibition of MAPK phosphorylation did not correlate with cellular potency in vitro or activity in vivo, suggesting that the antiproliferative activity of **3** is consistent with inhibition of IGF-1R primarily through the antiapoptotic Akt pathway.[18]

With in vitro activity consistent with IGF-1R inhibi-

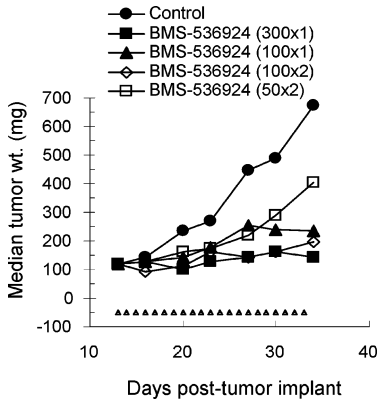
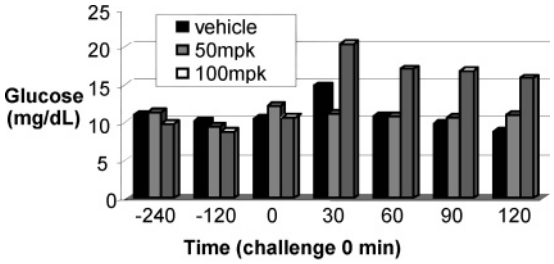


Figure 2. Efficacy of **3** in Colo205 (human colon carcinoma).



Insulin Levels 2h post glucose challenge	
Vehicle control	0.3 +/- 0.2ng/mL
50mpk	2.0 +/- 1.0ng/mL
100mpk	10.7 +/-5.2ng/mL

Figure 3. OGTT results following 21 days of dosing. Final dose of **3** was given on day 21 of the Colo205 efficacy experiment, and glucose levels (ng/mL) were measured for 2 h (240, 120, and 0 min). A glucose bolus was given at $t = 0$, and glucose levels (mg/dL) were measured every 30 min.

tion and favorable oral exposure, the in vivo activity of **3** could be investigated. Beginning with the constitutively activated IGR-1R Sal tumor model described previously, strong in vivo activity could be demonstrated following oral administration of 100−300 mpk once a day for 14 days.[16] Efficacy is also observed in the nonengineered Colo205 human colon carcinoma model (Figure 2). Oral administration of **3** on a once a day schedule (100−300 mpk) or a twice a day schedule (50, 100 mpk) demonstrated antitumor activity in this tumor model.

Table 3. Pharmacokinetics Parameters for **3** in Multiple Species[a]

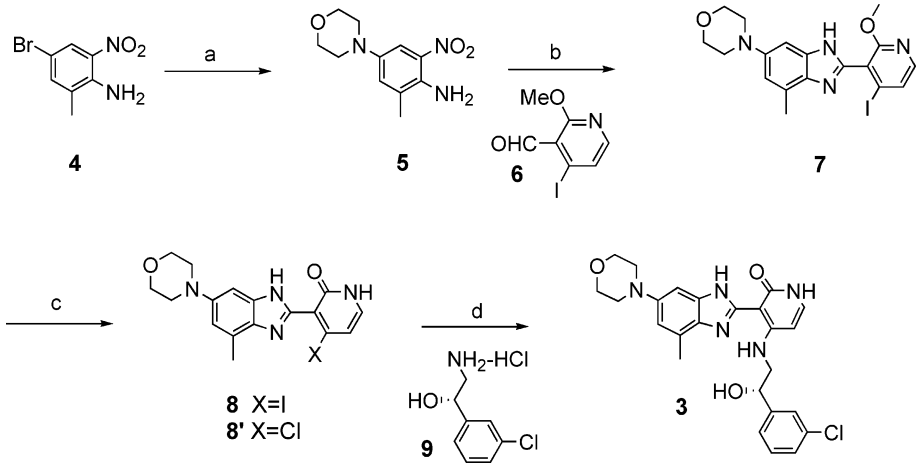
	mouse	rat
iv/po dose (mg kg^{-1})	4/20	4/50
F_{po} (%)	50	>100
$C_{max,po}$ (μM)	3.8	69
CL_{tot} (mL min^{-1} kg^{-1})	37.8	5.8
V_{ss} (L kg^{-1})	1.9	0.8
	dog	**monkey**
iv/po dose (mg kg^{-1})	2/5	2/5
F_{po} (%)	70	32
$C_{max,po}$ (μM)	4.1	1.3
CL_{tot} (mL min^{-1} kg^{-1})	4.1	16.5
V_{ss} (L kg^{-1})	1.3	1.4

[a] Administered as a solution in PEG400/water (80:20 v/v).

With in vivo activity demonstrated for **3**, the potential disruption of glucose homeostasis by **3** arising from inhibition of the IR could be evaluated in an in vivo context. An oral glucose tolerance test (OGTT) was performed following 21 days of dosing in the Colo205 efficacy experiment (Figure 3). The active doses of 50 and 100 mpk (b.i.d.) did not cause a significant elevation in glucose levels prior to glucose challenge. However, after glucose challenge a significant elevation in glucose levels is observed at the 100 mpk dose. While there is no IGF-1R/IR selectivity in the in vitro kinase assay, there is a 2-fold window between antitumor efficacy and glucose elevation observed in vivo. Insulin levels 2 h after glucose challenge did show a dose-dependent increase over vehicle control. While it would appear that the hyperglycemia and hyperinsulinemia observed are a direct result of IR inhibition, the role of Akt inhibition cannot be dismissed because Akt-2 knockout animals show similar effects on glucose and insulin levels.[19]

The pharmacokinetic parameters of **3**, administered orally in poly(ethylene glycol) 400 and water (80:20 v/v), were determined in mouse, rat, dog, and monkey (Table 3). Good bioavailability is evident in all species. Significant nonlinear pharmacokinetics is observed in rodents at increasing po dose (greater than dose pro-

Scheme 1[a]



[a] (a) Morpholine, 2.5% $Pd_2(dba)_3$, 5% 2-[(*t*-$C_4H_9)_2$P]biphenyl, NaO*t*-Bu, THF, reflux (61%); (b) $Pd(OH)_2C$, MeOH, 60 psi of H_2; **6**, MeOH (63%); (c) 4 N HCl, dioxane (quantitative); (d) **9**, Et_3N, CH_3CN, 85 °C (75%).

portional increases in AUC). Greater than 100% bioavailability at higher po doses suggests that **3** can saturate clearance (elimination) pathways. The total body clearance is moderate in mouse and monkey and low in rat and dog with moderate to high tissue distribution in all species. Compound **3** was administered to bile duct cannulated rats (10 mpk, iv, in PEG400 and water 80:20 by volume). Less than 5% of the parent drug is eliminated in bile and urine, with the major metabolites being associated with oxidation and cleavage of the morpholine ring. Compound **3** is highly protein bound (>99% in mouse and human plasma).

Compound **3** is prepared starting from the commercially available nitroaniline **4** (Scheme 1). Palladium-catalyzed amination of **4** with morpholine[20] provides nitroaniline **5**. Reduction to the diamine followed directly by addition of aldehyde **6**[14] gives the desired benzimidazole **7** without the need for the addition of oxidant. There was no obvious benefit in yield when oxidants such as iodine are added. Cleavage of the methoxy group of **7** occurs smoothly under acidic conditions to provide the 4-iodopyridone **8** along with varying amounts of the 4-chloropyridone **8′**. The 4-chloropyridones and 4-iodopyridones participate in the addition/elimination reaction with various amines including the chiral amino alcohol **9**. Amino alcohol **9** is prepared from the known α-chloroketone[21] using a chiral oxazaborolidine[22] catalyzed reduction followed by stirring in 7 M ammonia/methanol solution. The resulting hydrochloride can then be crystallized to high enantiomeric purity. Compound **3** is then converted to the mono-HCl salt for biological and pharmacokinetics evaluation.

The discovery of BMS-536924 (**3**) represents a novel class of IGF-1R inhibitor with cellular and in vivo activity. This compound represents a useful tool for further understanding of the biological effects of IGF-1R inhibition.

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Supporting Information Available: Experimental details and analytical data for **3** and **5**−**9**. This material is available free of charge via the Internet at http://pubs.acs.org.

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