

**Discovery and Evaluation of 4-(2-(4-chloro-1H-pyrazol-1-yl)ethylamino)-3-(6-(1-(3-fluoropropyl)piperidin-4-yl)-4-methyl-1H-benzo[d]imidazol-2-yl)pyridin-2(1H)-one (BMS-695735), an Orally Efficacious Inhibitor of Insulin-like Growth Factor-1 Receptor Kinase with Broad Spectrum in Vivo Antitumor Activity**

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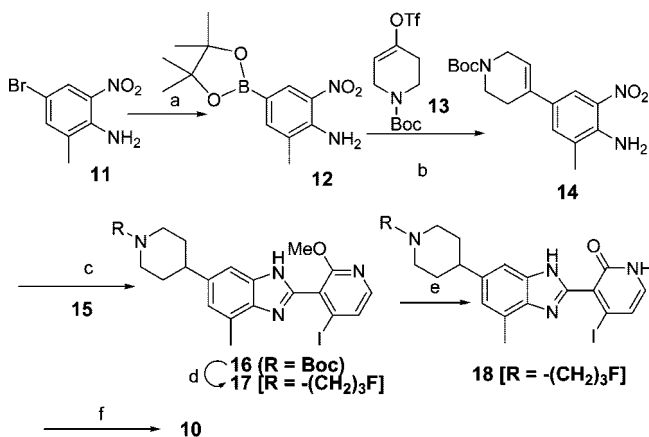
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**Abstract:** We previously reported that **1** (BMS-536924), a benzimidazole inhibitor of the insulin-like growth factor-1 receptor, had demonstrated in vivo antitumor activity. This lead compound was found to have potent CYP3A4 inhibition, CYP3A4 induction mediated by PXR transactivation, poor aqueous solubility, and high plasma protein binding. Herein we disclose the evolution of this chemotype to address these issues. This effort led to **10** (BMS-695735), which exhibits improved ADME properties, a low risk for drug–drug interactions, and in vivo efficacy in multiple xenograft models.

Receptor tyrosine kinases (RTKs) play a central role in signal transduction of cellular functions and aberration of this signaling contributes to a wide range of diseases.<sup>1</sup> Recent success with inhibiting these RTKs by small molecules has generated considerable interest in the search for additional RTKs for targeted therapeutic intervention.<sup>2</sup> The insulin-like growth factor-1 receptor (IGF-1R) belongs to the super family of RTKs and has been implicated in the pathophysiology of a several human neoplasms.<sup>3</sup> The insulin-like growth factor (IGF) family consists of two ligands (IGF-I and IGF-II), two receptors (IGF-1R and IGF-1IR), six high-affinity binding proteins (IGFBP 1–6), which serve to modulate effective serum concentration of IGF-1, and several IGFBP-related proteins. IGF-1 mediates cell signaling through the IGF-1R, which upon binding undergoes conformational changes resulting in the activation of intrinsic tyrosine kinase domain and subsequent multisite

**Scheme 1.** Synthesis of Compound **10**<sup>a</sup>



<sup>a</sup> Reagents and conditions: (a) bis(pinacolato)diborane, PdCl<sub>2</sub>(dppf)<sub>2</sub>, KOAc, DMSO; (b) **13**, Pd(PPh<sub>3</sub>)<sub>4</sub>, LiCl, Na<sub>2</sub>CO<sub>3</sub>, DME; (c) 10% Pd–C/MeOH H<sub>2</sub>, 4-iodo-2-methoxynicotinaldehyde (**15**)/MeOH; (d) TFA, CH<sub>2</sub>Cl<sub>2</sub>, 3-fluoropropylbromide; (e) 4NHCl/dioxane; (f) 2-(4-chloro-1H-pyrazol-1-yl)ethanamine, Et<sub>3</sub>N/CH<sub>3</sub>CN/85 °C.

autophosphorylation. This phosphorylation step further activates two distinct signaling pathways, namely the Ras/Raf/MEK/ERK and PI3/Akt/mTOR pathways.<sup>4</sup> These downstream pathways synergize to promote cellular proliferation, inhibit apoptosis, and increase cell survival. Overexpression and overactivation of IGF-1 and IGF-1R have been demonstrated in a variety of tumors, including glioma, lung, ovary, and breast carcinomas and sarcomas.<sup>5</sup> Down regulation of IGF-1R function by strategies such as antisense,<sup>6</sup> antibody,<sup>7</sup> and dominant negative mutant<sup>8</sup> approaches was found to interfere with cell growth and proliferation. Additionally, epidemiological studies have also highlighted the importance of IGF-1R in key tumor types by correlating elevated IGF-1 levels with increased risk of developing colon, breast, prostate, and lung tumors.<sup>9</sup> As a consequence, the identification of IGF-1R inhibitors has recently attracted considerable attention for cancer therapy and several classes of inhibitors have been described.<sup>10–17</sup> While several monoclonal antibodies have entered clinical trials, many small molecule inhibitors are still currently being investigated in the preclinical stages.<sup>18</sup>

We have recently reported a small molecule IGF-1R inhibitor **1** (BMS-536924),<sup>10</sup> which demonstrated in vivo efficacy in the IGF-Sal tumor model and xenograft models. Despite its utility as a useful tool compound, the potential to cause drug–drug interactions was considered problematic. Compound **1** exhibited potent inhibition (<1 μM) against cytochrome P450 3A4 (CYP3A4) and more moderate inhibition against other isozymes (Table 5). In a medium-throughput time-dependent inhibition (TDI) assay using recombinant CYP3A4, compound **1** caused a 6-fold decrease in IC<sub>50</sub> between 5 and 45 min of incubation. Subsequent studies in human liver microsomes showed that compound **1** inhibited CYP3A4 in a metabolism-dependent manner. Together, these results suggest that **1** has the potential to interfere with the metabolism of other drugs predominately metabolized by CYP3A4. Furthermore, compound **1** was found to be a potent transactivator of the pregnane-X-receptor (PXR) (125% of rifampicin at 10 μM). PXR is a xenobiotic nuclear hormone receptor and its activation has been implicated in the induction of CYP3A4, which could potentially result in reduced efficacy of the drug (autoinduction) or concomitantly admin-

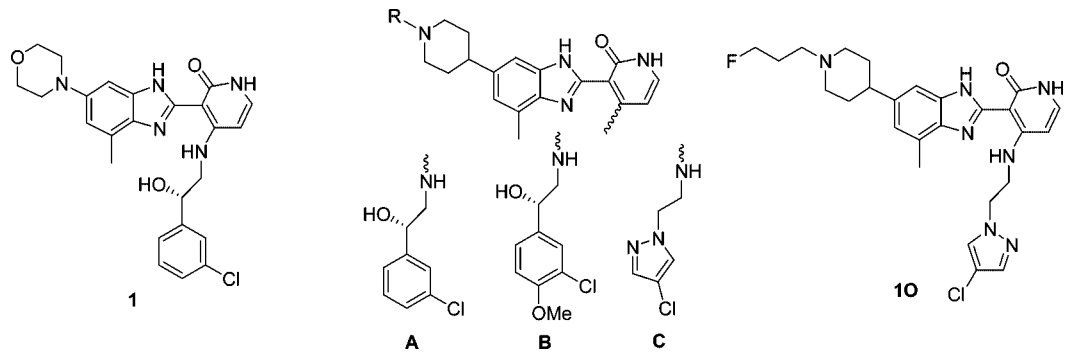
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**Table 1.** Profile of Carbon attached Piperidine Series


compd	R	side chain	IGF-1R IC <sub>50</sub> (μM) <sup>a</sup>	IGF-Sal IC <sub>50</sub> (μM) <sup>b</sup>	CYP3A4 IC <sub>50</sub> (μM) <sup>c</sup>	PXR EC <sub>20</sub> (μM) <sup>d</sup>	AUC (μM·h) <sup>e</sup>	PPB (%) <sup>f</sup>	pK <sub>a</sub> <sup>g</sup>
<b>1</b>			0.100	0.110	0.05	1.1	50.0	99.9	
<b>2</b>	CH <sub>3</sub>	A	0.022	0.085	14.0	>50	1.2		9.4
<b>3</b>	CH <sub>2</sub> CH <sub>2</sub> OMe	A	0.018	0.217	11.0	>50	0.0		8.56
<b>4</b>	CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> F	A	0.031	0.076	28.0	>50	0.0		8.87
<b>5</b>	CH <sub>2</sub> CH <sub>2</sub> OMe	B	0.023	0.013	7.7	>50	0.49		8.56
<b>6</b>	CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> F	B	0.020	0.040	10.0	>50	0.28		8.87
<b>7</b>	CH <sub>3</sub>	C	0.026	0.162	40.0	>50	0.4		9.43
<b>8</b>	CH <sub>2</sub> CH <sub>2</sub> OH	C	0.025	0.241	23.0	>50	0.1		8.56
<b>9</b>	CH <sub>2</sub> CH <sub>2</sub> OMe	C	0.018	0.046	19.5	>50	1.8	96.2	8.56
<b>10</b>	CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> F	C	0.034	0.185	26.0	>50	3.7	86.9	8.87

<sup>a</sup> Values are reported as the mean of at least two individual determinations, in duplicate; standard deviations ranged from 0.001 to 0.13. <sup>b</sup> This cell line is derived from salivary tumors that develop in transgenic mice.<sup>20</sup> <sup>c</sup> Values are determined for inhibition of dealkylation of BFC (7-benzoxo-4-trifluoromethylcoumarin). <sup>d</sup> Compounds are tested at ten concentrations (50 μM to 2.5 nM, 1:3 serial dilution), and concentrations of compound at which a 20% activation (EC<sub>20</sub>) occur are reported when rifampicin is used as a positive control. <sup>e</sup> Compounds are evaluated in 4 h exposure studies in mice at 20 mg/kg and formulated as solutions of 80:20 PEG400 and water. <sup>f</sup> PPB in mouse was determined at 10 μM using equilibrium dialysis. <sup>g</sup> pK<sub>a</sub> values are calculated using ACDlabs software.

istered drugs as well as enhanced metabolism-dependent toxicity.<sup>19</sup> The degree of transactivation noted for **1** was significant and similar to that found for the positive control rifampicin, which is known to cause clinically significant drug–drug interactions due to induction of CYP3A4. In a follow-up study in primary human hepatocytes, compound **1** increased CYP3A4 mRNA expression levels as determined by real time-PCR in a dose-dependent manner. Thus, compound **1**, being both an inhibitor (reversible and time-dependent) and an inducer of CYP3A4, was deemed unsuitable for development due to uncertain clinical outcome. Additional drawbacks of compound **1** included its poor aqueous solubility (<1 μg/mL) and high plasma protein binding (>99.8% for human and >99.9% for mouse).

To improve ADME<sup>a</sup> properties, including CYP 3A4 induction and inhibition so as to minimize clinical drug–drug interactions, we further explored the series and undertook a systematic survey of structure–activity relationship (SAR) studies. In particular, we investigated morpholine replacements on the top left-hand side and phenethylamine side chain on the bottom right-hand side of compound **1**. Herein we describe the optimization of these regions, leading to the discovery of **10** (BMS-695735)<sup>21</sup> as an orally efficacious antitumor agent devoid of PXR transactivation and CYP3A4 inhibition.

The synthesis of compound **10** began with the commercially available bromonitroaniline **11**, which was subjected to palladium mediated boronation. The resultant pinacol boronate ester **12** was subjected to Suzuki reaction with piperidine enol triflate **13** to yield the coupled product **14**. Hydrogenation of **14** and subsequent condensation with the aldehyde **15** furnished the

benzimidazole **16**. Deprotection of the Boc group followed by alkylation gave fluoropropyl piperidine **17**. Methoxy cleavage and incorporation of amino pyrazole provided compound **10**.

The lead optimization was facilitated by cocrystallization of several inhibitors from this benzimidazole scaffold bound to the truncated IGF-1R, which revealed that the morpholine group in **1** is solvent exposed and therefore could be replaced with other groups to optimize PK properties and reduce CYP inhibition without affecting IGF-1R potency.<sup>14</sup> Appending various substituted morpholines in general did not improve CYP3A4 inhibition and/or PXR transactivation. Replacing the morpholine with its isosteres such as piperazines and 4-amino piperidines and attenuating the basicity of the distal nitrogen with various groups did not yield an optimal compound that balanced CYP3A4 inhibition, PXR transactivation, and oral exposure. However, a significant improvement was observed in both CYP3A4 inhibition and PXR transactivation when a C-4 connected piperidine was appended on the benzimidazole core in place of morpholine (Table 1). Removal of nitrogen atom that connected the heterocycle to the benzimidazole core and replacing it with a carbon appeared to have diminished the affinity for CYP3A4. This modification also eradicated the PXR transactivation associated with **1**. This was a significant development that could not have been predicted given the paucity of SAR information related to PXR transactivation in the literature.<sup>19b</sup>

As shown in Table 1, this new carbon linked series showed consistently improved CYP3A4 inhibition and PXR transactivation. Electron withdrawing groups on the terminal piperidine nitrogen such as amides, carbamates, and sulfonamides reduced both enzyme and cell potencies (data not shown). Small alkyl groups on the piperidine provided compounds with good enzyme and cellular potencies. However, oral exposure was almost negligible in the compounds with the phenethylamine side chain (side chain A; compounds **2–4**). Placing a methoxy group at

<sup>a</sup> Abbreviations: ADME, Absorption, Distribution, Metabolism and Excretion; PPB, Plasma Protein Binding; MTD, Maximum tolerated dose; IV, intravenous; PO, per os (oral); F<sub>po</sub>, oral bioavailability; C<sub>max</sub>, maximum concentration; CL<sub>tot</sub>, total clearance; V<sub>ss</sub>, Steady-state volume of distribution; T<sub>1/2</sub>, Elimination half-life.

**Table 2.** Pharmacokinetic Parameters for **10** in Multiple Species<sup>a</sup>

	mouse	rat
IV/PO dose (mg/kg)	5/50	2/10
$F_{po}$ (%)	>100	23
$C_{max, po}$ ( $\mu$ M)	2.3	0.20 $\pm$ 0.10
$CL_{tot}$ (mL/min/kg)	159	76 $\pm$ 23
$V_{ss}$ (L/kg)	18.2	20 $\pm$ 8.8
$T_{1/2}$ (h)	2.3	4 $\pm$ 2.4
	dog	monkey
IV/PO dose (mg/kg)	2/10	2/10
$F_{po}$ (%)	35	48
$C_{max, po}$ ( $\mu$ M)	0.27 $\pm$ 0.15	0.4 $\pm$ 0.010
$CL_{tot}$ (mL/min/kg)	23 $\pm$ 2.5	27 $\pm$ 3.3
$V_{ss}$ (L/kg)	21 $\pm$ 5.6	17 $\pm$ 4.9
$T_{1/2}$ (h)	10.5 $\pm$ 1.9	7.3 $\pm$ 1.1

<sup>a</sup> Administered as a solution in PEG400/water (80:20 v/v).**Table 3.** Kinase Selectivity Profile of **10**

kinases	<sup>a</sup> IC <sub>50</sub> ( $\mu$ M)	kinases	<sup>a</sup> IC <sub>50</sub> ( $\mu$ M)
IGF-1R	0.034	P38	30.97
IR	0.072	MK2	>50
FAK	0.165	KDR	0.369
PKC- $\alpha$	11.00	FGFR1	<5
PKC- $\delta$	20.3	HER1	21
PKA-B	37.68	HER2	6
CDK2	59.07	Met	3.99
IKK	>100	GSK3	8.56
Lck	0.14	PDE4	4
Akt	48.39	Emt	0.37

<sup>a</sup> IC<sub>50</sub> were determined with ATP concentration at 1/2 K<sub>m</sub> for each kinase.

the *para* position on the side chain (side chain **B**) improved enzyme and cellular potencies, but oral exposure still remained low. After extensive investigation, molecules with chloropyrazole (side chain **C**) generally showed reduced plasma protein binding along with some improvement in oral exposure.<sup>22</sup> Attenuating the basicity of piperidine nitrogen gave compounds (**9** and **10**) with modest oral exposure, reduced plasma protein binding, and good enzyme potency in the biochemical assay. Thus, these two compounds were evaluated in full pharmacokinetic (PK) experiments, with compound **10** showing favorable oral bioavailability (>100% for mice and 23% for rats) compared to **9** (10.3% for mice and 2.9% for rats).

Encouraged by the superior oral bioavailability and reduced plasma protein binding (13.1% free fraction), compound **10** was selected for further pharmacokinetic characterization in multiple species, kinase selectivity, and in vivo efficacy studies. The pharmacokinetic parameters obtained for **10** in multiple species are summarized in Table 2. In a mouse pharmacokinetic study, compound **10** was characterized as having a high volume of distribution ( $V_{ss}$  = 18.2 L/kg), excellent bioavailability (132% at 50 mg/kg), high clearance (159 mL/min/kg), and a flat, extended absorption phase out to 6 h. A nonlinear increase in exposure was noted with this compound.

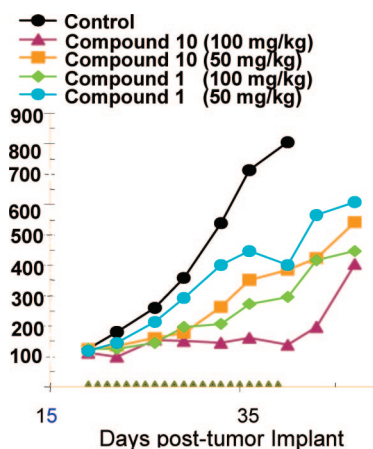
To better understand the kinase selectivity of **10**, the compound was evaluated against an in-house kinase panel and was also confirmed to be an ATP-competitive inhibitor. As illustrated in Table 3, compound **10** was found to be a potent inhibitor of IGF-1R and IR.<sup>23</sup> It also showed a moderate activity against FAK, Lck, and Emt. A greater than 100-fold selectivity was observed for all other receptor and nonreceptor kinase targets found in the panel. To assess ramifications of cross reactivity against T cell kinases such as Lck and Emt, an in vivo MLR (mixed lymphocyte reaction) study was conducted at 50 and 100 mg/kg and **10** was found to have no effect on CD4 T cell proliferation.

**Table 4.** In Vivo Antitumor Activity of **10** against Tumor Xenografts Implanted Subcutaneously in Athymic Mice

tumor model	dose (mg/kg)	schedule	<sup>a</sup> TGI (%)
IGF-Sal	50	BID $\times$ 5	81
Colo205	100	BID $\times$ 21	93
JJN3	100	BID $\times$ 21	80
Geo	100	BID $\times$ 21	73

<sup>a</sup> Percent tumor growth inhibition determined at the end of treatment (IGF-Sal) or averaged over at least one tumor volume doubling time during a prolonged dosing regimen. Values >50% is considered an active result.**Table 5.** In Vitro Profile for Compounds **1** and **10**

	<b>1</b>	<b>10</b>
IGF-1R <sup>a</sup> IC <sub>50</sub> ( $\mu$ M)	0.100	0.034
CYP1A2 <sup>a</sup> IC <sub>50</sub> ( $\mu$ M)	34 <sup>a</sup>	>40
CYP2C9 <sup>a</sup> IC <sub>50</sub> ( $\mu$ M)	1.2 <sup>a</sup>	>40
CYP2C19 <sup>a</sup> IC <sub>50</sub> ( $\mu$ M)	2.0 <sup>a</sup>	34
CYP2D6 <sup>a</sup> IC <sub>50</sub> ( $\mu$ M)	>40 <sup>a</sup>	>40
CYP3A4-BFC <sup>a</sup> IC <sub>50</sub> ( $\mu$ M)	0.5 <sup>a</sup>	26
CYP3A4-BzRes <sup>a</sup> IC <sub>50</sub> ( $\mu$ M)	5.3	ND
Caco (nm/s)	18	109
solubility ( $\mu$ g/mL)	<1	137
plasma protein binding (m,%)	>99.9	86.9

<sup>a</sup> Values represent an average of 10 determinations.**Figure 1.** Efficacy of **1** and **10** in Colo205 (human colon carcinoma, BID  $\times$  21).

The encouraging pharmacokinetic profile exhibited by **10** supported further characterization of the compound in in vivo efficacy studies. Compound **10** was evaluated in vivo in the constitutively activated IGF-Sal tumor model<sup>20</sup> and found to be active when administered orally at 50 mg/kg twice a day for 4 days. Compound **10** was also found to have activity against several human tumor xenografts grown in nude mice including Colo205 colon carcinoma (Figure 1), Geo colon carcinoma, and JJN3 multiple myeloma models. Figure 1 illustrates a comparison of dose-dependent growth inhibition of **10** and **1** in the Colo205 tumor model. Oral administration of **10** on a twice a day schedule of either 50 or 100 mg/kg for 21 days demonstrated antitumor activity, with the activity at 100 mg/kg superior to that of our prototypical lead **1** dosed at MTD. As a single agent, both of these IGF-1R inhibitors reduced the rate of tumor growth but did not cause tumor regression. Moreover, tumor growth rapidly resumed at the cessation of treatment. These results are suggestive of cytostatic antitumor activity. Compound **10** also demonstrated synergistic antitumor efficacy in combination with Cetuximab (data not shown). Safety profiling of **10** showed it to be negative in Ames mutagenicity and SOS chromotest and noncytotoxic in human hepatocyte assays.

In summary, we report the continued development of the benzimidazole scaffold and the discovery of C-4 carbon-tethered



piperidines with potent IGF-1R inhibition. The work led to the identification of **10**, a compound with reduced CYP3A4 inhibition and PXR transactivation and thereby lowered the risk for potential for drug–drug interactions. Compound **10** was also shown to have improved aqueous solubility, reduced plasma protein binding, and efficacy on oral administration in multiple xenograft in vivo models.

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**Note Added after ASAP Publication.** This manuscript was released ASAP on September 3, 2008 with typographical errors in Table 5. The correct version was released on September 5, 2008.

**Supporting Information Available:** Experimental details and analytical data for compound **10** are included. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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