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2-(1*H*-Imidazol-4-yl)ethanamine and 2-(1*H*-pyrazol-1-yl)ethanamine side chain variants of the IGF-1R inhibitor BMS-536924

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Abstract—A series of IGF-1R inhibitors is disclosed, wherein the (*m*-chlorophenyl)ethanol side chain of BMS-536924 (**1**) is replaced with a series of 2-(1*H*-imidazol-4-yl)ethanamine and 2-(1*H*-pyrazol-1-yl)ethanamine side chains. Some analogs show improved IGF-1R potency and oral exposure. Analogs from both series, **16a** and **17f**, show in vivo activity comparable to **1** in our constitutively activated IGF-1R Sal tumor model. This may be the due to the improved protein binding in human and mouse serum for imidazole **16a** and the excellent oral exposure of pyrazole **17f**.

Over the last decade, the strategy of inhibiting oncogenic tyrosine kinases has proven itself to be an effective and powerful tool for the treatment of cancer: this is demonstrated by the US-FDA approval of the mAbs Herceptin (binds to HER2/Erb2), Erbitux (EGF), and Avastin (VEGF), as well as the small molecule receptor tyrosine kinase (RTK) inhibitors, Gleevec (targets Bcr-Abl), Iressa and Tarceva (EGFR), Sutent (VEGFR/PDGFR/c-Kit), and Sprycel (Bcr-Abl/Src). In March 2007, the pan-Her kinase inhibitor Lapatinib gained approval for HER2-positive breast cancer.[1]

While the marketed drugs cited above demonstrate clinically relevant validation for inhibition of some of the RTK pathways, the insulin-like growth factor I receptor (IGF-1R) signaling pathway remains, so far, an unproven target of small molecule intervention in human oncology. Nevertheless, since signal transduction through IGF-1R, via its over-expression or constitutive activation, leads to an oncogenic state, and since high levels of its soluble ligands (IGF-1 and IGF-2) correlate with an increased risk of developing various human malignancies,[2] inhibition of IGF signaling represents an attractive target for cancer therapy. While there are multiple complex downstream targets that are turned on (or off, ie GSK-3β)[3] following IGF-1R receptor activation, the two distinct major downstream signaling pathways which are activated via the IGF axis are (1) PI3K/AKT (PKB, which blocks multiple pro-apoptotic proteins such as caspase 9 and Bad, and thus signals 'survival', as well as metastasis and angiogenesis)[4] and

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(2) Sos/Ras/Raf/Mek/Erk (MAP kinase pathway, which signals mitogenesis, as well as anti-apoptosis, and expression of the VEGF target genes).[2,3]

One concern for targeting the IGF-1R pathway is the effect such an inhibitor may have on the highly homologous insulin receptor (IR), which is involved in metabolism and glucose regulation.[2] While IGF-1R inhibitors may be efficacious for treating human cancers, the trade off with simultaneous IR inhibition may be to initiate insulin resistance and cause a diabetic state.[5] However, there is also evidence to suggest that simultaneous inhibition of IR (in particular hybrid receptors between IGF-1R and IR isoform A) and IGF-1R might be required for effective antitumor efficacy.[2c,6c]

One[6a] of our group's recent reports[6a–e] describes the in vitro and in vivo biological activity of a novel IGF-1R inhibitor, BMS-536924 (**1**), wherein a 2-fold window between antitumor efficacy and glucose elevation is observed in vivo.[7] In an effort to improve **1** in terms of its IGF-1R potency (IC_{50} = 100 nM), high human serum protein binding (99.6%), and oral exposure (50.9 mM h), we replaced the lipophilic (*m*-chlorophenyl)ethanol side chain with various heterocyclic side chains. In fact, early work from our laboratories on a related series reveals the superiority of a 2-pyridine side chain vis-à-vis its 3- or 4-isomers[6e] indicating that *ortho*-substitution of an aromatic ring carbon with an unsubstituted sp^2 nitrogen leads to improved IGF-1R potency. It turns out that both **1** and its pyridine side chain variant shown in Figure 1 have nearly identical IGF-1R potency and oral exposure. A further survey of related heterocycles led us to both imidazole (**16e**) and pyrazole (**17e**) analogs which emerged as initial hits. We subsequently focused our synthetic chemistry efforts on these two series in order to systematically expand the SAR of these leads.[8]

Herein, we describe the synthesis and evaluation of a series of imidazole and pyrazole side chain analogs of **1**, from which **16a** and **17f** display reduced protein binding and enhanced oral exposure vis-à-vis **1**, respectively. Both **16a** and **17f** display comparable in vivo antitumor activity to **1** in a constitutively activated IGF-1R Sal tumor model. All of these new analogs are equipotent for IGF-1R and IR, a result that is not unexpected given the high degree of homology between these RTK's.[6]

Results and discussion: Whereas C-5 unsubstituted $N(1)^{\tau}$-alkyl histamine analogs (e.g., **7e–f** in Scheme 1) are known in the literature,[9] their preparation by direct alkylation of a suitably protected histamine results in

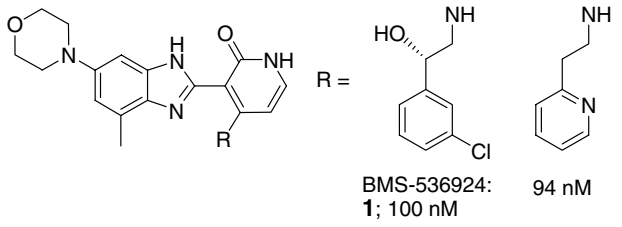
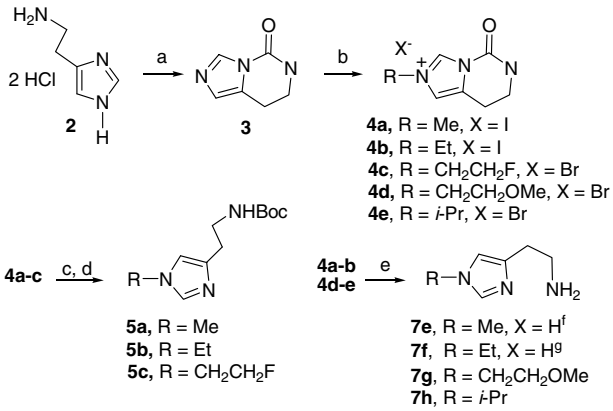


Figure 1. IGF-1R IC_{50}'s of **1** and its pyridine side chain analog.



Scheme 1. Reagents and conditions: (a) $(Imid)_2CO$ (1.0 equiv), DMF (400 mL), 120 °C, 14 h, 50% (40.1 g), **3** crystallizes from reaction using 100 g of **2**; (b) RX, CH_3CN reflux 10–72 h: product crystallizes from reaction; 94% (**4a**), 85% (**4b**): $Br(CH_2)_2F$, CH_3CN, microwave 150 °C, 1.5 h, used crude for step c for **4c**; $Br(CH_2)_2OMe$, CH_3CN, 100 °C, 20 h, 62% after reverse phase purification for **4d**; *i*-PrBr, CH_3CN, microwave 125 °C, 2 h, crystallizes from reaction for **4e**; (c) 8–10 N HCl, 100–110 °C, 60–96 h, evaporate in vacuo; (d) $(Boc)_2O$, CH_2Cl_2, aq $NaHCO_3$, rt, 120 h, 99% (**5a**), 97% (**5b**), 16% (**5c**); (e) H_2O, 100 °C, 16 h, then purify on SCX resin and elute with 2 M NH_3/MeOH, 51% for **7g** as its free base; 6 N HCl, reflux, 96 h, then apply to Bio-Rad chloride ion exchange resin and elute with H_2O to give **7h** as bis HCl salt; (f) **7e** was purchased from Sigma Chemical Company; (g) **7f** is obtained from **4b** using conditions in (c), followed by application to Bio-Rad chloride ion exchange resin and elution with H_2O to give **7f** as a bis HCl salt (99%).

mixtures of the τ (1) and π (3) regioisomers. A strategy for exclusive formation of τ (1)-alkylated histamines is initially described by Durant et al.[9a] and later improved upon by Jain and Cohen,[9b] and proceeds via cyclization of histamine (**2**) with carbonyl diimidazole to give cyclic urea **3** as shown in Scheme 1. Alkylation of **3** to salts **4a–b**, followed by hydrolysis, leads to such τ (1)-alkylated histamines as **7e–f**. We have now further improved upon the Durant/Cohen alkylation and hydrolysis sequence as applied to salts **4a–e** and histamines **5a–c** and **7e–h** as shown in Scheme 1. Intermediate **3** is now obtained directly by crystallization from the reaction mixture on a 100 g scale as shown below in Scheme 1.

We intended to apply a similar strategy for the synthesis of 5-halo-$N(1)^{\tau}$-alkyl histamines such as **7a–d** and **7i–k** (Scheme 2). However, we were surprised to find that no reports of 5-halo-$N(1)^{\tau}$-alkyl histamines existed, although ring halogenation of the parent (unalkylated) histamines is described to give both 5-halo and 2,5-dihalo analogs.[9c] The first syntheses of such 5-halo-$N(1)^{\tau}$-alkyl histamines are now described, as shown in Scheme 2, and some chemistry of the 5-halo-$N(1)^{\tau}$-ethyl and methyl histamines is shown in Scheme 3.

The N-Boc-protected intermediates **5a–c** undergo regioselective halogenation exclusively at C-5 using NCS or NBS in acetonitrile at 40–60 °C to provide **6a–e** in 40–61% yield as shown in Scheme 2. Boc-deprotection is best accomplished by 4 N HCl in dioxane/methylene chloride to give the bis HCl salts of the final 5-halo-$N(1)^{\tau}$-alkyl histamines **7a–d** in excellent yield as filter-