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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

Mark G. Saulnier,[a,*] David B. Frennesson,[a] Mark D. Wittman,[a] Kurt Zimmermann,[a] Upender Velaparthi,[a] David R. Langley,[b] Charles Struzynski,[a] Xiaopeng Sang,[a] Joan Carboni,[c] Aixin Li,[c] Ann Greer,[c] Zheng Yang,[d] Praveen Balimane,[d] Marco Gottardis,[c] Ricardo Attar[c] and Dolatrai Vyas[a]

[a]*Department of Discovery Chemistry, Bristol-Myers Squibb Pharmaceutical Research Institute, 5 Research Parkway, Wallingford, CT 06492, USA*
[b]*Department of Computer-assisted Drug Design, Bristol-Myers Squibb Pharmaceutical Research Institute, 5 Research Parkway, Wallingford, CT 06492, USA*
[c]*Department of Oncology Drug Discovery, Bristol-Myers Squibb Pharmaceutical Research Institute, PO Box 4000, Princeton, NJ 08543, USA*
[d]*Department of Metabolism and Pharmacokinetics, Bristol-Myers Squibb Pharmaceutical Research Institute, PO Box 4000, Princeton, NJ 08543, USA*

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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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* Corresponding author. Tel.: +1 203 677 6325; fax: +1 203 677 7702; e-mail: Mark.Saulnier@bms.com

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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

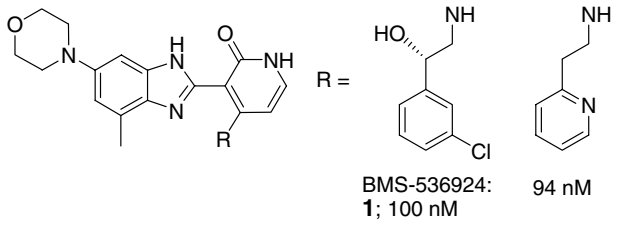
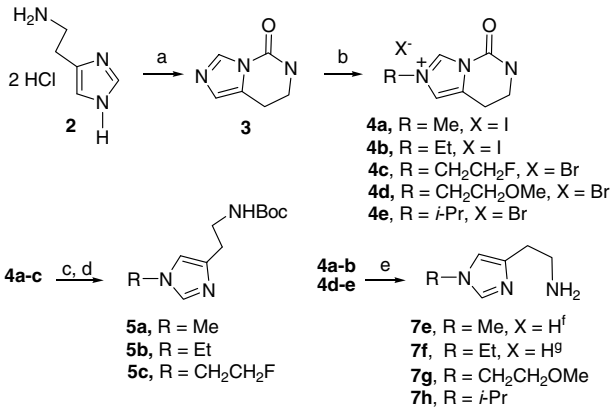


Figure 1. IGF-1R IC_{50}'s of **1** and its pyridine side chain analog.

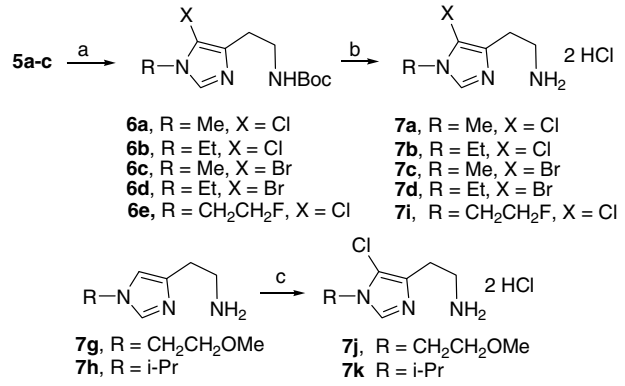


Scheme 1. Reagents and conditions: (a) $(Imid)_2CO$ (1.0 equiv), DMF (400 mL), 120 °C, 14 h, 50% (40.1 g), **3** crystallizes from reaction using 100 g of **2**; (b) RX, CH_3CN reflux 10–72 h: product crystallizes from reaction; 94% (**4a**), 85% (**4b**): $Br(CH_2)_2F$, CH_3CN, microwave 150 °C, 1.5 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%).

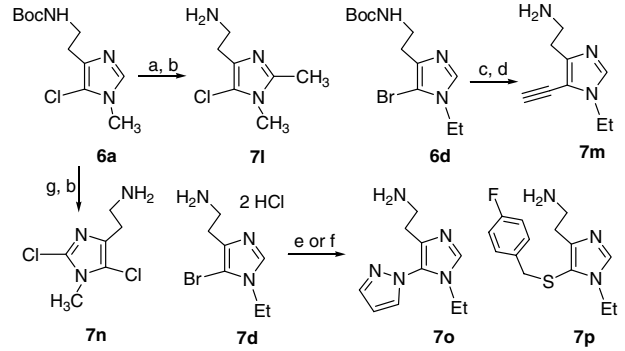
mixtures of the τ (1) and π (3) regioisomers. A strategy for exclusive formation of τ (1)-alkylated histamines is initially described by Durant et al.[9a] and later improved upon by Jain and Cohen,[9b] and proceeds via cyclization of histamine (**2**) with carbonyl diimidazole to give cyclic urea **3** 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-



Scheme 2. Reagents and conditions: (a) NCS or NBS, CH_3CN, 40–60 °C, 8–16 h, flash chromatography, 59% (**6a**), 61% (**6b**), 49% (**6c**), 44% (**6d**), 40% (**6e**); (b) 4 N HCl in dioxane, CH_2Cl_2, rt, 2 h, product precipitates from reaction after adding Et_2O, 92% (**7a**), 99% (**7b**), 84% (**7c**), 76% (**7d**): for **6e**–**7i** (TFA salt); TFA, CH_2Cl_2, 70 min (100%, used directly); (c) NCS, CH_3OH, 2 equiv 1 N HCl, rt, 72 h (100%, used directly) for **7j**; NCS, CH_3OH, rt, 18 h (100%, used directly) for **7k** (from **7h** as a bis HCl salt).



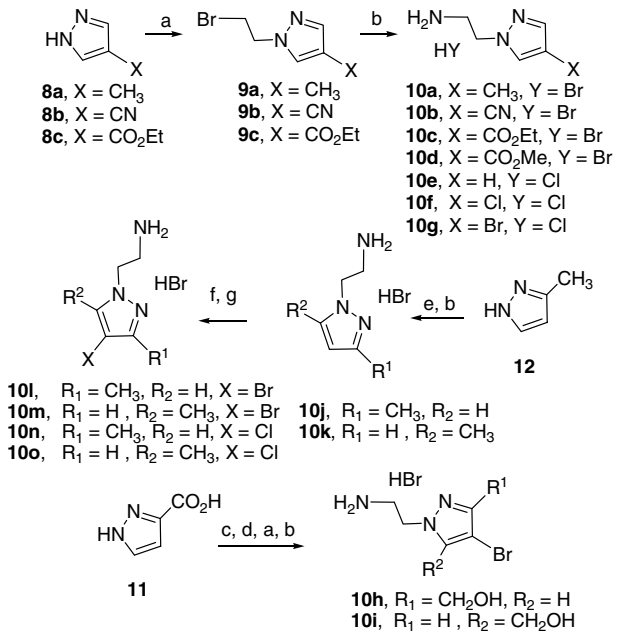
Scheme 3. Reagents and conditions: (a) 2.5 equiv *n*-BuLi, THF, hexane, −78 to −15 °C, 1.5 h then 1.3 equiv CH_3I, −78 °C to rt, 75% after flash chromatography; (b) TFA, CH_2Cl_2, gives **7l** and **7n** as bis TFA salts, quantitative; (c) 5% $(Ph_3P)_2PdCl_2$, 10% CuI, 12% Ph_3P, TMSCCH, THF, 95 °C, microwave, 2 h, 70% after flash chromatography; (d) $Bu_4NF{\cdot}H_2O$, THF, 65 °C, 15 min then 4 N HCl/dioxane, rt, 30 min, purify by SCX resin, elute with 2 M NH_3 in MeOH, 90%, **7m** as free base; (e) pyrazole, K_2CO_3, CuI, NMP, microwave, 195 °C, 45 min (low yield of **7o**); (f) *p*-FC_6H_4SH, Cs_2CO_3, CuI, NMP, microwave, 190 °C, 5 min (low yield of **7p**); (g) NCS, CH_3CN, rt, 36%.

able solids. Alternatively, C-5 chlorination of the unprotected histamines **7g**–**h** gives **7j**–**k** using NCS in methanol in the presence of 2 equiv of 1 N HCl (Scheme 2). In this case, the product is not purified but is used directly with 4-halopyridone **15**, as shown in Scheme 6 (vide infra).[10]

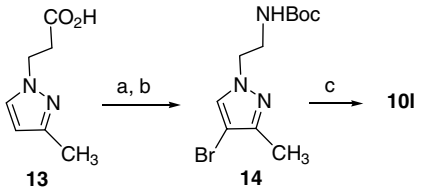
The Boc-protected 5-chloro-*N*(1)-methyl histamine **6a** can be lithiated at C-2 and quenched with methyl iodide in good yield to give the C-5-chloro-*N*-(1,2)-dimethyl analog **7l** following Boc-deprotection (Scheme 3). Chlorination of **6a** at C-2 followed by N-deprotection yields the 2,5-dichloro-*N*(1)-methyl histamine **7n**. In addition, the unprotected 5-bromo-histamine **7d** undergoes copper(I) catalyzed N and S bond formation to give **7o** and **7p**, respectively, albeit in low yield.[11]

In the context of our interest in the synthesis of the requisite *N*-(2-aminoethyl)pyrazole analogs **10a**–**o** in Scheme 4, we recently described a high yield microwave-assisted synthesis of primary amine HX salts from halides and 7 M ammonia in methanol.[12] This method describes the synthesis of **10e**–**g**,[12] and is also used for the synthesis of **10a**–**d**, readily available from **9a** to **9c**, as shown below in Scheme 4. Note that under the conditions of the 7 M ammonia in methanol microwave reaction, ethyl ester **9c** yields a 79:21 mixture of ethyl ester **10c** and methyl ester **10d** which are carried forward as a mixture and separated after coupling with 4-halopyridone **15** (Scheme 6) to give the final products **17c**–**d**.

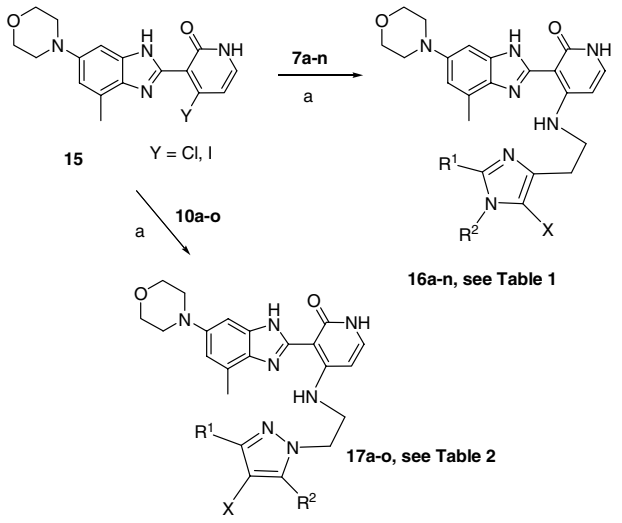
The synthesis of the C-3 and C-5-methyl-*N*-(2-aminoethyl)pyrazole analogs **10j**–**k** (HBr salts) is accomplished by non-regioselective alkylation of 3-methylpyrazole (**12**), followed by processing as shown in Scheme 4. Interestingly, attempted chlorination of these HBr salts **10j**–**k** with NCS in methanol yields, exclusively instead, the products of C-4-bromination, **10l**–**m**. Switching the HBr salts of **10j**–**k** to HCl salts using anion exchange (see Scheme 4, step g), followed by chlorination with NCS, gives the C-4 chlorination products **10n**–**o**. Note that pairs of regioisomers **10l**–**m** and **10n**–**o** are not separated at this stage, but are coupled as a mixture with 4-halopyridone **15** as shown in Scheme 6. Separation by reverse phase HPLC then yields the final products, **17l**–**o**. A bromination, reduction, and non-regioselective



Scheme 4. Reagents and condtions: (a) $BrCH_2CH_2Br$, K_2CO_3 acetone (**9a**, 32%), (**9b**, 57%), (**9c**, 72%); (b) 7 M NH_3 in MeOH, microwave, 130 °C, 2.5 h as in Ref. 12 which also describes **10e**–**g**; (c) NBS, CH_3CN, rt, 16 h, 63%; (d) BH_3/THF, 55 °C, 0.5 h; (e) $BrCH_2CH_2Br$, $PhCH_3$, 40% aq NaOH, Bu_4NBr, gives an unseparated mixture of regioisomers, 56% after flash chromatography, which is carried on to step (b) to give a mixture of **10j**–**k**; (f) NCS, MeOH, rt, 18 h for **10l**–**m**; (g) conversion of the HBr salt of **10j**–**k** to its HCl salt using Bio-Rad chloride ion exchange resin and elution with H_2O is followed by NCS, MeOH, rt, 18 h, to give **10n**–**o**.



Scheme 5. Reagents and conditions: (a) $(PhO)_2PON_3$, Et_3N, $PhCH_3$, 50 °C, 2 h, then *t*-BuOH, 70 °C, 18 h, 67% after flash chromatography; (b) NBS, CH_3CN, rt, 2 h, 94% after flash chromatography; (c) TFA, CH_2Cl_2, rt 16 h, to give **10l** as bis TFA salt, quantitative.



Scheme 6. Reagents and conditions: (a) DMSO, EtN(*i*-Pr)$_2$, 80–90 °C, 18–24 h, purification by reverse phase prep HPLC, yields range from 10% to 70%.

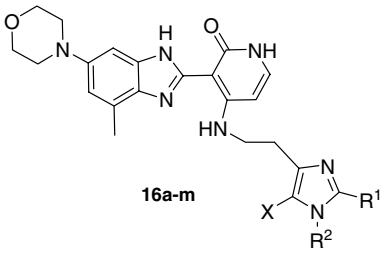
alkylation sequence is applied to 3-pyrazole carboxylic acid **11**[13] to give a mixture of **10h–i**, which is similarly processed to **17h–i**.

Since the final product **17l** shows exceptionally good oral exposure (Table 2, vide infra), we required an improved synthesis of the corresponding amine **10l**. Curtius rearrangement of commercially available acid **13**, followed by bromination and Boc-deprotection, readily affords **10l** in good overall yield as shown in Scheme 5.

Coupling of amines **7a–n** and **10a–o** with 4-halopyridone **15** is straightforward as shown in Scheme 6 and yields the final products **16a–n** (Table 1) and **17a–o** (Table 2) using the method described in Ref. 6a.

Inspection of Table 1 reveals some key SAR trends in regards to IGF-1R potency and oral exposure[14] for the 2-(1*H*-imidazol-4-yl)ethanamine series (compounds **16a–n**): substitution of the C-5 imidazolyl hydrogen in **16e** and **16f** with chlorine to give **16a–b** results in a 5-fold increase in potency toward IGF-1R. The corresponding C-5 bromo-analogs **16c–d** show a similar, but somewhat lesser trend. Note that small R^2 groups on the imidazole nitrogen are favored over larger substitutions (compare **16e–h**). Large groups at C-5 are not tolerated[15] and both methyl (**16l**) and chloro (**16n**) substitution at imidazole C-2 somewhat decreases IGF-1R potency while increasing oral exposure. Analog **16a** shows the best overall balance of enzyme (IGF-1R IC_{50}) and cellular (IGF-Sal IC_{50})[6a] potencies, and oral exposure. The fact that **16a** shows comparable in vivo activity to **1** in our constitutively activated IGF-1R Sal tumor model,[6a,b]

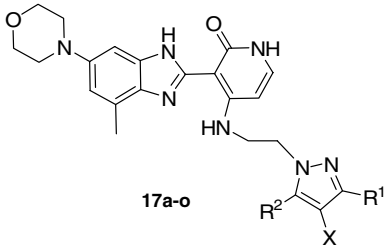
Table 1. SAR of imidazole side chain analogs[a]



Compound	R^1	R^2	X	IGF-1R IC_{50} (nM)	IGF-SAL IC_{50} (nM)	0–4 h AUC (mM h)
1	—	—	—	100	110	50.9
16a[b]	H	CH_3	Cl	38	336	8.2
16b	H	Et	Cl	83	469	21.5
16c	H	CH_3	Br	75	343	
16d	H	Et	Br	172	284	
16e	H	CH_3	H	190	521	3.8
16f	H	Et	H	480	583	
16g	H	$MeO(CH_2)_2$	H	550	1510	
16h	H	*i*-Pr	H	360	365	
16i	H	FCH_2CH_2	Cl	82	451	
16j	H	$MeO(CH_2)_2$	Cl	290	622	
16k	H	*i*-Pr	Cl	360	1140	
16l	CH_3	CH_3	Cl	66	266	36
16m	H	Et	HCC	243	2034	
16n	Cl	CH_3	Cl	160	306	32.2

[a] None of the analogs show selectivity over IR.
[b] Protein binding in human serum is 94.1% for **16a** versus 99.6% for **1**.

Table 2. SAR of pyrazole side chain analogs[a]



17a-o

Compound	X	R^1	R^2	IGF-1R IC_{50} (nM)	IGF-SAL IC_{50} (nM)	0–4 h AUC (mM h)
1	—	—	—	100	110	50.9
17a	CH_3	H	H	110	397	2.7
17b	CN	H	H	680	821	
17c	CO_2Et	H	H	68	531	4.9
17d	CO_2Me	H	H	91	711	14.1
17e	H	H	H	330	613	1.6
17f[b]	Cl	H	H	120	376	90.3
17g	Br	H	H	82	144	
17h	Br	CH_2OH	H	96	697	2
17i	Br	H	CH_2OH	470	796	
17j	H	CH_3	H	290	422	1.2
17k	H	H	CH_3	270	542	5.2
17l	Br	CH_3	H	110	197	132.5
17m	Br	H	CH_3	510	700	33.0
17n	Cl	CH_3	H	96	292	57.8
17o	Cl	H	CH_3	630	777	

[a] None of the analogs show selectivity over IR.
[b] Protein binding in human serum is 98.3% for **17f** versus 99.6% for **1**.

despite its lower exposure and 3-fold reduced cellular potency, is likely due to its significantly improved protein binding properties (94.1%, 96.9% for **16a** vs 99.6%, >99.9% for **1** in human and mouse serum, respectively).

Table 2 summarizes the SAR trends of the 2-(1*H*-pyrazol-1-yl)ethanamine side chain analog series **17a**–**o**. Compounds with bromine or chlorine substitution at the C-4 pyrazole position and methyl or hydrogen at the C-3 pyrazole position (R^1) (**17f**, **17l**, **17n**, **17g**[16]) have comparable IGF-1R potency and improved oral exposure vis-à-vis **1**, however their cellular potency is somewhat compromised by 1.3- to 3-fold. Substitution of the C-3 position (R^1) within this series shows improved potency over such identically substituted C-5 (R^2) regioisomers (compare **17h**–**i** and **17l**–**o**). The lack of exposure shown by parent analog **17e** (with hydrogen at C-4) shows that C-4 halogen substitution drives the excellent oral exposure. Analog **17f** demonstrates the best overall balance of enzyme and cellular potencies, while exceeding **1** with excellent oral exposure. In fact, **17f** demonstrates similar in vivo activity to both **1** and **16a** in the IGF-1R Sal tumor model. In addition to its superior oral exposure over **1**, **17f** also has modestly improved protein binding (98.3%, 96.2% in human and mouse serum, respectively). These two advantages serve to offset its 3-fold weaker cellular potency in terms of its equivalent antitumor activity.

In summary, we have described a series of IGF-1R inhibitors wherein the (*m*-chlorophenyl)ethanol side chain of **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, oral exposure, and human and mouse serum protein binding. Analogs containing chlorine atoms from both series, **16a** and **17f**, show comparable in vivo activity to **1** in our IGF-1R Sal tumor model.[6a,b] This may be the due to their improved protein binding properties for imidazole **16a** and the excellent oral exposure of pyrazole **17f**. Additional disclosures within this series of active IGF-1R inhibitors will be forthcoming from our group.[16]

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2. (a) Breuhahn, K.; Nussbaum, T.; Singer, S.; Schirmacher, P. *Curr. Cancer Ther. Rev.* **2006**, *2*, 157, and the references cited therein; (b) Gennigens, C.; Menetrier-Caux, C.; Droz, J. P. *Crit. Rev. Oncol. Hematol.* **2006**, *58*, 124; (c) Garcia-Echeverria, C. *IDrugs* **2006**, *9*, 415.
3. Another key signaling pathway which can be activated by IGF-1 and IGF-2 is the Wnt pathway, which regulates the key transcription factor, β-catenin. Signaling though IGF-1R (via PI3K/AKT) can activate Wnt signaling through GSK-3β inhibition. GSK-3β is a key component in the degradation of β-catenin, and therefore in the maintenance of the 'normal' state. See Illyas, M. *J. Pathol.* **2005**, *205*, 130.
4. The combination of a PI3K/AKT pathway inhibitor and doxorubicin represent an effective strategy for treating

tumor cells in which the PI3K/AKT pathway is constitutively activated and the p53 pathway is functional. See Fujiwara, Y.; Kawada, K.; Takano, D.; Tanimura, S.; Ozaki, K.; Kohno, M. *Biochem. Biophys. Res. Commun.* **2006**, *340*, 560.

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16. The utility of the **17f** chloropyrazole side chain in a related series of benzimidazoles will be the subject of future reports from our laboratories. Whereas the oral exposure data were not obtained for 4-bromopyrazole **17g**, the advantages of 4-chloro over 4-bromopyrazoles in these related series will also be reported therein.