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Novel 1*H*-(benzimidazol-2-yl)-1*H*-pyridin-2-one inhibitors of insulin-like growth factor I (IGF-1R) kinase

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Abstract—A novel class of 1*H*-(benzimidazol-2-yl)-1*H*-pyridin-2-one inhibitors of insulin-like growth factor I (IGF-1R) kinase is described. This report discusses the SAR of 4-(2-hydroxy-2-phenylethylamino)-substituted pyridones with improved IGF-1R potency.

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] Binding of the ligands IGF-I and/or IGF-II to the extracellular domain of the receptor leads to receptor autophosphorylation and activation of the intrinsic kinase activity present in the cytoplasmic domain of the receptor. Activation of the kinase activity results in the phosphorylation of the downstream signaling molecules IRS-1 and IRS-2 which in turn activates the mitogenic RAS/Raf/MAPK and PI-3/Akt survival signaling cascades.[2,3] The current level of interest in finding kinase inhibitors of IGF-1R stems from the expectation that such inhibitors would block signaling through both the mitogenic an anti-apoptotic pathways. From a clinical perspective, epidemiological studies have correlated elevated IGF-I levels with an increased risk of developing colon, breast, prostate, and lung tumors.[4–8]A significant challenge in developing ATP-competitive inhibitors of IGF-1R kinase is building in selectivity over the related insulin receptor (IR) due to the high sequence homology (84%) between these two receptors and the fact that the residues which contact ATP are identical.[9] Not surprisingly, no kinase selectivity over IR was observed for the inhibitors within the 1*H*-(benzimidazol-2-yl)-1*H*-pyridin-2-one series. This paper describes SAR that contributed to the identification of BMS-536924, an inhibitor of IGF-1R kinase with broad-spectrum in vivo activity.[10]

Keywords: Insulin-like growth factor; IGF-1R; Inhibitor; Kinase; ATP competitive; Benzimidazole; 4-Aminopyridone; Substituted 2-hydroxy-2-phenyl-aminoethanol.
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Results and discussion: In the course of exploring the SAR of the initial lead (**1**), we identified the chromen-4-one (**2**) as a sub-micromolar inhibitor of IGF-1R. Crystallization of this inhibitor with the kinase domain of IGF-1R revealed potential new interactions to explore via the 4-position of the pyridone ring. Figure 1 shows the overlay of the crystal structures of (**1**) and (**2**), each bound to IGF-1R (the structure of IGF-1R has been removed for clarity). The key features of the binding of (**2**) with IGF-1R are the hydrogen bond donor/acceptor diad across the top of the molecule with extension of the benzyl piperidine into the unfilled region corresponding to the 4-position of pyridine (**1**). This observation prompted an exploration of the effect of substituents at the 4-position of the pyridone ring. Using chemistry originally described by Curran[11a] and Fang[11b] in the course of their campothecin work, the 4-iodopyridone (**7**) was prepared according to Scheme 1. Starting from the commercially available 5-fluoro-2-nitro-toluene (**3**), S_NAr addition of imidazole followed by catalytic reduction provided aniline (**4**). Acylation and *ortho*-nitration provided (**5**). De-acetylation followed by reduction of the nitro group provided the requisite diamine for condensation with the known iodopyridine aldehyde to provide benzimidazole (**6**). It is interesting to note that the benzimidazole formation occurs without the need for additional oxidant. Addition of oxidants such as iodine did not improve the yield of the benzimidazole. Cleavage of the methoxy group under acidic conditions provided the 4-iodopyridone (**7**). Addition of excess amine to pyridone (**7**) provided analogs (**8**–**33**).

The racemic amino alcohols used in this study were prepared according to Scheme 2. Optimally, the aldehyde was condensed with nitromethane[12] and the resulting nitroaldol adduct trapped as the TES ether (**34**). Reduction of the nitro group followed by cleavage of the TES

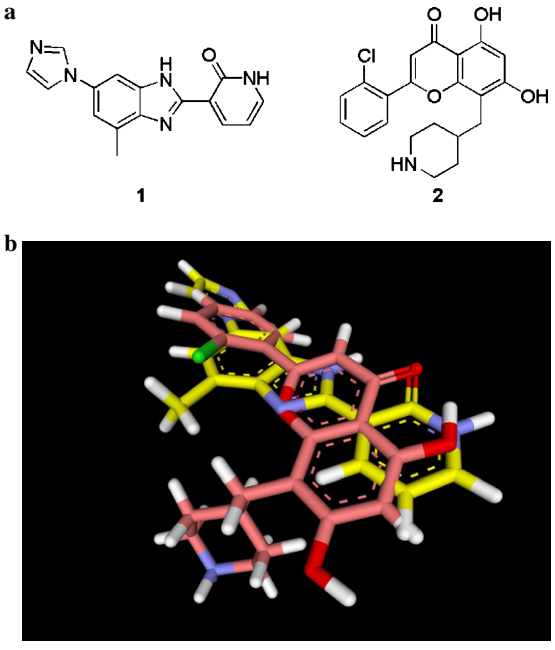
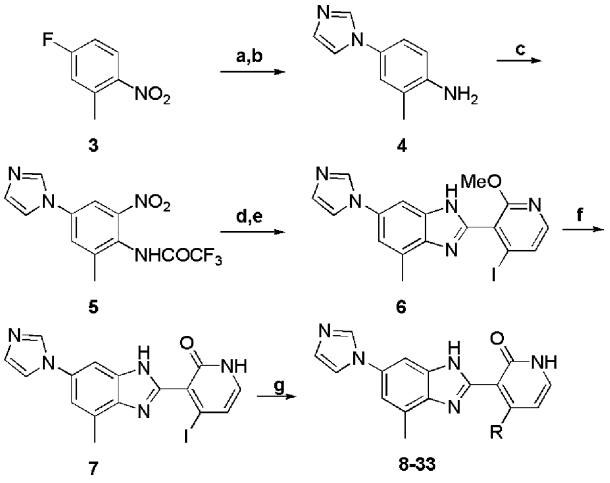
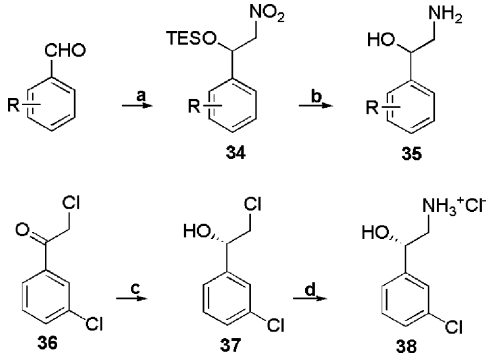


Figure 1.



Scheme 1. Reagents and conditions: (a) KOH, DMSO, imidazole (95%); (b) Pd–C, EtOH, cyclohexene, reflux (quant); (c) TFAA, pyridine, DMAP; H_2SO_4/HNO_3 (50:50) (70%); (d) EtOH, KOH (72%); (e) Pd–C, EtOH, HOAc, H_2 then 4-iodo-3-formyl-2-methoxy-pyridine, MeOH (61%) open to air; (f) 1 N HCl 70 °C (63%); (g) amine, DMF, 80 °C.



Scheme 2. Reagents and conditions: (a) CH_3NO_2, EtOH, 2% HOAc, 10% NaOH; TESCl, imidazole, CH_2Cl_2; (b) Raney nickel, H_2, methanol; Bu_4NF, THF; (c) *S*-CBS methyl oxazaborolidine (0.02 equiv); BH_3·THF, THF; (d) 7 M NH_3 in methanol (recrystallized from EtOAc/ethanol).

Table 1. SAR of 4-aminopyridone analogs

Compound	R	IGF-1R IC_{50}[a] (μM)
1	H	3.50
8	$NHCH_2CH_2OH$	3.00
9	$NHCH_2CH_2$–Ph	3.05
10	(*R*/*S*) $NHCH_2CH(OH)$–Ph	0.72

[a] IC_{50} values were determined using 125 ng of baculovirus-expressed enzyme, 2.5 μg of poly(Glu/Tyr), 25 μM of ATP, and 0.1 μCi of [γ-^{33}P]ATP.

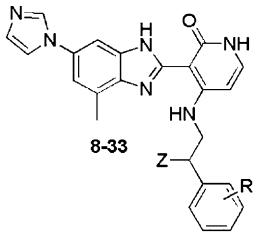
ether afforded the desired amino alcohol (**35**). The (*R*) and (*S*) enantiomers were prepared using a sequence in which the α-chloromethyl ketone (**36**)[13] was reduced with Corey's CBS oxazaborolidine catalyst.[14] Reductions to the chlorohydrin typically proceeded in high yield and >95% ee. Treatment of the chlorohydrin (**37**) with excess 7 M NH_3 in methanol provided the hydrochloride salt (**38**) directly which could be recrystallized to high enantiomeric purity (>99% ee).[15a]

The addition of amines to the 4-iodopyridone via an addition/elimination sequence provided a straightforward means to explore a wide range of chemical diversity at this position. The addition of secondary amines and anilines provided compounds devoid of IGF-1R activity. In contrast, the addition of primary amines did provide compounds with IGF-1R inhibitory activity. A key breakthrough was realized when the ethanol amine (**8**) and phenyl ethylamine (**9**) elements were combined in the 2-hydroxy-2-phenylethylamine (**10**). Each of these elements alone did not provide a significant improvement in potency over R = H (**1**) but together provided sub-micromolar IGF-1R inhibitory activity (Table 1).

With the identification of 2-hydroxy-2-phenylethylamine (**10**), a focused exploration of the SAR of the aryl ring was initiated. Scanning the various positions on the aromatic group revealed that *meta*-substitution was optimal. Introduction of methyl, electron-donating, and electron-withdrawing *meta*-substituents indicated that halogen or hydroxyl substitution was preferred (**13**–**16**). The potency observed for the hydroxyl analog (**16**) may be the result of a hydrogen-bond in the active site. This would be consistent with the observed loss in potency of the methoxy derivative (**21**). The combination of a 3-halogen with a 4-substituent also provided an improvement in IGF-1R potency. Optimal substituents were the 4-fluoro group (**27**) and the 4-methoxy group (**28**). Increasing the size of the 4-methoxy group to an *n*-propoxy (**29**) resulted in a significant loss of activity. Methylation of the secondary hydroxyl group (**30** vs **14**) resulted in a loss of potency as did steric shielding of the hydroxyl group with the addition of a benzylic methyl group (**31** vs **15**).

Compounds with in vitro kinase potency were tested for their effect on cellular proliferation in the engineered cell line IGF-1R Sal.[16] This cell line overexpresses a constitutively activated IGF-1R receptor and is particularly sensitive to IGF-1R inhibitors. Halogen or alkyl substitution gave compounds (**13**, **14**, **19**, **28**) with the most potent cell-based effects, with 3-substituted derivatives being preferred (**13**, **14**, **19**). Compounds with polar substituents tended to show a decrease in cell potency (**17**, **18**). The optimal cell activity was observed with the

Table 2. SAR of phenylethylamine analogs **8**–**33**



8-33

Compound	R	Z	IGF-1R IC_{50}[a] (μM)	IGF-1R Sal IC_{50}[b] (μM)
11	2-Cl	OH(*R*/*S*)	0.80	
12	2-$NHSO_2CH_3$	OH(*R*/*S*)	1.59	
13	3-F	OH(*R*/*S*)	0.52	0.47
14	3-Cl	OH(*R*/*S*)	0.18	0.37
15	3-Br	OH(*R*/*S*)	0.14	
16	3-OH	OH(*R*/*S*)	0.19	
17	3-CN	OH(*R*/*S*)	0.24	1.64
18	3-$NHSO_2CH_3$	OH(*R*/*S*)	0.30	3.63
19	3-CH_3	OH(*R*/*S*)	0.34	0.42
20	3-CF_3	OH(*R*/*S*)	0.53	0.78
21	3-OCH_3	OH(*R*/*S*)	0.71	0.78
22	4-$NHSO_2CH_3$	OH(*R*/*S*)	1.20	
23	4-CH_3	OH(*R*/*S*)	0.35	0.75
24	4-OCH_3	OH(*R*/*S*)	0.52	0.61
25	3,5-Cl	OH(*R*/*S*)	0.25	
26	3,4-Cl	OH(*R*/*S*)	0.47	1.27
27	3-Cl–4-F	OH(*R*/*S*)	0.16	0.76
28	3-Cl–4-OMe	OH(*R*/*S*)	0.15	0.54
29	3-Cl–4-O-*n*-Pr	OH(*R*/*S*)	>25	
30	3-Cl	OMe(*R*/*S*)	3.63	
31	3-Br	Me, OH(*R*/*S*)	0.79	1.79
32	3-Cl	OH(*S*)	0.14	0.19
33	3-Cl	OH(*R*)	0.83	0.44

[a] IC_{50} values represent the average of two determinations using 125 ng of baculovirus-expressed enzyme, 2.5 μg of poly(Glu/Tyr), 25 μM of ATP, and 0.1 μCi of [γ-^{33}P]ATP. Standard deviations ranged from 0.01 to 0.17.

[b] The effect on cell proliferation was measured in the engineered cell line IGF-1R Sal[16] and was determined using thymidine incorporation.

Table 3. Oral exposure

Compound	R	Z	AUC 0–4 h μM h[a]
14	3-Cl	OH(*R*/*S*)	43
15	3-Br	OH(*R*/*S*)	5
32	3-Cl	OH(*S*)	124
33	3-Cl	OH(*R*)	25

[a] AUC was determined after dosing three mice 20 mpk of compound in 80:20 PEG400 water solution. Time points were taken at 1 and 4 h. AUC are in μM h for 0–4 h.

3-Cl derivative (**14**). The enantiomers of this derivative were resolved chromatographically. The (*S*) enantiomer (**32**) was more potent than the corresponding (*R*) enantiomer (**33**) in both the in vitro kinase assay and against the IGF-1R Sal cell line (Table 2).

Evaluation of the oral exposure of compounds (**14**) and (**15**) revealed that the 3-chloro (**14**) had significantly better exposure than the more potent 3-bromo derivative (**15**). The (*S*) enantiomer (**32**) maintained the good exposure observed with the racemate, while the less active (*R*) enantiomer (**33**) had significantly lower exposure. While the potency and oral exposure of compound **32** were very promising, this compound was not active in the IGF-Sal in vivo tumor model[16] most likely due to high protein binding (>99%). Further improvements in cellular potency did lead to compounds with in vivo activity[10] (Table 3).

In summary, the initial screening lead (**1**) has been optimized for IGF-1R potency, cell potency, and oral exposure via substitution of the 4-position of the pyridone ring to provide (*S*)-2-hydroxy-2-(3-Cl-phenyl)-ethylamine analog (**32**). Future communications will focus on the replacement of the imidazole ring to reduce protein binding and optimize ADME and drug safety parameters.

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