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Discovery of potent, selective, and orally bioavailable inhibitors of interleukin-1 receptor-associate kinase-4

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ABSTRACT

In this Letter, we report the continued optimization of the *N*-acyl-2-aminobenzimidazole series, focusing in particular on the *N*-alkyl substituent and 5-position of the benzimidazole based on the binding mode and the early SAR. These efforts led to the discovery of **16**, a highly potent, selective, and orally bioavailable inhibitor of IRAK-4.

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Interleukin-1 (IL-1) receptor-associated kinase-4 (IRAK-4) is a ubiquitously expressed serine/threonine kinase and is responsible for initiating signaling from Toll-like receptors (TLRs) and members of the IL-1/18 receptor family. IRAK-4 and its IRAK isoforms share a domain structure and activate similar signal transduction of NF-kB and MAPK pathways.[1–4] However, unlike the other IL-1 receptor-associated kinases (IRAK-1,[1] IRAK-2,[2] and IRAK-M[3]), IRAK-4 requires its kinase activity to activate NF-kB.[4] Endogenous IRAK-4 interacts with IRAK-1 and TRAF6 in an IL-1-dependent manner but is not redundant with IRAK-1, indicating that IRAK-4 may play a major role in the early signal transduction of Toll/IL-1 receptors. To this end, we found that mice with either IRAK-4 knockout or IRAK-4 targeted deletion had reductions in TLR and IL-1 induced pro-inflammatory cytokines and were resistant to induced joint inflammation in both antigen-induced arthritis (AIA) and serum transfer-induced (K/BxN) arthritis models.[5] These results strongly suggest that IRAK-4 is indispensable for IL-1 signal transduction and its kinase activity is required for signal transduction. Furthermore, human patients who lack full-length IRAK-4 expression suffer from a compromised immune response.[6] Therefore, selective inhibition of IRAK-4 has emerged as a potential therapeutic strategy for the treatment of inflammatory pathologies such as atherosclerosis.[7–12]

Previously, we reported the identification of a novel series of *N*-acyl-2-aminobenzimidazole IRAK-4 inhibitors exemplified by **1** (Fig. 1) from initial optimization efforts on an HTS lead.[11] Compound **1** inhibited both IRAK-4 and its isoform IRAK-1 in a chemiluminescent ELISA assay,[13] with an IC_{50} of 0.15 μM and 0.9 μM, respectively. The early structure–activity relationship (SAR) studies in this series[13] identified the pharmacophore required for IRAK inhibition: (a) the secondary amide connection between the two aryl groups is favorable for potency as alkylation of the amide led to a substantial loss of activity, (b) both 3-nitro and 3-trifluoromethyl groups at the benzamide were beneficial for activity against IRAK-4, and (c) substitutions on the nitrogen and 5-positions of the benzimidazole significantly improved IRAK-4 inhibition.

Binding affinity of **1** to IRAK-4 can be explained by key interactions of three hydrogen bonds and van der Waals interactions, which were observed in the co-crystal structure of **1** with IRAK-4 (Fig. 2).[14] As an ATP-site inhibitor, compound **1** makes a typical hinge hydrogen bond with the amide carbonyl accepting a hydrogen bond from the backbone amide of Met265. The nitro group forms a weak hydrogen bond with the side-chain NH_3^+ of catalytic

Abbreviations: MeCN, acetonitrile; CL, clearance; Dess–Martin periodinane, 1,1,1-tris(acetyloxy)-1,1-dihydro-1,2-benziodoxol-3-(1*H*)-one; DIBALH, diisobutylaluminum hydride; DMF, *N*,*N*-dimethylformamide; EtOAc, ethyl acetate; HBTU, *N*,*N*,*N*′,*N*′-tetramethyl-*O*-(1*H*-benzotriazol-1-yl)uronium hexafluorophosphate; HOBT, hydroxybenzotriazole; NMM, *N*-methylmorpholine; THF, tetrahydrofuran.

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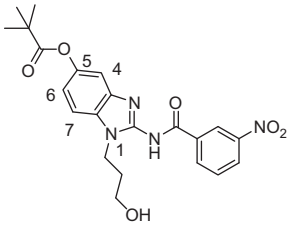


1

IRAK-4 IC_{50}: 0.15 μM and IRAK-1 IC_{50}: 0.9 μM

Figure 1. Structure and biochemical potency of **1**. Values of IC_{50} are means of at least two determinations from a chemiluminescent ELISA assay.

Lys213 while the phenyl ring engages in a partial π–π aromatic stacking interaction with the gatekeeper, Tyr262. In addition, the pivalate ester is exposed to solvent and the carbonyl forms a non-conserved hydrogen bond with Arg273 of helix αD in the C-terminal lobe. Based on the aforementioned binding mode of **1** and associated SAR data, we decided to preserve the most important structural features for IRAK-4 binding and optimize substituents at the nitrogen and 5-position of the benzimidazole in order to improve potency, selectivity, and physicochemical properties.

Optimization of the benzimidazole N-alkyl substituent: Initial optimization of **1** began with modification of the benzimidazole *N*-alkyl substituent. Since the 3-nitro group of the benzamide interacts with Lys213 and the 5-substituton on the benzimidazole is favorable for IRAK-4 inhibition, 3-nitro-5-fluorobenzimidazole **2** (R = H, IC_{50} = 4.5 μM, Table 1)[11] was used as a template for optimization. Adding a polar *N*-propanol group (**3**) improved potency by more than 100-fold, which was consistent with early SAR data (**3** vs **2**).[11] Increasing the size of the polar group from propanol to cyclohexanol led to a further improvement in potency. The *trans* *N*-cyclohexanol **4** (IC_{50} = 6.5 nM) was almost six-fold more potent than **3** in the biochemical assay. Furthermore, expanding the *N*-cyclohexanol to an *N*-cyclohexylmethyl alcohol, produced compounds **5** and **6**. The *cis* isomer **5** was fourfold more potent than **4,** while the *trans* isomer **6** had potency similar to **4** in the biochemical assay. However, changing the ring size from six-membered to five-membered resulted in a slight loss of potency (**7** vs **5** and **8** vs **6**).

Optimization of the benzimidazole 5-position substituent: Although compounds such as **4** were of high potency, they suffered from poor solubility and permeability. Therefore, we introduced a solubilizing group at the 5-position of the benzimidazole to improve the physicochemical properties. The cocrystal structure of **1** with IRAK-4 suggests that the pivalate ester projects out toward a solvent-exposed region and the carbonyl moiety acts as a hydrogen bond acceptor to Arg273. With these considerations in mind, a small group of analogs incorporating with hydroxyl, amine, and other solubilizing groups, were explored (Table 2). The 5-hydroxymethyl analog **9** was twofold less potent than **4** and showed no improvement in solubility or permeability. Gratifyingly, the piperidine analog **10** was more potent (IC_{50} = 2.8 nM) than **4** and had improved solubility (50 μg/mL at pH 7.4) and permeability (6.6×10^{-6} cm/s). Interestingly, both morpholine **11** and lactam **12** were found to be more potent than **10** but with no significant improvement in permeability. The improved permeability of **10** may contribute to its low polar surface area.

Having identified the 5-piperidine as the key feature for potent IRAK-4 inhibition with good solubility and permeability, we turned our attention to selectivity over off-target enzymes. In general,

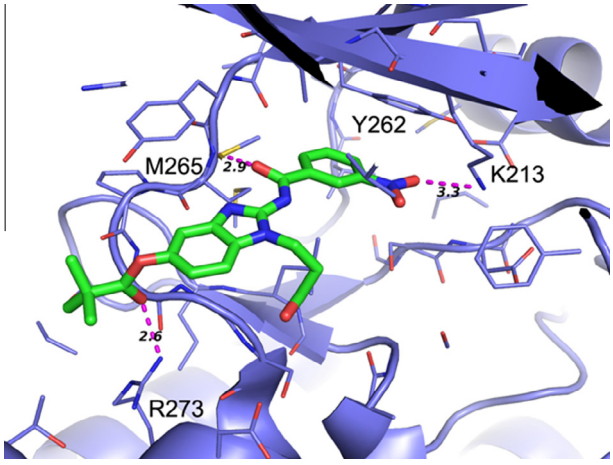
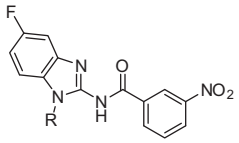
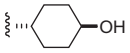
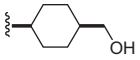
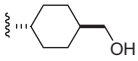
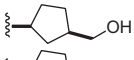


Figure 2. Co-crystal structure of **1** bound to IRAK-4 (2NRU.pdb).

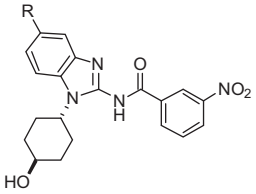
Table 1
Optimization of *N*-alkyl substituent of benzimidazole

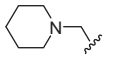
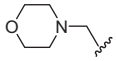


Compound	R	IRAK-4 K_i[a] (nM)
2	H	4500
3	$(CH_2)_3OH$	38.5
4		6.5
5		1.6
6		6.4
7		7.8
8		11

[a] Values are means of at least two determinations.[13]

Table 2
Solubility and permeability data of analogs **9**–**12**



Compound	R	IRAK-4 K_i[a] (nM)	Solubility (pH = 7.4, μg/mL)	Permeability (10^{-6} cm/s)	PSA (Å^2)
9		11	4.9	<1	137
10		2.8	>50	6.6	120
11		3.8	29	<1	129
12		0.5	0.8	<1	137

[a] Values are means of at least two determinations.[13]

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