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Initial optimization and series evolution of diaminopyrimidine inhibitors of interleukin-1 receptor associated kinase 4

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ABSTRACT

IRAK4 plays a key role in TLR/IL-1 signaling. Previous efforts identified a series of aminopyrimidine IRAK4 inhibitors that possess good potency, but modest kinase selectivity. Exploration of substituents at the C-2 and C-5 positions generated compounds that maintained IRAK4 potency and improved kinase selectivity. Additionally, it was found that the pyrimidine core could be replaced with a pyridine and still retain potency and kinase selectivity. The optimization efforts led to compound **26** which had an IRAK4 IC_{50} of 0.7 nM, an IC_{50} of 55 nM on THP-1 cells stimulated with LPS, a TLR4 agonist, and greater than 100-fold selectivity versus 96% of a panel of 306 kinases.

Interleukin-1 receptor associated kinase 4 (IRAK4) is an intracellular serine–threonine kinase that is part of the interluekin-1/Toll-like receptor (IL-1/TLR) signaling cascade.[1] These receptors play a key role in the innate immune response to pathogen associated molecular patterns (PAMPs) and damage associated molecular patterns (DAMPs). PAMPs include viral and bacterial components that, when detected, can trigger an immune response. DAMPs include host components such as cytokines and cellular debris, but also can include external stimuli such as asbestos. Signaling through these receptors eventually results in the activation of the transcription factors kappa light chain enhancer of activated B cells (NF-κB) and activator protein-1 (AP-1), resulting in the generation of inflammatory cytokines.[2,3] In normal homeostasis, the inflammatory response elicited by these molecular patterns is transient. However, several diseases such as inflammatory bowel disease and rheumatoid arthritis involve chronic stimulation of the inflammatory response which leads to significant damage to the surrounding tissue and resulting disease pathology. Accordingly, the ability to block or control chronic inflammation would have significant therapeutic benefits.

As IRAK4 is a key upstream target of the TLR/IL signaling cascade,[4] it is hypothesized that inhibitors of IRAK4 could potentially block this cascade and subsequently reduce the effects of chronic activation of these pathways.[3,5–7] There have been numerous reports detailing the efforts toward small molecule IRAK4 inhibitors, and this area has been recently reviewed.[8–10]

We previously identified a series of aminopyrimidine IRAK4 inhibitors such as **1** from a high throughput screen (Table 1).[11] Initial optimization of the lead compound focused on demonstrating tractable structure–activity relationships (SAR) for the series. The result of these efforts were significant improvements in potency while maintaining or improving the ligand binding efficiency.[12] However, kinase selectivity remained a concern for the series. One of our goals was the generation of an in vivo tool compound that could be used in disease state animal models and ultimately demonstrate the in vivo efficacy of an IRAK4 inhibitor. In order to meet this goal, a highly kinase selective IRAK4 inhibitor would be required. In particular, selectivity versus other kinases involved in inflammatory responses would be crucial in order to

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avoid confounding in vivo efficacy data.[13] Accordingly, our medicinal chemistry efforts toward an IRAK4 inhibitor focused on not only developing a potent compound (<10 nM IRAK4 enzyme inhibition, LBE >0.30), but also identifying a clear path forward for gaining highly selective kinase inhibitors. In this regard, we defined a highly selective compound as one that had >100 fold selectivity against a panel of kinases, and in particular against kinases that have been identified as having a role in inflammation related pathways.[13]

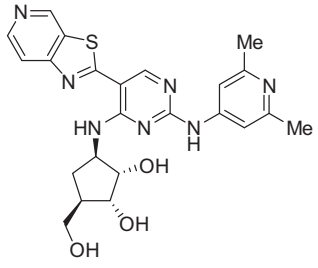
A key piece of SAR data that was identified early in the development of the aminopyrimidine series was the ability to gain significant IRAK4 inhibition by incorporation of an azabenzothiazole at the 5-position of the pyrimidine ring, exemplified by compound **1**. Although this compound had sub-nanomolar potency on IRAK4, the kinase selectivity was modest against a large panel of kinase targets ($n = 308$). In particular, several kinases with aromatic gatekeepers (like IRAK4)[14,15] proved to be problematic (e.g. FLT3) but the compound was also not selective against inflammation-related kinases (e.g. LCK, IRAK1, RIP, and several MAP kinases). We first sought to retain the azabenzothiazole and design new analogs changing the groups at the C-2 position. The goal was to try to maintain the IRAK4 potency while improving the off target kinase selectivity. The results are summarized in Table 2.

Initial SAR demonstrated that compounds with nitrogen at either the 5 or 6 position of the benzothiazole ring were potent and thus new compounds incorporated either of these ring systems. For the 5-azabenzothiazole compounds **2**–**7**, modifications of the C-2 amino substituents universally provided compounds with IRAK4 potencies comparable to compound **1**. Pyridine (compounds **2**, **5**, **6**), pyrimidine (compound **4**) and phenyl (compounds **3** and **7**) rings were all tolerated. In contrast, significant loss of activity was observed when making a change from an aryl to a cycloalkyl ring (cyclobutyl **8**). When analogs containing a 6-azabenzothiazole were examined, a similar potency to the 5-azabenzothiazole was observed. (compounds **9**–**12**). Because it appeared that modification of the C-2 amino aryl was well tolerated, it was hoped that these modifications would translate to SAR that would allow for an enhancement of the kinase selectivity.

Several of these analogs were tested for their kinase selectivity (compounds **3**, **5** and **9**). Unfortunately, none of these changes showed improvements in kinase selectivity compared to compound **1** (data not shown) and it was hypothesized that the azabenzothiazole itself was the cause of the poor kinase selectivity, possibly due to interactions between the azabenzothiazole nitrogen and a highly conserved lysine residue.[15]

Accordingly, we looked at modifying the heterocycle at the 5-position of the pyrimidine ring (Table 3). When monocyclic 5-membered heterocycles were examined, they universally lost IRAK4 potency compared to the fused heteroaromatic systems (benzothiazole). The most potent compounds are shown in Table 3 (compounds **13**–**17**) and contained either a thiazole or a pyrazole ring. Connecting the thiazole at the 4-position appeared to offer the best potency (compound **14**). However, when the

Table 1
Profile of lead aminopyrimidine 1

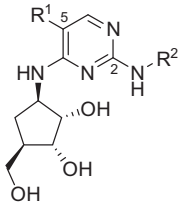


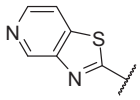
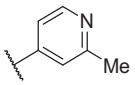
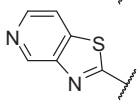
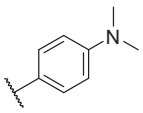
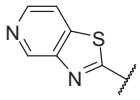
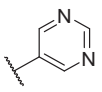
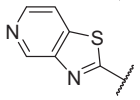
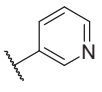
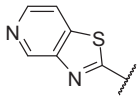
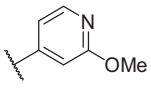
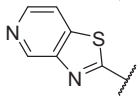
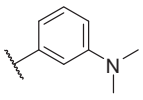
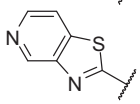
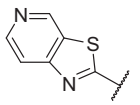
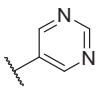
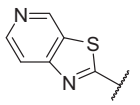
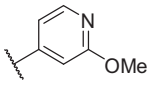
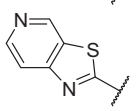
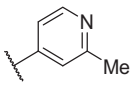
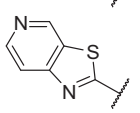
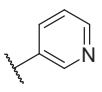
1

IRAK4 IC_{50}	0.30 nM
LBE[a]	0.38
Solubility (pH 2, 7)	131, 5 μM
Clog P[b]	2.5
Kinase Selectivity (>100 fold against 308 kinases)[c]	85%

[a] Ligand binding efficiency.
[b] From ACD Labs v10.
[c] Fold selectivity calculated versus IRAK4 IC_{50} determined at Merck Research Laboratories.

Table 2
SAR of azabenzothiazole analogs



Compd	R^2	R^2	IRAK4 IC_{50} (nM)	LBE
2			3	0.36
3			4	0.33
4			12	0.34
5			11	0.34
6			7	0.33
7			12	0.31
8			647	0.29
9			6	0.35
10			2	0.35
11			12	0.34
12			18	0.34