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Identification of *N*-(1*H*-pyrazol-4-yl)carboxamide inhibitors of interleukin-1 receptor associated kinase 4: Bicyclic core modifications

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ABSTRACT

IRAK4 plays a critical role in the IL-1R and TLR signalling, and selective inhibition of the kinase activity of the protein represents an attractive target for the treatment of inflammatory diseases. A series of permeable *N*-(1*H*-pyrazol-4-yl)carboxamides was developed by introducing lipophilic bicyclic cores in place of the polar pyrazolopyrimidine core of 5-amino-*N*-(1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamides. Replacement of the pyrazolo[1,5-*a*]pyrimidine core with the pyrrolo[2,1-*f*][1,2,4]triazine, the pyrrolo[1,2-*b*]pyridazine, and thieno[2,3-*b*]pyrazine cores guided by *c*Log*D* led to the identification of highly permeable IRAK4 inhibitors with excellent potency and kinase selectivity.

Interleukin-1 receptor associated kinase 4 (IRAK4) is an intracellular serine–threonine kinase that belongs to the IRAK family kinases (IRAK1, IRAK2, IRAK-M, and IRAK4).[1,2] Interleukin-1 receptor (IL-1R) and toll-like receptor (TLR) superfamily mediates the innate immune response by upregulating the expression of inflammatory genes in multiple target cells.[3] Upon stimulation of this superfamily, the adaptor protein MyD88 binds to the receptors through the conserved Toll/IL-1 receptor (TIR) domain. MyD88-dependent TIR signalling is followed by recruitment of IRAK4 which interacts with multiple key downstream signalling molecules. IRAK4$^{-/-}$ mice showed severe defects in cytokine responses and downstream signalling pathways induced by IL-1R and TLRs.[4] In addition, cells derived from IRAK4 deficient patients failed to induce downstream cytokines in response to known ligands of TIR-bearing receptors.[5] In view of the genetic evidence of the critical role of IRAK4 in IL-1R and TLR signalling, IRAK4 could be an attractive target for the treatment of inflammatory diseases,[6] including rheumatoid arthritis,[7,8] inflammatory bowel disease,[9,10] asthma,[11] and systemic lupus erythematosus.[12] To date, various structural classes of IRAK4 inhibitors have been reported in the literature by both Merck[13–15] and others.[16–23]

In a previous publication, we reported the discovery of 5-amino-*N*-(1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamides exemplified by **1** (Fig. 1) as a novel series of IRAK4 inhibitors.[15] Although introduction of diamines at the 5-position of the pyrazolo[1,5-*a*]pyrimidine ring offered greatly improved potency and kinase selectivity, the compounds suffered from poor passive permeability and lack of bioavailability in rats due to the added high intrinsic polarity by the diamines. We overcame the poor permeability and bioavailability issue in this series by replacing substituents responsible for poor permeability and improving physical properties guided by *c*Log*D*[24,25] that offered a good correlation with permeability. In designing new targets with improved physical properties, however, our selection of substituents at the 5-position of the pyrazolopyrimidine ring and the 3-position of the pyrazole ring was limited to the ones that offered significantly higher *c*Log*D* values. Indeed, many substituents that offered *c*Log*D* values similar to or lower than that of **1** suffered from poor permeability and bioavailability, albeit some showed improved

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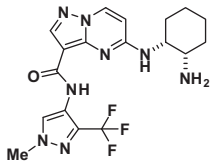


1

Figure 1. 5-Amino-*N*-(1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide IRAK4 inhibitor.

properties in potency and plasma clearance in rats. We envisioned that we could expand the scope of substituents while maintaining the optimal range of polarity of the molecules by replacing the pyrazolopyrimidine core with more lipophilic bicyclic cores. To this end, we explored an array of bicyclic cores in place of the pyrazolopyrimidine ring.

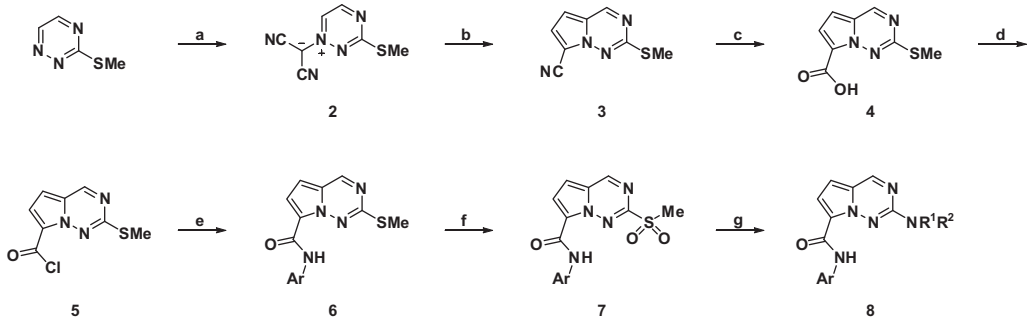
Herein, we report bicyclic core modifications to 5-amino-*N*-(1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamides. Identification of several novel bicyclic cores that offer higher *c*Log*D* values than pyrazolo[1,5-*a*]pyrimidine with various promising substituents on the bicyclic core and at the 3-position of the pyrazole ring is described. Improvements in passive permeability in response to the bicyclic core modifications as well as metabolic stabilities of selected compounds are also reported.

Syntheses of the target molecules discussed in this communication are described in Schemes 1–3. The pyrrolo[2,1-*f*][1,2,4]triazine core was synthesized in two steps starting from 3-(methylsulfanyl)-1,2,4-triazine via formation of the triazinium dicyanomethylide (**2**) with tetracyanoethylene oxide followed by [2,3]-cycloaddition between **2** and phenyl vinyl sulfoxide at an elevated temperature (Scheme 1).[26,27] Intermediate **3** was hydrolysed to afford acid **4** and subsequently converted to acid chloride **5** with $POCl_3$. Acid chloride **5** was coupled with various arylamines followed by sequential oxidation of the thioether to the sulfone (**7**) with mCPBA and S_NAr reaction with an array of amines to afford **8**.

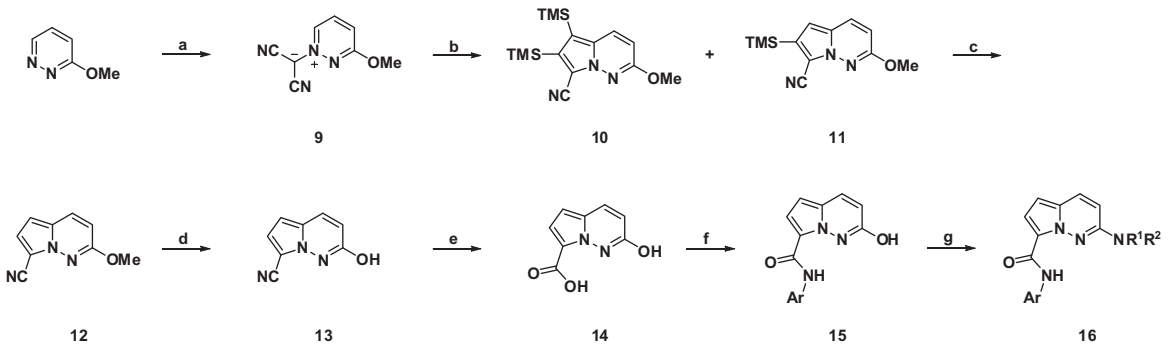
The pyrrolo[1,2-*b*]pyridazine core was prepared in an analogous manner. Pyridazinium dicyanomethylide **9** was coupled to bis(trimethylsilyl)acetylene at an elevated temperature, and then intermediates **10** and **11** were protodesilylated to afford **12** (Scheme 2). Intermediate **12** was converted to 2-hydroxypyrrolo[1,2-*b*]pyridazine-7-carboxylic acid (**14**) via $AlCl_3$-mediated demethylation followed by hydrolysis of the nitrile. Intermediate **14** was coupled with various arylamines employing a coupling reagent to afford **15**. An array of amines were introduced to the 2-poistion of the pyrrolo[1,2-*b*]pyridazine core of **15** via sequential triflate formation and S_NAr reaction to afford **16**.

Intermediate **20** was prepared from 7-bromothieno[2,3-*b*]pyrazine via sequential palladium-mediated carbonylation in methanol, N-oxidation with mCPBA, chlorination with $POCl_3$, and saponification (Scheme 3). Intermediate **20** was readily derivatized at the carboxylic acid and the 2-position of the thieno[2,3-*b*]pyrazine core via coupling with arylamines followed by S_NAr reaction with amines to afford **22**.

Several 5,6-fused bicyclic core analogues that offer higher *c*Log*D* values were prepared and compared with **1** in potency and passive permeability (Fig. 2). Gratifyingly, the pyrrolo[2,1-*f*][1,2,4]triazine, the pyrrolo[1,2-*b*]pyridazine, and the thieno[2,3-*b*]pyrazine analogues (**23**, **24**, and **25**, respectively) offered the enzymatic, human PBMC, and rat whole blood potencies comparable to those of **1** (Table 1). The analogues are more lipophilic than **1** judged by their *c*Log*D* values higher than that of **1** by 1.1, 1.5, and 2.2 units for **23**, **24**, and **25**, respectively. As envisioned, higher



Scheme 1. Reagents and conditions: (a) Tetracyanoethylene oxide, THF, 83%; (b) phenyl vinyl sulfoxide, 1,4-dioxane, reflux, 41%; (c) KOH, water, reflux, 60%; (d) $POCl_3$, 100 °C; (e) $ArNH_2$, Hünig's base, CH_2Cl_2; (f) mCPBA, CH_2Cl_2; (g) R^1R^2NH, Hünig's base, NMP, 160 °C.



Scheme 2. Reagents and conditions: (a) Tetracyanoethylene oxide, THF; (b) bis(trimethylsilyl)acetylene, toluene, reflux; (c) TBAF, THF, 62% over 3 steps; (d) $AlCl_3$, CH_2Cl_2, reflux, 94%; (e) NaOH, EtOH, reflux, 97%; (f) $ArNH_2$, HATU, Hünig's base, DMF; (g) $PhNTf_2$, Hünig's base, DMF, room temperature; R^1R^2NH, 110 °C.