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The discovery and optimization of aminooxadiazoles as potent Pim kinase inhibitors.

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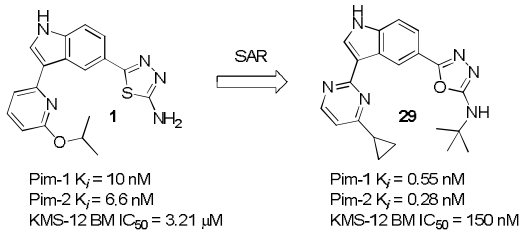
Abstract—High levels of Pim expression have been implicated in several hematopoietic and solid tumor cancers. These findings suggest that inhibition of Pim signaling by a small molecule Pim-1,2 inhibitor could provide patients with therapeutic benefit. Herein, we describe our progress towards this goal starting from the highly Pim-selective indole-thiadiazole compound (**1**), which was derived from a nonselective hit identified in a high throughput screening campaign. Optimization of this compound's potency and its pharmacokinetic properties resulted in the discovery of compound **29**. Cyclopropane **29** was found to exhibit excellent enzymatic potency on the Pim-1 and Pim-2 isoforms (K_i values of 0.55 nM and 0.28 nM, respectively), and found to inhibit the phosphorylation of BAD in the Pim-overexpressing KMS-12 cell line (IC_{50} = 150 nM). This compound had moderate clearance and bioavailability in rat (CL = 2.42 L/kg/h; %F = 24) and exhibited a dose-dependent inhibition of p-BAD in KMS-12 tumor pharmacodynamic (PD) model with an EC_{50} value of 6.74 μM (18 μg/mL) when dosed at 10, 30, 100 and 200 mg/kg P.O. in mice.



Proviral **I**ntegration site of **M**oloney (Pim) murine leukemia virus kinases are serine/threonine kinases that are involved in cell survival and proliferation as well as a number of other signal transduction pathways.[1,2] The Pim-1, -2 and -3 isoforms share a high level of sequence homology and appear largely redundant in function. High levels of Pim expression have been implicated as oncogenic drivers in