

## Optimization of Pim Kinase Inhibitors: Heterocyclic Chemistry and Macrocycles in a Pyrrole Series of Compounds

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Pim-1, -2, and -3 are highly homologous and constitutively active serine/threonine kinases. The three Pim isoforms phosphorylate a diverse group of proteins with known roles in proliferation, survival, apoptosis, and differentiation. The identification of oncogene-driven aberrant Pim kinase overexpression in subsets of B-cell malignancies including lymphomas, leukemias, and multiple myeloma, as well as in subsets of solid tumors, has led to intense efforts to identify small molecule Pim kinase inhibitors. A high-throughput screen of our corporate compound collection identified a hit composed of a 1,5-naphthyridine connected to a 6,7-dihydro-1H-pyrrolo[3,2-c]pyridin-4(5H)-one. A hit-to-lead optimization campaign resulted in the identification of improved inhibitors based on quinoxaline and quinazolin-4(3H)-one cores. A series of macrocyclic inhibitors in which the quinoxaline core and the dihydro-pyrrolo[3,2-c]pyridinone were connected was also found to possess improved properties. The heterocyclic chemistry of dihydro-pyrrolo[3,2-c]pyridinones, dihydropyrrolo[3,4-b]pyrrolones, and quinazolin-4(3H)-ones will be described, as well as the approaches used to synthesize macrocycles. Finally, the preclinical characterization of the lead molecules and their potential as treatments of Pim-driven malignancies will be presented.

