Pim Kinase Inhibitors

Pim kinases are serine/threonine kinases that play a significant role in cell cycle progression and apoptosis. There are two isoforms of Pim kinase: Pim-1 and Pim-2. Both kinases are expressed in lymphoid cells and are necessary for cytokine-dependent proliferation[1].

Most current research has examined the structure and function of Pim-1, although both are potentially involved in tumorigenesis. Pim-1 activates cell cycle regulator Cdc25, stimulating cell cycle progression. As a result, it may induce unregulated cell growth. Single nucleotide polymorphisms in the gene that encodes Pim-1 have been associated with the presence of diffuse large cell lymphoma and increased risk of lung cancer. Because of its role in cell division, inhibition of Pim-1 shows activity in the treatment of various cancers[2].

AZD-1208 (A9708) is a Pim-1 inhibitor that induces cell cycle arrest and apoptosis in leukemia cells and inhibits phosphorylation of downstream targets such as Bcl-2, 4EBP1, p70S6K, and S6[3].

SMI-4a (S4932) is another inhibitor of Pim-1. SMI-4a limits phosphorylation of eIF4B, suppresses tumor growth, and induces cell cycle arrest and apoptosis in myeloid and lymphoid cells[4].

Proteasome inhibitor **MLN-2238 (M4455)** modulates expression of tumor suppressor miR33b and downregulates Pim-1 activity in multiple myeloma cells[5].

Mitoxantrone Dihydrochloride (M3379) is a DNA intercalator used to treat multiple sclerosis, lymphomas, and leukemias. Research shows it likely derives some activity from the direct inhibition of Pim-1[6].

References:
1. Bachmann M, Möröy T. Int J Biochem Cell Biol. 2005 Apr;37(4):726-30.
2. Kim DS, Sung JS, Shin ES, et al. Cancer Res Treat. 2008 Dec;40(4):190-6.
3. Keeton EK, McEachern K, Dillman KS, et al. Blood. 2014 Feb 6;123(6):905-13.
4. Yang J, Wang J, Chen K, et al. Cancer Res. 2013 Aug 1;73(15):4898-908.
5. Tian Z, Zhao JJ, Tai YT, et al. Blood. 2012 Nov 8;120(19):3958-67.
6. Wan X, Zhang W, Li L, et al. J Med Chem. 2013 Mar 28;56(6):2619-29.