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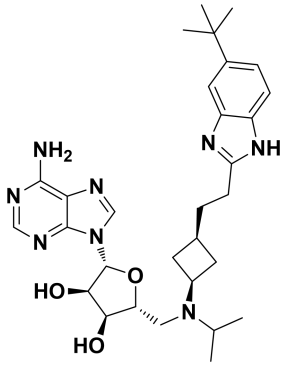
DOT1L inhibitor – EPZ-5676

Chemical Name: (2R,3R,4S,5R)-2-(6-amino-9H-purin-9-yl)-5-((((1r,3S)-3-(2-(5-(tert-butyl)-1H-benzo[d]imidazol-2-yl)ethyl)cyclobutyl)(isopropyl)amino)methyl)tetrahydrofuran-3,4-diol



Molecular Weight:	562.71
Formula:	$C_{30}H_{42}N_8O_3$
Purity:	≥ 98%
CAS#:	1380288-87-8
Solubility:	DMSO up to 50 mM
Storage	Powder: 4 °C 1 year DMSO: 4 °C 3 months -20 °C 1 year

Biological Activity:

EPZ-5676 is a highly potent and selective inhibitor of DOT1L methyltransferase with Ki of 70 pM, selectively blocking the binding of the cofactor, S-adenosylmethionine. It inhibits proliferation of MLL-AF4 rearranged cell line MV4-11 with an IC_{50} of 9 nM. It reduces H3K79 dimethylation with a cellular IC_{50} of 2.6 nM in MV4-11 cells. EPZ-5676 has over 10,000-fold selectivity against other HMTs. Its superior potency is associated with its increased enzyme residence time and prolonged cellular effects after washout. It can reduce H3K79 methylation in all cells, but only kill cells with MLL rearrangement, making it a good drug candidate for cancer therapy. Now EPZ-5676 is in phase I clinical trials for advanced hematologic malignancies, including acute Leukemia with rearrangement of the MLL gene.

How to Use:

In vitro: EPZ-5676 was used at 1 μM final concentration in vitro and in cellular assays.

In vivo: Continuous intravenous infusion of EPZ-5676 at 70.5 mg/kg once per day for 21 days achieved complete tumor regressions in a nude rat subcutaneous xenograft model of MLL-rearranged leukemia.

Reference:

1. Robert A Copeland. Protein methyltransferases in cancer. (2013) AACR Annual Meeting.
2. Roy M Pollock. Preclinical Characterization of a Potent, Selective Inhibitor of the Protein Methyltransferase DOT1L for Use in the Treatment of MLL-Rearranged Leukemia. (2012) 54th ASH Annual Meeting and Exposition.