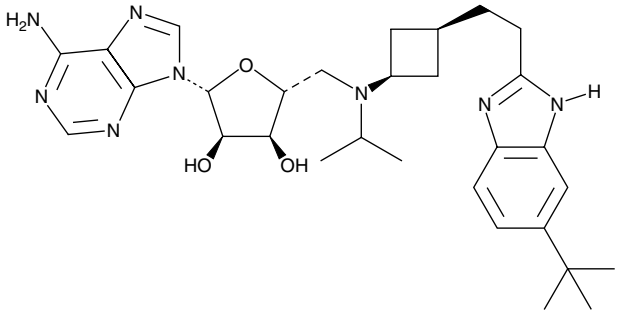
Product Information

EPZ5676

Item No. 16175



CAS Registry No.: 1380288-87-8
Formal Name: 9-[5-deoxy-5-[[*cis*-3-[2-[6-(1,1-dimethylethyl)-1H-benzimidazol-2-yl]ethyl]cyclobutyl](1-methylethyl)amino]-β-D-ribofuranosyl]-9H-purin-6-amine
MF: $C_{30}H_{42}N_8O_3$
FW: 562.7
Purity: ≥98%
Stability: ≥2 years at -20°C
Supplied as: A crystalline solid
UV/Vis.: λ_{max}: 255 nm

Laboratory Procedures

For long term storage, we suggest that EPZ5676 be stored as supplied at -20°C. It should be stable for at least two years.

EPZ5676 is supplied as a crystalline solid. A stock solution may be made by dissolving the EPZ5676 in the solvent of choice. EPZ5676 is soluble in organic solvents such as ethanol, DMSO, and dimethyl formamide (DMF), which should be purged with an inert gas. The solubility of EPZ5676 in ethanol and DMF is approximately 30 mg/ml and approximately 25 mg/ml in DMSO.

EPZ5676 is sparingly soluble in aqueous buffers. For maximum solubility in aqueous buffers, EPZ5676 should first be dissolved in ethanol and then diluted with the aqueous buffer of choice. EPZ5676 has a solubility of approximately 0.1 mg/ml in a 1:8 solution of ethanol:PBS (pH 7.2) using this method. We do not recommend storing the aqueous solution for more than one day.

DOT1L is a non-SET domain containing methyltransferase whose function is important for the transcriptional activation of certain genes, DNA damage repair, and cell cycle regulation. DOT1L is known to play an essential role in MLL-rearranged leukemias, and thus has emerged as a drug target for these leukemias.[1,2] EPZ5676 is a highly potent aminonucleoside inhibitor of DOT1L histone methyltransferase activity (K_i = 80 pM) that demonstrates 37,000-fold selectivity over other methyltransferases.[3,4] In various human leukemia cell lines, EPZ5676 has been shown to inhibit the methylation of lysine 79 on histone 3 (IC_{50}s = 3-5 nM), decreasing MLL-fusion target gene expression (IC_{50}s = 53-67 nM).[3] It can selectively inhibit the proliferation of acute leukemia cell lines bearing MLL translocations (IC_{50}s range from 3.5 nM - 1.3 µM).[3] Continuous intravenous infusion of EPZ5676 at a dose of 35 mg/kg has been reported to cause complete and sustained tumor regression in a rat xenograft model of MLL-rearranged leukemia.[3]

Reference

1. Nguyen, A.T., He, J., Taranova, O., *et al.* Essential role of DOT1L in maintaining normal adult hematopoiesis. *Cell Res.* **21(9)**, 1370-1373 (2011).
2. Bernt, K.M. and Armstrong, S.A. A role for DOT1L in MLL-rearranged leukemias. *Epigenomics* **3(6)**, 667-670 (2011).
3. Daigle, S.R., Olhava, E.J., Therkelsen, C.A., *et al.* Potent inhibition of DOT1L as treatment of MLL-fusion leukemia. *Blood* **122(6)**, 1017-1025 (2013).
4. Basavapathruni, A., Olhava, E.J., Daigle, S.R., *et al.* Nonclinical pharmacokinetics and metabolism of EPZ5676, a novel DOT1L histone methyltransferase inhibitor. *Biopharm. Drug Dispos.* **35(4)**, 237-252 (2014).

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