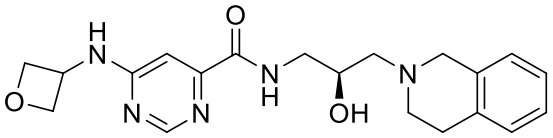
Product data sheet

MedKoo Cat#: 407226 Name: EPZ015666 (GSK3235025) CAS#: 1616391-65-1 Chemical Formula: $C_{20}H_{25}N_5O_3$ Exact Mass: 383.19574 Molecular Weight: 383.452	
Product supplied as:	Powder
Purity (by HPLC):	≥ 98%
Shipping conditions	Ambient temperature
Storage conditions:	Powder: -20°C 3 years; 4°C 2 years.
	In solvent: -80°C 3 months; -20°C 2 weeks.

1. Product description:
EPZ015666, also known as GSK3235025, is a potent and selective and orally active PRMT5 inhibitor with a half-maximal inhibitory concentration (IC50) of 22 nM and broad selectivity against a panel of other histone methyltransferases. Treatment of MCL cell lines with EPZ015666 led to inhibition of SmD3 methylation and cell death, with IC50 values in the nanomolar range. Oral dosing with EPZ015666 demonstrated dose-dependent antitumor activity in multiple MCL xenograft models. EPZ015666 represents a validated chemical probe for further study of PRMT5 biology and arginine methylation in cancer and other diseases.

2. CoA, QC data, SDS, and handling instruction
SDS and handling instruction, CoA with copies of QC data (NMR, HPLC and MS analytical spectra) can be downloaded from the product web page under "QC And Documents" section. Note: copies of analytical spectra may not be available if the product is being supplied by MedKoo partners. Whether the product was made by MedKoo or provided by its partners, the quality is 100% guaranteed.

3. Solubility data

Solvent	Max Conc. mg/mL	Max Conc. mM
DMSO	76	198.21
Ethanol	39	101.71

4. Stock solution preparation table:

Concentration / Solvent Volume / Mass	**1 mg**	**5 mg**	**10 mg**
1 mM	2.61 mL	13.04 mL	26.08 mL
5 mM	0.52 mL	2.61 mL	5.22 mL
10 mM	0.26 mL	1.30 mL	2.61 mL
50 mM	0.05 mL	0.26 mL	0.52 mL

5. Molarity Calculator, Reconstitution Calculator, Dilution Calculator
Please refer the product web page under section of "Calculator"

6. Recommended literature which reported protocols for in vitro and in vivo study
In vitro study

1. Chan-Penebre E, Kuplast KG, Majer CR, Boriack-Sjodin PA, Wigle TJ, Johnston LD, Rioux N, Munchhof MJ, Jin L, Jacques SL, West KA, Lingaraj T, Stickland K, Ribich SA, Raimondi A, Scott MP, Waters NJ, Pollock RM, Smith JJ, Barbash O, Pappalardi M, Ho TF, Nurse K, Oza KP, Gallagher KT, Kruger R, Moyer MP, Copeland RA, Chesworth R, Duncan KW. A selective inhibitor of PRMT5 with in vivo and in vitro potency in MCL models. Nat Chem Biol. 2015 Jun;11(6):432-7. doi: 10.1038/nchembio.1810. Epub 2015 Apr 27. PMID: 25915199.

2. Strobl CD, Schaffer S, Haug T, Völkl S, Peter K, Singer K, Böttcher M, Mougiakakos D, Mackensen A, Aigner M. Selective PRMT5 Inhibitors Suppress Human CD8+ T Cells by Upregulation of p53 and Impairment of the AKT Pathway Similar to the Tumor Metabolite MTA. Mol Cancer Ther. 2020 Feb;19(2):409-419. doi: 10.1158/1535-7163.MCT-19-0189. Epub 2019 Nov 11. PMID: 31712395.

In vivo study

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1. Chan-Penebre E, Kuplast KG, Majer CR, Boriack-Sjodin PA, Wigle TJ, Johnston LD, Rioux N, Munchhof MJ, Jin L, Jacques SL, West KA, Lingaraj T, Stickland K, Ribich SA, Raimondi A, Scott MP, Waters NJ, Pollock RM, Smith JJ, Barbash O, Pappalardi M, Ho TF, Nurse K, Oza KP, Gallagher KT, Kruger R, Moyer MP, Copeland RA, Chesworth R, Duncan KW. A selective inhibitor of PRMT5 with in vivo and in vitro potency in MCL models. Nat Chem Biol. 2015 Jun;11(6):432-7. doi: 10.1038/nchembio.1810. Epub 2015 Apr 27. PMID: 25915199.

7. Bioactivity

Biological target:

EPZ015666 (GSK3235025) is an orally available inhibitor of PRMT5 with an IC50 of 22 nM.

In vitro activity

The impact of EPZ015666 on T-cell proliferation and viability was checked. EPZ015666 reduced T-cell proliferation with increasing concentrations. Cells were more sensitive to this inhibitor as suppression was already detectable at much lower doses, but even the highest tested concentration was less effective compared with MTA (Fig. 1E). Freshly isolated human CD8+ T cells were stimulated with autologous Mart-1 peptide-loaded mDCs in the presence or absence of 10 μmol/L EPZ015666. The frequency of Mart-1–specific CTLs was monitored by Mart-1 multimer staining over 18 days. No Mart-1+ cells could be detected in the presence of EPZ015666 after 18 days (Fig. 2D). In addition, there was a stronger reduction of Mart-1+ CTLs after 18 days compared with MTA-treated cells (Fig. 2B and E).

Reference: Mol Cancer Ther. 2020 Feb;19(2):409-419. http://mct.aacrjournals.org/cgi/pmidlookup?view=long&pmid=31712395

In vivo activity

EPZ015666 is orally bioavailable and amenable to in vivo studies. 21-d efficacy studies were performed in severe combined immunodeficiency (SCID) mice bearing subcutaneous Z-138 and Maver-1 xenografts, with twice-daily (BID) oral dosing on four dose groups: 25, 50, 100 and 200 mg per kilogram of body weight (mg kg−1). After 21 d of continuous dosing, animals were euthanized, and blood and tissues were analyzed to determine the relationship between methylmark pharmacodynamics and tumor-growth inhibition (TGI). EPZ015666 showed dose-dependent exposure and TGI after 21 d in both MCL models (Fig. 4c,d). Tumors in all EPZ015666 dose groups measured on day 21 showed statistically significant differences in weight, volume and tumor growth compared to vehicle-treated tumors. EPZ015666 was well tolerated in all three models, with minimal bodyweight loss in the 200 mg kg−1 dose group and no other clinical observations (Supplementary Fig. 16). To measure in vivo target inhibition, a highly quantitative SDMA ELISA was developed to allow for higher throughput and to complement the SDMA western blot. In the SDMA ELISA, Z-138 xenograft tumors collected on day 21 showed dose-dependent changes of >40% and >95% inhibition (>48% and >87% for Maver-1 tumors at day 21; >66% and >95% for Granta-519 tumors at day 18) of the methyl mark achieved at the lowest dose and highest dose, respectively (Fig. 4e,f and Supplementary Figs. 17–22).

Reference: Nat Chem Biol. 2015 Jun;11(6):432-7. https://doi.org/10.1038/nchembio.1810