

Product Data Sheet

Product Name: EPZ015666

Cat. No.: GC15302

Chemical Properties

Cas. No. 1616391-65-1

Chemical Name (R)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-6-(oxetan-3-ylamino)pyrimidine-4-carboxamide

SMILES O=C(C1=CC(NC2COC2)=NC=N1)NC[C@@H](O)CN(CC3)CC4=C3C=CC=C4

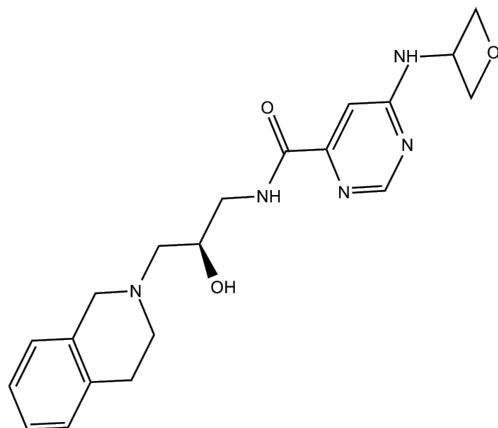
Formula $C_{20}H_{25}N_5O_3$ M.Wt 383.44

Solubility $\geq 19.17\text{mg/mL}$ in DMSO Storage Store at -20°C

General tips For obtaining a higher solubility, please warm the tube at 37°C and shake it in the ultrasonic bath for a while. Stock solution can be stored below -20°C for several months.

Shipping Condition Evaluation sample solution: ship with blue ice. All other available size: ship with RT, or blue ice upon request.

Structure



Protocol

Cell experiment [1]:

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Cell lines Retinoblastoma (RB) cells

Preparation Method Retinoblastoma(RB) cells were plated in 96-well plates at 5000 cells per well and were treated with different concentrations of EPZ015666 (0, 5, 10, 20, and 30μM). After incubation for different times(24, 48,and 72h), 20μl of MTT[3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2-H-tetrazolium bromide] was added, and the cells were incubated for another 4 h. Cell viability was represented by optical density (OD) values after dissolving cells in DMSO.

Reaction Conditions 0, 5, 10, 20, and 30μM; 24, 48,and 72h

Applications EPZ015666 inhibited retinoblastoma cells proliferation in a concentration- and time-dependent manner.

Animal experiment [2]:

Animal models C57BL/6 mice

Preparation Method U14 cells in 100 μL (5×10^6 cells/mouse) were subcutaneously implanted into the right flanks of C57BL/6 mice. At day 3 after inoculation of U14 cells, the PRMT5 inhibitor EPZ015666(0, 25, and 75mg/kg/day) Was intraperitoneally injected for 12 consecutive days.The tumor length (L) and width (W) were monitored by measurement with a digital caliper every day.

Dosage form 25mg/kg/day and 75mg/kg/day for12 days; i.p.

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Applications EPZ015666 therapy on cervical cancer mice model and found that EPZ015666 treatment reduced the tumor volume, tumor size and tumor weight in mice, and this therapeutic effect was dose-dependent

References:

[1]Liu X, He J, Mao L, Zhang Y, Cui W, Duan S, Jiang A, Gao Y, Sang Y, Huang G. EPZ015666, a selective protein arginine methyltransferase 5 (PRMT5) inhibitor with an antitumour effect in retinoblastoma. *Exp Eye Res.* 2021 Jan;202:108286.

[2]Jiang Y, Yuan Y, Chen M, Li S, Bai J, Zhang Y, Sun Y, Wang G, Xu H, Wang Z, Zheng Y, Nie H. PRMT5 disruption drives antitumor immunity in cervical cancer by reprogramming T cell-mediated response and regulating PD-L1 expression. *Theranostics.* 2021 Aug 28;11(18):9162-9176.

Background

EPZ015666 is a novel and selective inhibitor of protein arginine methyltransferase 5 (PRMT5) [1] with an IC₅₀ value <10nM[2]. a key member of the protein arginine methyltransferase (PRMTs) family [3]. PRMT5 plays a critical role in various cellular processes, including transcriptional repression, RNA splicing, and signal transduction[4]. EPZ015666 demonstrates potent inhibitory activity against PRMT5 in multiple cancer types[5].

In vitro, treatment of Retinoblastoma (RB) cells with EPZ015666 (0–30μM) for 24–72h significantly inhibited cell proliferation in a time-and dose-dependent manner. This was accompanied by a reduction in Cyclin-Dependent Kinase 2 (CDK2) protein levels and an increase in the expression of key tumor suppressor proteins Cyclin-Dependent Kinase Inhibitor 1A, CDK-interacting protein 1 (P21), Cyclin-Dependent Kinase Inhibitor 1B (P27), and Tumor Protein P53 (P53) [1]. In U14 cells, exposure to EPZ015666 (10μM) did not affect cell viability or proliferation but suppressed PD-L1 expression[6]. Similarly, treatment of iSLK.RGB cells with EPZ015666 (50μM) for 48h resulted in marked inhibition of cell proliferation [7].

In vivo, administration of EPZ015666 (25 mg/kg/day and 75 mg/kg/day) via intraperitoneal injection for 12 days in mice bearing U14 cell xenografts resulted in a reduction in tumor volume, tumor size, and tumor weight in a dose-dependent manner [6]. Furthermore, oral treatment with EPZ015666

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(150mg/kg of body weight twice a day) for 21 days in a xenograft mouse model using Retinoblastoma cells (Y79 cells) significantly suppressed tumor growth [1].

References:

- [1] Liu X, He J, Mao L, Zhang Y, Cui W, Duan S, Jiang A, Gao Y, Sang Y, Huang G. EPZ015666, a selective protein arginine methyltransferase 5 (PRMT5) inhibitor with an antitumour effect in retinoblastoma. *Exp Eye Res.* 2021 Jan;202:108286.
- [2] 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.
- [3] Zhang S, Ma Y, Hu X, Zheng Y, Chen X. Targeting PRMT5/Akt signalling axis prevents human lung cancer cell growth. *J Cell Mol Med.* 2019 Feb;23(2):1333-1342.
- [4] Liu C, Zou W, Nie D, Li S, Duan C, Zhou M, Lai P, Yang S, Ji S, Li Y, Mei M, Bao S, Jin Y, Pan J. Loss of PRMT7 reprograms glycine metabolism to selectively eradicate leukemia stem cells in CML. *Cell Metab.* 2022 Jun 7;34(6):818-835.e7.
- [5] Zheng J, Li B, Wu Y, Wu X, Wang Y. Targeting Arginine Methyltransferase PRMT5 for Cancer Therapy: Updated Progress and Novel Strategies. *J Med Chem.* 2023 Jul 13;66(13):8407-8427.
- [6] Jiang Y, Yuan Y, Chen M, Li S, Bai J, Zhang Y, Sun Y, Wang G, Xu H, Wang Z, Zheng Y, Nie H. PRMT5 disruption drives antitumor immunity in cervical cancer by reprogramming T cell-mediated response and regulating PD-L1 expression. *Theranostics.* 2021 Aug 28;11(18):9162-9176.
- [7] Niu D, Ma Y, Ren P, Chang S, Li C, Jiang Y, Han C, Lan K. Methylation of KSHV vCyclin by PRMT5 contributes to cell cycle progression and cell proliferation. *PLoS Pathog.* 2024 Sep 10;20(9):e1012535.

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