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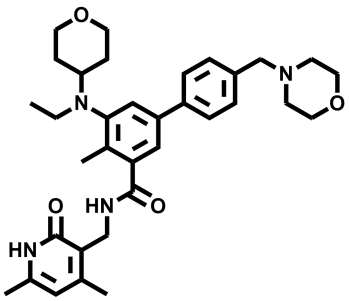
EZH2 Methyltransferase Inhibitor – EPZ-6438 (E7438)

Chemical Name: N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-5-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-4-methyl-4'-(morpholinomethyl)-[1,1'-biphenyl]-3-carboxamide



Molecular Weight:	572.74
Formula:	$C_{34}H_{44}N_4O_4$
Purity:	≥98%
CAS#:	1403254-99-8
Solubility:	DMSO up to 100 mM
Storage	Powder: 4 °C 1 year DMSO: 4 °C 3 months -20 °C 1 year

Biological Activity:

EPZ-6438 (E7438) is a potent and selective small molecule inhibitor of histone methyltransferase EZH2. It inhibited the activity of human PRC2-containing wild-type EZH2 with an inhibition constant (Ki) value of 2.5 ± 0.5 nM, and similar potency was observed for EZH2 proteins bearing all known lymphoma change-of-function mutations. EPZ-6438 inhibits EZH2 in a manner competitive with the substrate S-adenosylmethionine (SAM). EPZ-6438 displayed a 35-fold selectivity versus EZH1 and >4,500-fold selectivity relative to 14 other HMTs (encompassing both lysine and arginine HMTs) tested. It specifically inhibits cellular H3K27 methylation leading to selective apoptotic killing of SMARCB1 mutant MRT Cells. It also induced genes of neuronal differentiation and cell cycle inhibition while suppressing expression of Hedgehog pathway genes, MYC and EZH2. Moreover EPZ-6438 leads to complete and sustained regression of SMARCB1 mutant MRT xenografts, and sevral EZH2 mutant xenografts including WSU-DLCL2 (Y614F), Pfeiffer (Y677G), KARPAS-422 (Y641N) etc. Epizyme has initiated a Phase 1/2 clinical trials targeting the treatment of non-Hodgkin lymphoma.

How to Use:

In vitro: EPZ-6438 was used at 1 μM final concentration in vitro and in cellular assays.

In vivo: EPZ-6438 was orally dosed to mice at 250-500 mg/kg twice per day for 21-28 days, leaded to complete and sustained regression of SMARCB1 mutant MRT xenografts (SCID mice bearing s.c. G401 xenograft).

Reference:

1. Knutson SK, et al. Durable tumor regression in genetically altered malignant rhabdoid tumors by inhibition of methyltransferase EZH2. (2013) Proc Natl Acad Sci U S A. 110(19):7922-7.
2. Robert A Copeland. Protein methyltransferases in cancer. (2013) AACR Annual Meeting.