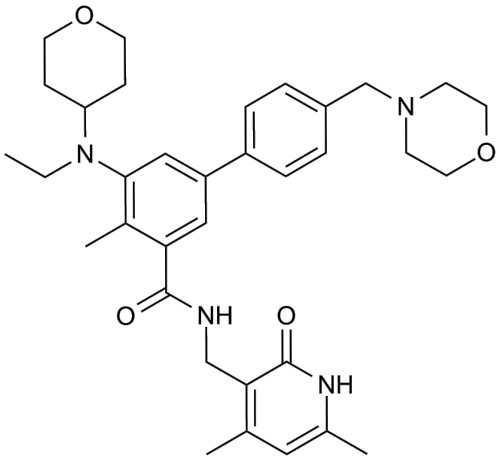
Product Data Sheet

Product Name: EPZ-6438
Cat. No.: GC14062

Chemical Properties

Cas. No.	1403254-99-8		
Chemical Name	N-[(4,6-dimethyl-2-oxo-1H-pyridin-3-yl)methyl]-3-[ethyl(oxan-4-yl)amino]-2-methyl-5-[4-(morpholin-4-ylmethyl)phenyl]benzamide		
SMILES	CCN(C1CCOCC1)C2=CC(=CC(=C2C)C(=O)NCC3=C(C=C(NC3=O)C)C)C4=CC=C(C=C4)CN5CCOCC5		
Formula	$C_{34}H_{44}N_4O_4$	M.Wt	572.74
Solubility	≥ 28.637mg/mL in DMSO	Storage	Desiccate 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]:

Cell lines SMARCB1-deficient MRT cells

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Preparation method	Limited solubility. General tips for obtaining a higher concentration: Please warm the tube at 37 °C for 10 minutes and/or shake it in the ultrasonic bath for a while. Stock solution can be stored below -20°C for several months.
Reaction Conditions	4-7 days
Applications	EPZ-6438 induces a reduction of global H3K27Me3 level in a concentration-dependent manner. In addition, EPZ-6438 leads to a substantial antiproliferative effects as IC50 values within nanomolar range. Treatment of EPZ-6438 results in expression of CD133, DOCK4, and PTPRK and up-regulates CDKN1A and CDKN2A and BIN1in a time-dependent manner.

Animal experiment [2]:

Animal models	SCID mice bearing EZH2-mutant lymphoma xenografts.
Dosage form	3 times daily every 8 hours, 2 times a day every 12 hours, or once a day schedules for either 7 or 28 days by oral gavage.
Applications	EPZ-6438 dose-dependently causes a reduction of tumor H3K27Me3 levels (EC50 =23 nmol/L). EPZ-6438 also shows a remarkable antitumor effects in a dose dependent manner with 2 cycles of 7-day on/7-day off and 21-day on/7-day off schedules. All EPZ-6438 dose groups except the lowest one leads to complete tumor regressions.
Other notes	Please test the solubility of all compounds indoor, and the actual solubility may slightly differ with the theoretical value. This is caused by an experimental system error and it is normal.

Caution: Product has not been fully validated for medical applications. For research use only.
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References:

1. Knutson SK, Warholic NM, Wigle TJ et al. Durable tumor regression in genetically altered malignant rhabdoid tumors by inhibition of methyltransferase EZH2. Proc Natl Acad Sci U S A. 2013 May 7;110(19):7922-7.

2. Knutson SK, Kawano S, Minoshima Y et al. Selective inhibition of EZH2 by EPZ-6438 leads to potent antitumor activity in EZH2-mutant non-Hodgkin lymphoma. Mol Cancer Ther. 2014 Apr;13(4):842-54.

Background

EPZ-6438 is a potent and bio-available inhibitor of EZH2, the catalytic subunit of polycomb repressive complex 2 (PRC2) catalyzing the methylation of lysine 27 of histone H3 (H3K27), that inhibits the activity of human PRC2-containing wild-type EZH2 with a value of inhibition constant K_i of 2.5 nM. EPZ-6438 competitively binds to the S-adenosylmethionine (SAM) binding site of EZH2 and also non-competitively binds to the binding sites of peptide or nucleosome substrate. EPZ-6438 selectively inhibits EZH2 with selectivity 35-fold greater than EZH1. Study results have suggested that EPZ-6438 exhibits dramatic and permanent anti-tumor activity in MRT models through synergistic effects of EPZ-6438-mediated EZH2 inhibition on several cancer pathways.

Reference

[1].Sarah K. Knutson1, Natalie M. Warholic, Tim J. Wigle, Christine R. Klaus, Christina J. Allain, Alejandra Raimondi, Margaret Porter Scott, Richard Chesworth, Mikel P. Moyer, Robert A. Copeland, Victoria M. Richon, Roy M. Pollock, Kevin W. Kuntz, and Heike Keilhack. Durable tumor regression in genetically altered malignant rhabdoid tumors by inhibition of methyltransferase EZH2. PNAS 2013; 110(19): 7922-7927

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