Product Data Sheet

Product Name: CPI-1205
Cat. No.: GC16298

Chemical Properties

Cas. No.	1621862-70-1		
Chemical Name	(R)-N-((4-methoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-1-(1-(1-(2,2,2-trifluoroethyl)piperidin-4-yl)ethyl)-1H-indole-3-carboxamide		
SMILES	CC1=CC(OC)=C(CNC(C2=C(C)N([C@H](C)C3CCN(CC(F)(F)F)CC3)C4=C2C=CC=C4)=O)C(N1)=O		
Formula	$C_{27}H_{33}F_3N_4O_3$	M.Wt	518.57
Solubility	Soluble in DMSO	Storage	Store at -20°C
General tips	For obtaining a higher solubility , please warm the tube at 37 ℃ and shake it in the ultrasonic bath for a while.Stock solution can be stored below -20℃ 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	CPI-1205		

Protocol

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Kinase experiment:

PRC2 (wt or Y641N mutant), biotinylated nucleosome, H3K27me3 activator peptide and CPI-1205 (in DMSO) are incubated in 50 mM Tris, pH 8.5, 5 mM MgCl2, 1 mM DTT, 70 uM Brij-35, and 0.1 mg/mL BSA for 30 minutes. Reaction is initiated by addition of [3H]-SAM to final conditions of 5 nM PRC2, 200 nM nucleosome (concentration expressed as H3), activator peptide (3.6 μM) and 200 nM [3H]-SAM in a total volume of 25 μL in 384 well Greiner plates. For CPI-1205 analysis assays are either single point or ten point dose-responses with final total DMSO of 0.8 or 1.6% (v/v). Typically assays are run for 60 minutes with <35% substrate turnover. After reaction assays are quenched by addition of 20 μL of 2 mM SAH and 200 mM EDTA in 50 mM Tris, pH 8.5. Reactions are transferred to streptavidin-coated FlashPlates, incubated for 2 h, aspirated, washed, and read on a TopCount[1].

Cell experiment:

Ten different doses of each test compound (in a series of 3-fold dilutions) are plated in duplicate 384-well tissue culture treated plates. HeLa cells grown in culture are trypsinized and counted. Cell are diluted to 67,000 cells per mL in10% DMEM and 15 μL (1,000 cells) are plated into each well using the Biotek MicroFloTM Select Dispenser. Plates are incubated at 37°C/5% CO2 for 72 hrs. One of the duplicate plates is processed for AlphaLISA and the other for viability. Cell viability is assayed by adding 15 μL of Cell Titer Glo to each well with cells with media. The plates are incubated at RT for 15-20 minutes on a plate shaker at low speed. The plates are then read using an EnVision-Alpha Reader[1].

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Animal experiment:

Rats[1] CPI-1205 is orally administered in a GLP compliant toxicity study for 4 weeks to both Sprague-Dawley rats and beagle dogs followed by a 4-week recovery period. CPI-1205 is administered by oral gavage at single daily doses (QD) of 100, 300, and 600 mg/kg to rats for 28 days and at twice daily doses (BID) of 50, 150, and 500 mg/kg for 28 days to dogs. In general, CPI-1205 is well-tolerated in the 28-day GLP toxicology studies, and any findings are reversible over the recovery period.

References:

[1]. Vaswani RG, et al. Identification of (R)-N-((4-Methoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-1-(1-(1-(2,2,2-trifluoroethyl)piperidin-4-yl)ethyl)-1H-indole-3-carboxamide (CPI-1205), a Potent and Selective Inhibitor of Histone Methyltransferase EZH2, Suitable for Phase I Clinical Trials for B-Cell Lymphomas. J Med Chem. 2016 Nov 10;59(21):9928-9941.

Background

0.002 μM for biochemical IC50; 0.032 μM for cellular EC50.

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CPI-1205 is an EZH2 inhibitor.

Polycomb repressive complex 2 (PRC2) plays a key role in transcriptional silencing partially by installing methylation marks on lysine 27 of histone 3. Dysregulation of PRC2 function relates with certain malignancies and poor prognosis. EZH2 is thus representing a promising candidate oncology target for pharmacological intervention.

In vitro: Previous study reported that the treatment with CPI-1205 caused apoptosis in multiple myeloma and plasmacytoma cell models. CPI-1205 also had a clean selectivity profile when tested against 30 other histone or DNA methyltransferases. In addition, CPI-1205 demonstrated modest selectivity when tested against enhancer of zeste homologue 1 (EZH1) that is a methyltransferase highly related to EZH2 [1].

In vivo: In animal study, CPI-1205 was dosed at 160 mg/kg orally twice daily for 25 days in tumor bearing female CB-17 SCID mice. By the treatment of tumor-bearing mice with CPI-1205, tumor regression was observed within two weeks. By the end of day 25, significant tumor growth inhibition was recorded. CPI-1205 was found to be well-tolerated for repeat dosing as observed by the absence of significant body weight loss. In addition, analysis of plasma and tumor at 1 h post last dose on day 25 showed sufficient plasma and tumor tissue concentrations [1].

Clinical trial: A study to evaluate CPI-1205 in patients with B-cell lymphomas is currently recruiting participants [2].

References:
[1] Vaswani RG et al. Identification of (R)-N-((4-Methoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-1-(1-(1-(2,2,2-trifluoroethyl)piperidin-4-yl)ethyl)-1H-indole-3-carboxamide (CPI-1205), a Potent and Selective Inhibitor of Histone Methyltransferase EZH2, Suitable for Phase I Clinical Trials for B-Cell Lymphomas. J Med Chem. 2016 Nov 10;59(21):9928-9941.
[2] https://clinicaltrials. gov/ct2/show/NCT02395601 term=CPI-1205&rank=1.

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