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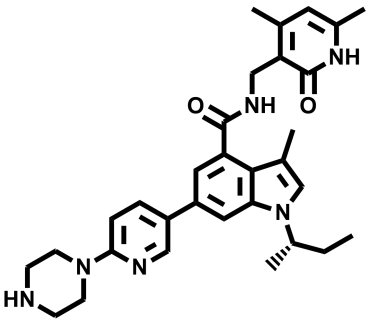
EZH2 Methyltransferase Inhibitor – GSK126

Chemical Name: (S)-1-(sec-butyl)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3-methyl-6-(6-(piperazin-1-yl)pyridin-3-yl)-1H-indole-4-carboxamide



Molecular Weight:	526.67
Formula:	$C_{31}H_{38}N_6O_2$
Purity:	≥98%
CAS#:	1346574-57-9
Solubility:	DMSO up to 100 mM
Storage	Powder: 4°C 1 year DMSO: 4°C 3 month -20°C 1 year

Biological Activity:

GSK126 is a highly potent and selective small molecule inhibitor of histone methyltransferase EZH2. It potently inhibits both wild-type and mutant EZH2 methyltransferase activity with similar potencies (Ki^{app} 0.5–3 nM), independent of substrate used, and is competitive with S-adenosylmethionine (SAM) and non-competitive with peptide substrates. GSK126 is highly selective against other methyltransferases and multiple other protein classes, even 150-fold more selective for the closest EZH1 (Ki^{app} 89 nM) and more than 1,000-fold selective for 20 other human methyltransferases, including both SET-domain-containing and non-SET domain-containing methyltransferases. It induced a 50% loss of H3K27me3 in both EZH2 wild-type and mutant DLBCL cell lines at nM concentrations independent of EZH2 mutation status. GSK126 can decrease global H3K27me3 levels and reactivate silenced PRC2 target genes. It effectively inhibits the proliferation of EZH2 mutant DLBCL cell lines, and markedly inhibits the growth of EZH2 mutant DLBCL xenografts in mice. Pharmacological inhibition of EZH2 activity may provide a promising treatment for EZH2 mutant lymphoma.

How to Use:

In vitro: GSK126 was used at 0.5-2 μM final concentration in vitro and in cellular assays.

In vivo: GSK126 was intraperitoneally (IP) dosed to mice at 50-150 mg/kg once per day, or 300 mg/kg twice per week in subcutaneous xenografts of KARPAS-422 and Pfeiffer cells.

Reference:

1. McCabe MT, et al. EZH2 inhibition as a therapeutic strategy for lymphoma with EZH2-activating mutations. (2012) Nature. 492(7427):108-12.