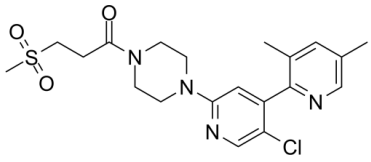
Data Sheet

Product Name:	PF-5274857
Cat. No.:	CS-1206
CAS No.:	1373615-35-0
Molecular Formula:	C20H25ClN4O3S
Molecular Weight:	436.96
Target:	Smo
Pathway:	Stem Cell/Wnt
Solubility:	DMSO : 125 mg/mL (286.07 mM; Need ultrasonic)



BIOLOGICAL ACTIVITY:

PF-5274857 is a potent and selective Smoothened (Smo) antagonist, inhibits Hedgehog (Hh) signaling with IC50 and Ki of 5.8 nM and 4.6 nM, respectively, and can penetrate the blood–brain barrier. IC50 value: 5.8 nM Target: Smoothened in vitro: PF-5274857 completely inhibits Shh-induced Hh pathway activity with IC50 of 2.7 nM measured by the transcriptional activity of Smo downstream gene Gli1 in MEF cells. The μ-opioid receptor is weakly inhibited by PF-5274857 with a dissociation constant of 36 μM subsequently determined in a functional assay [1]. in vivo: PF-5274857 shows significant dose-dependent tumor growth inhibition (TGI) and induces tumor regression at high doses(>10 mg/kg)., PF-5274857 downregulates Gli1, Gli2, Ptch1, and Ptch2 gene expression levels to various degrees with maximal effects being achieved between 6 and 12 hours post-dose (Gli1 is the most sensitive gene), whereas PF-5274857 has little effect on Smo levels. In skin tissue, downregulation of Gli1 and Gli2 is also observed with a similar time course by PF-5274857. The model-derived drug concentration for half maximal inhibition of the tumor Gli1 mRNA production rate (IC50) by PF-5274857 is determined to be 8.9 nM in the Ptch+/ p53+/ medulloblastoma allograft mice, which mathematically corresponds to tumor regression of 119% TGI after 6 days of plasma exposure at this concentration. In the Ptch+/ p53 / medulloblastoma allograft mice, the IC50 value is estimated to be 3.5 nM, consistent with the Ptch+/ p53+/ results. PF-5274857 is also able to cross the blood–brain barrier in rats within 4 hours post-dose [1].

PROTOCOL (Extracted from published papers and Only for reference)

Cell assay [1] HEK293 cells overexpressing human Smo (amino acids 181–787) were grown in Dulbecco's Modified Eagle's Media (DMEM) supplemented with 10% FBS (Invitrogen), Pen–Strep, and 0.1 mg/mL hygromycin to 90% confluence. After washing with cold Dulbecco's PBS, the cell pellet was resuspended in membrane preparation buffer (50 mmol/L Tris-HCl, pH 7.5, 250 mmol/L sucrose with Roche complete protease cocktail) and homogenized. The homogenate was centrifuged and the cell pellet was resuspended in assay buffer (50 mmol/L Tris-HCl, pH 7.5, 100 mmol/L NaCl, 25 mmol/L MgCl2, 1 mmol/L EDTA, and 0.1% protease-free bovine serum albumin) and homogenized in a glass tissue grinder. Total protein in the membrane preparation containing Smo was determined using the Pierce BCA protein assay (Pierce Chemical).

References:

[1]. Rohner A, et al. Effective targeting of Hedgehog signaling in a medulloblastoma model with PF-5274857, a potent and selective Smoothened antagonist that penetrates the blood-brain barrier. Mol Cancer Ther. 2012, 11(1), 57-65.

CAIndexNames:

1-Propanone, 1-[4-(5'-chloro-3,5-dimethyl[2,4'-bipyridin]-2'-yl)-1-piperazinyl]-3-(methylsulfonyl)-

SMILES:

O=C(N1CCN(C2=NC=C(Cl)C(C3=NC=C(C)C=C3C)=C2)CC1)CCS(=O)(C)=O

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

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