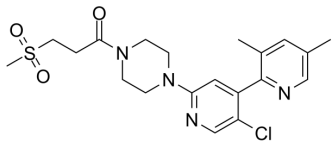
PF-5274857

Cat. No.:	HY-13459
CAS No.:	1373615-35-0
Molecular Formula:	$C_{20}H_{25}ClN_4O_3S$
Molecular Weight:	436.96
Target:	Smo
Pathway:	Stem Cell/Wnt
Storage:	Powder -20°C 3 years 4°C 2 years In solvent -80°C 2 years -20°C 1 year



SOLVENT & SOLUBILITY

In Vitro

DMSO : 125 mg/mL (286.07 mM; Need ultrasonic)

H_2O : < 0.1 mg/mL (ultrasonic;warming;heat to 60°C) (insoluble)

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	2.2885 mL	11.4427 mL	22.8854 mL
5 mM	0.4577 mL	2.2885 mL	4.5771 mL
10 mM	0.2289 mL	1.1443 mL	2.2885 mL

Please refer to the solubility information to select the appropriate solvent.

In Vivo

1. Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
   Solubility: ≥ 2.08 mg/mL (4.76 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.08 mg/mL (4.76 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.08 mg/mL (4.76 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

PF-5274857 is a potent, selective, orally active and brain-penetrant antagonist of Smo, with an IC_{50} of 5.8 nM and K_i of 4.6 nM. PF-5274857 has potential for research of tumor types including brain tumors and brain metastasis driven by an activated Hh pathway[1].

IC_{50} & Target

IC50: 5.8 nM (Smo); Ki: 4.6 nM (Smo)[1]

In Vitro

PF-5274857 completely inhibits Shh-induced Hh pathway activity with an IC_{50} of 2.7±1.4 nM measured by the transcriptional activity of Smo downstream gene Gli1 in MEF cells[1].

PF-5274857 shows less than 20% inhibition against a broad panel of protein kinases at 1 μM[1].

MCE has not independently confirmed the accuracy of these methods. They are for reference only.

In Vivo

PF-5274857 (1-30 mg/kg; p.o. once daily for 6 days) shows robust antitumor efficacy and correlation between PK and PD in medulloblastoma allograft mice models[1].

PF-5274857 (10 mg/kg; i.h.) in the plasma is able to cross the blood-brain barrier in rats within 4 hours postdose[1].

PF-5274857 (10-100 mg/kg; p.o. once daily for 4 days) is able to target Smo in the brain leading to the downregulation of Hh pathway activity in the brain tumor[1].

PF-5274857 (30 mg/kg; p.o. once daily for 34 days) increases the survival rates of primary $Ptch^{+/-}$ $p53^{-/-}$ medulloblastoma mice[1].

PF-5274857 (5-30 mg/kg; p.o.) exhibits the apparent volume of distribution of 5.6±0.5 L/kg and the half-life ($T_{1/2}$) of 1.7±0.1 hours[1].

MCE has not independently confirmed the accuracy of these methods. They are for reference only.

Animal Model:	Severe combined immunodeficient (SCID)-beige mice (6-8 weeks old) are genetically engineered[1]
Dosage:	0, 1, 5, 10, 30 mg/kg
Administration:	P.o. once daily for 6 days
Result:	Showed robust antitumor activity with an in vivo IC_{50} of 8.9±2.6 nM.

Animal Model:	Severe combined immunodeficient (SCID)-beige mice (6-8 weeks old)[1]
Dosage:	0, 5, 10, 30 mg/kg (Pharmacokinetic Analysis)
Administration:	A single p.o.
Result:	The apparent volume of distribution of 5.6±0.5 L/kg; the half-life ($T_{1/2}$) of 1.7±0.1 hours.

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.

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