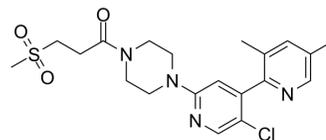


PF-5274857

Cat. No.:	HY-13459		
CAS No.:	1373615-35-0		
Molecular Formula:	C ₂₀ H ₂₅ ClN ₄ O ₃ S		
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)
 H₂O : < 0.1 mg/mL (ultrasonic;warming;heat to 60°C) (insoluble)

Preparing Stock Solutions	Solvent Concentration	Mass		
		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

- 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
- 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
- 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 IC₅₀ 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].

IC₅₀ & Target

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

In Vitro	<p>PF-5274857 completely inhibits Shh-induced Hh pathway activity with an IC₅₀ of 2.7±1.4 nM measured by the transcriptional activity of Smo downstream gene Gli1 in MEF cells^[1].</p> <p>PF-5274857 shows less than 20% inhibition against a broad panel of protein kinases at 1 μM^[1].</p> <p>MCE has not independently confirmed the accuracy of these methods. They are for reference only.</p>																
In Vivo	<p>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].</p> <p>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].</p> <p>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].</p> <p>PF-5274857 (30 mg/kg; p.o. once daily for 34 days) increases the survival rates of primary Ptch^{+/-} p53^{-/-} medulloblastoma mice^[1].</p> <p>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].</p> <p>MCE has not independently confirmed the accuracy of these methods. They are for reference only.</p> <table border="1" data-bbox="347 659 1515 932"> <tr> <td>Animal Model:</td> <td>Severe combined immunodeficient (SCID)-beige mice (6-8 weeks old) are genetically engineered^[1]</td> </tr> <tr> <td>Dosage:</td> <td>0, 1, 5, 10, 30 mg/kg</td> </tr> <tr> <td>Administration:</td> <td>P.o. once daily for 6 days</td> </tr> <tr> <td>Result:</td> <td>Showed robust antitumor activity with an in vivo IC₅₀ of 8.9±2.6 nM.</td> </tr> </table> <table border="1" data-bbox="347 974 1515 1205"> <tr> <td>Animal Model:</td> <td>Severe combined immunodeficient (SCID)-beige mice (6-8 weeks old)^[1]</td> </tr> <tr> <td>Dosage:</td> <td>0, 5, 10, 30 mg/kg (Pharmacokinetic Analysis)</td> </tr> <tr> <td>Administration:</td> <td>A single p.o.</td> </tr> <tr> <td>Result:</td> <td>The apparent volume of distribution of 5.6±0.5 L/kg; the half-life (T_{1/2}) of 1.7±0.1 hours.</td> </tr> </table>	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.
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REFERENCES

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

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

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