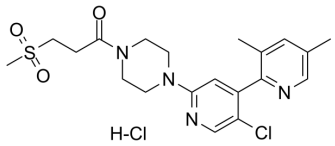
PF-5274857 hydrochloride

Cat. No.:	HY-13459A
CAS No.:	1613439-62-5
Molecular Formula:	$C_{20}H_{26}Cl_2N_4O_3S$
Molecular Weight:	473.42
Target:	Smo
Pathway:	Stem Cell/Wnt
Storage:	Please store the product under the recommended conditions in the Certificate of Analysis.



BIOLOGICAL ACTIVITY

Description	PF-5274857 hydrochloride 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 hydrochloride 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 Jan;11(1):57-65.

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