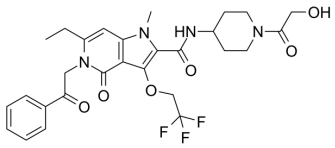
TAK-441

Cat. No.:	HY-16475
CAS No.:	1186231-83-3
Molecular Formula:	$C_{28}H_{31}F_3N_4O_6$
Molecular Weight:	576.56
Target:	Hedgehog
Pathway:	Stem Cell/Wnt
Storage:	-20°C, protect from light * In solvent : -80°C, 6 months; -20°C, 1 month (protect from light)



SOLVENT & SOLUBILITY

In Vitro

DMSO : 100 mg/mL (173.44 mM; Need ultrasonic)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	1.7344 mL	8.6721 mL	17.3442 mL
	5 mM	0.3469 mL	1.7344 mL	3.4688 mL
	10 mM	0.1734 mL	0.8672 mL	1.7344 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: 2.5 mg/mL (4.34 mM); Clear solution; Need ultrasonic
2. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: 2.5 mg/mL (4.34 mM); Clear solution; Need ultrasonic

BIOLOGICAL ACTIVITY

Description

TAK-441 is a highly potent and orally active hedgehog (Hh) signaling inhibitor with an IC_{50}value of 4.4 nM. TAK-441 has strong antitumor activity in solid tumors[1][2][3].

IC_{50} & Target

IC50: 4.4 nM (Gli-luc reporter)[1]

In Vitro

TAK-441 (compound 11d) (0.03–1000 nM, 48 h) has potent activity in the Gli-luc reporter with an IC_{50} value of 4.4 nM and good solubility[1].
TAK-441 (0.03–1000 nM, 48 h) inhibits Gli1 mRNA with IC_{50} values of 0.0457 and 0.113 mg/ml in the tumor and skin, respectively[1].
TAK-441 (0.5-500 nM, 48-72 h) does not affect androgen withdrawal-induced Shh up-regulation or viability of LNCaP cells[3].
TAK-441 (0.5-500 nM, 48-72 h) leads to delayed castration-resistant progression of LNCaP xenografts by disrupting paracrine

Hh signaling with the tumor stroma[3].

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

Cell Viability Assay[1]

Cell Line:	NIH3T3/Gli-luc cells
Concentration:	0.03–1000 nM
Incubation Time:	48 h
Result:	Showed acceptable solubility and potent Hh inhibitory activity.

Cell Cytotoxicity Assay[3]

Cell Line:	LNCaP cells
Concentration:	0.5-500 nM
Incubation Time:	48-72 h
Result:	Did not affect up-regulation of Shh of in vitro viability of LNCaP cells under androgen-deprivedconditionsin.

Western Blot Analysis[3]

Cell Line:	LNCaP, C4-2, DU145 and PC3 cells
Concentration:	
Incubation Time:	
Result:	Reflected androgen-responsive PCa and express both Shh and Dhh in LNCaP and C4-2 cells and reflect restricted Shh expression of CRPC in DU145 and PC3 cells.

In Vivo

TAK-441 (compound 11d) (oral; 10 mg/kg, 100 mg/kg) has favorable exposure and good oral absorption in BALB/c-nu/nu mice[1].

TAK-441 (oral, 1 and 25 mg/kg, QD for 14 days) has strong antitumor activity and can achieve dose-dependent plasma and tumor concentrations by improving the solubility of TAK-441 in $Ptc1^{+/-}p53^{-/-}$ mice bearing medulloblastoma allografts[1].

TAK-441 (iv, 1 mg/kg; po, 10 mg/kg) is able to achieve sufficient exposure following oral administration in rats and dogs[1].

TAK-441 (oral; 1, 10, and 25 mg/kg) shows dose-dependent antitumor activity in xenografted mice, the IC_{50} value for the tumor growth inhibition is 0.075 mg/ml[1].

Pharmacokinetic Parameters of TAK-441 in BALB/c-nu/nu mice (oral and Alzet infusion administration; 100 mg/kg; single)[1].

Compd	Mouse PK 10mg/kg		Mouse PK 100mg/kg	
	Cmax (lg/mL)	AUC (lgh/mL)	Cmax (lg/mL)	AUC (lgh/mL)
1	2.65	12.1	3.63	32.3
11d	5.62	28.3	21.5	206

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

Animal Model:	rats and dogs[1]
Dosage:	1 mg/kg, 10 mg/kg
Administration:	iv, 1 mg/kg; po, 10 mg/kg
Result:	

Compd			Mouse PK 10mg/kg		
	V_{ss}(mL/kg)	CL (mL/h/kg)	$AUC_{0-24h,iv}$ (ng h/mL)	$AUC_{0-24h,po}$ (ng h/mL)	F (%)
Rat	681.6 ± 81.6	397.9 ± 10.1	2532.3 ± 69.1	8031.8 ± 1218.6	31.7
Dog	2181.3 ± 82.8	161.3 ± 35.6	5101.5 ± 685.5	45405.6 ± 5812.0	90.3 ± 8.8

Animal Model:	BALB/c-nu/nu mice[1]
Dosage:	10 mg/kg, 100 mg/kg
Administration:	oral; 10 mg/kg, 100 mg/kg
Result:	Inhibits Gli1 mRNA in the tumor and skin with IC_{50} values of 0.0457 mg/mL and 0.113 mg/mL, respectively.

Animal Model:	$Ptc1^{+/-}p53^{-/-}$ mice[1]
Dosage:	1 and 25 mg/kg
Administration:	oral, 1 and 25 mg/kg, QD for 14 days
Result:	Showed strong antitumor activity and resulted in a dose-dependent PK profile by improving solubility.

REFERENCES

[1]. Tomohiro Ohashi, et al. Discovery of the investigational drug TAK-441, a pyrrolo[3,2-c]pyridine derivative, as a highly potent and orally active hedgehog signaling inhibitor: modification of the core skeleton for improved solubility. Bioorg Med Chem. 2012

[2]. Akifumi Kogame, et al. Pharmacokinetic and pharmacodynamic modeling of hedgehog inhibitor TAK-441 for the inhibition of Gli1 messenger RNA expression and antitumor efficacy in xenografted tumor model mice. Drug Metab Dispos

[3]. Naokazu Ibuki, et al. TAK-441, a novel investigational smoothened antagonist, delays castration-resistant progression in prostate cancer by disrupting paracrine hedgehog signaling. Int J Cancer. 2013 Oct 15;133(8):1955-66.

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

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