Relacatib

Cat. No.: HY-10294

CAS No.: 362505-84-8

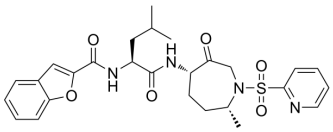
Molecular Formula: $C_{27}H_{32}N_4O_6S$

Molecular Weight: 540.63

Target: Cathepsin

Pathway: Metabolic Enzyme/Protease

Storage: 4°C, protect from light, stored under nitrogen
* In solvent : -80°C, 6 months; -20°C, 1 month (protect from light, stored under nitrogen)



SOLVENT & SOLUBILITY

In Vitro

DMSO : 40 mg/mL (73.99 mM; ultrasonic and warming and heat to 80°C)

Preparing Stock Solutions	Mass / Solvent / Concentration	1 mg	5 mg	10 mg
	1 mM	1.8497 mL	9.2485 mL	18.4969 mL
	5 mM	0.3699 mL	1.8497 mL	3.6994 mL
	10 mM	0.1850 mL	0.9248 mL	1.8497 mL

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

In Vivo

1. SB-462795 (12 mg/kg) or vehicle is in 70% aqueous PEG400(1 ml/kg)[2].
2. SSB-462795 is prepared as a nanosuspension containing 1.5% Methylcellulose and 2.0% sodium lauryl sulfate[2].

BIOLOGICAL ACTIVITY

Description

Relacatib (SB-462795) is a novel, potent, and orally active inhibitor of human cathepsins K, L, and V with K_i values of 41 pM, 68 pM, and 53 pM, respectively. Relacatib inhibits endogenous cathepsin K in situ in human osteoclasts and human osteoclast-mediated bone resorption with IC_{50} values of 45 nM and 70 nM, respectively. Relacatib inhibits bone resorption in vitro in human tissue as well as in cynomolgus monkeys in vivo[1][2].

IC_{50} & Target		
	cathepsin K	cathepsin L

In Vitro

Relacatib are incubated with human osteoclastoma-derived osteoclasts seeded onto bovine cortical bone slices in vitro biological activity, it shows inhibitory potency with K_i values of 0.041 nM, 0.068 nM,0.063 nM,1.6 nM,and 13 nM against human cathepsin K, cathepsin L, cathepsin V, cathepsin S and cathepsin B, respectively in the assay[1].
Relacatib is against Monkey cathepsin K, cathepsin L,cathepsin V and cathepsin B with K_i values of 0.041 nM, 0.28 nM, 0.72 nM and 11nM, respectively. Relacatib is against mouse cathepsin L and rat cathepsin L with K_i values of 0.20 nM and 0.17 nM, respectively[2].

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

In Vivo

Relacatib (1-2 mg/kg 0.5 h intravenous infusion; 2-4 mg/kg oral bolus gavage) exhibits $T_{1/2}$, CL or V_{dss} with 109 mins, 19.5 mL/min/kg, or 1.86 L/kg in male Sprague-Dawley rats and 168 mins, 11.7 mL/min/kg, and 1.79 L/kg in monkeys, respectively in a PK iv/po crossover studies. The oral bioavailability of Relacatib is 28% in the monkey and 89.4% in the rats[1].

SB-462795 (subcutaneous injection; 12 mg/kg; blood sample is drawn 1.5, 4, 24, 48, and 72 h post dose administration) significantly inhibits resorption as assessed by two markers of bone resorption,the N- (NTx) and C-telopeptides (CTx) of type I collagen measured in serum. SB-462795 does not exhibit difference of serum osteocalcin (a biomarker of osteoblast activity) between SB-462795 and vehicle treated animalsexcept for the 48 h time point where a significant reduction (42% lower than baseline vs. 18% lower than baseline with vehicle treatment)[2].

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

Animal Model:	Cynomolgus monkey[2]
Dosage:	12 mg/kg
Administration:	Subcutaneous injection; single dose; blood sample is drawn 1.5, 4, 24, 48, and 72 h post dose administration
Result:	Was sufficiently high to significantly suppress bone resorption from 1.5 to 72 h post dosing.

REFERENCES

[1]. Dennis S Yamashita, et al. Structure Activity Relationships of 5-, 6-, and 7-methyl-substituted azepan-3-one Cathepsin K Inhibitors.J Med Chem

[2]. S Kumar, et al.A Highly Potent Inhibitor of Cathepsin K (Relacatib) Reduces Biomarkers of Bone Resorption Both in Vitro and in an Acute Model of Elevated Bone Turnover in Vivo in Monkeys.Bone. 2007 Jan;40(1):122-31.

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