Cipemastat

Cat. No.: HY-19677

CAS No.: 190648-49-8

Molecular Formula: $C_{22}H_{36}N_4O_5$

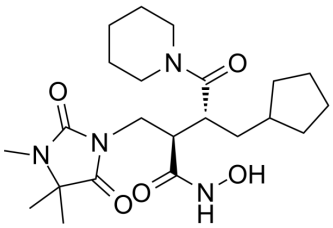
Molecular Weight: 436.55

Target: MMP

Pathway: Metabolic Enzyme/Protease

Storage:

Powder	-20°C	3 years
In solvent	-80°C	6 months
	-20°C	1 month



SOLVENT & SOLUBILITY

In Vitro

DMSO : 100 mg/mL (229.07 mM; Need ultrasonic)

Preparing Stock Solutions	Mass / Solvent / Concentration	1 mg	5 mg	10 mg
	1 mM	2.2907 mL	11.4534 mL	22.9069 mL
	5 mM	0.4581 mL	2.2907 mL	4.5814 mL
	10 mM	0.2291 mL	1.1453 mL	2.2907 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 (5.73 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.5 mg/mL (5.73 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (5.73 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Cipemastat is a potent, competitive inhibitor of human collagenases 1, 2 and 3 with K_is of 3.0, 4.4 and 3.4 nM, respectively.

IC_{50} & Target

collagenases 1 3.0 nM (Ki)	collagenases 2 4.4 nM (Ki)	collagenases 3 3.4 nM (Ki)	stromelysins 1 527 nM (Ki)
gelatinase A 154 nM (Ki)	gelatinase B 59.1 nM (Ki)		

In Vitro

Cipemastat (Ro 32-3555) is a potent, competitive inhibitor of human matrix metalloproteinases. Cipemastat is selective for

	collagenase 1, 2 and 3 relative to related matrix metalloproteinases. Cipemastat is also a potent inhibitor of rat collagenase (IC_{50}=44.7±3.4 nM (n=4)). In vitro cartilage degradation ± inhibited IL-1a induced cartilage degradation in vitro in a concentration-dependent manner with an IC_{50}=60 nM. The inhibition is not mediated by a cytotoxic action on explant chondrocytes. Cipemastat, at all concentrations tested, fail to modify glucose utilization when compared to explants cultured in the presence of IL-La alone[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	The amount of hydroxyproline in non-implanted cartilage is 119.3±4.2 nM/mg and this decreases in cartilages implanted in vehicle-dosed animals to 53.6±7.1 nM/mg over a fourteen day period. Animals administered Cipemastat orally at doses of 2.5, 5, 10 and 25 mg/kg show statistically increased levels of implanted cartilage hydroxypro-line. Fourteen days after the second challenge injection of P. acnes, the area of cartilage most consistently affected by pannus is the lateral femoral condyle, which is the area analysed. In non-arthritic animals the mean cartilage area is 0.17±0.02 mm^2 (n=5). In arthritic animals there is a significant decrease to a mean area of 0.086±0.01 mm^2 (n=10). The group of animals dosed with Cipemastat (50 mg/kg, p.o.) show a significantly greater area of cartilage with a mean value of 0.126±0.012 mm^2 (n=9). The pannus area in vehicle-dosed animals is 0.099±0.017 mm^2 and in Cipemastat dosed animals 0.102±0.019 mm^2. Adjuvant arthritis injection of adjuvant induced two phases of swelling of the injected paw in vehicle-dosed rats. The primary swelling phase occurred between days 0 to 5 and induced an increase in paw volume of 1.9±0.1 mL; the secondary phase occurrs between day 9 to 14 and there was an increase in paw swelling of 0.98±0.08 mL. The group of animals dosed with dexamethasone (0.1 mg/kg) shows a significant reduction in both primary (0.2±0.03 mL) and secondary inflammation (0.07±0.08 mL) paw swelling as well as total inhibition of the lesion score[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Animal Administration [1]	Rats[1] Cipemastat (Ro 32-3555) is formulated in 5% succinylated gelatin and the volume administered to rats is 10 mL/kg, p.o. Female, AHH/R strain rats are used. Rats are anaesthetized in an isoflurane-closed system, and an intra-articular injection of 20 mL of the P. acnes/Freund's incomplete adjuvant emulsion made into the right hind knee. Twenty-eight days later the injection is repeated with the same volume and concentration of antigen to induce the monoarthritis. Animals are orally dosed once daily with either 5% succinylated gelatin as the control vehicle or Cipemastat (50 mg/kg) starting on day 1 after challenge injection. Groups of eight female AHH/R rats are used in these experiments. The animals are dosed twice daily with either 50, 25 or 10 mg/kg Cipemastat, dexamethasone (0.1 mg/kg, s.c. once/day) or vehicle control (10 mL/kg, p.o., b.i.d.). The arthritis is induced by injection into the right hind paws with 0.1 mL of a 5 mg/mL homogenized suspension of Mycobacterium tuberculosis in liquid paraffin. The volume of both the right and left hind paws is measured by water plethysmography by immersing the paw up to the hair line of the ankle. Paw volumes are determined every two or three days[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

REFERENCES

[1]. E J Lewis, et al. Ro 32-3555, an orally active collagenase inhibitor, prevents cartilage breakdown in vitro and in vivo. Br J Pharmacol. 1997 May; 121(3): 540–546.

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