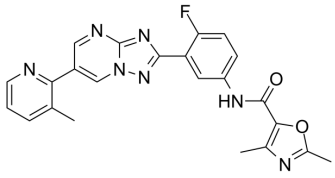
LXE408

Cat. No.:	HY-131350
CAS No.:	1799330-15-6
Molecular Formula:	$C_{23}H_{18}FN_7O_2$
Molecular Weight:	443.43
Target:	Proteasome; Parasite
Pathway:	Metabolic Enzyme/Protease; Anti-infection
Storage:	Powder -20°C 3 years 4°C 2 years In solvent -80°C 6 months -20°C 1 month



SOLVENT & SOLUBILITY

In Vitro

DMSO : 16.67 mg/mL (37.59 mM; ultrasonic and warming and heat to 60°C)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	2.2551 mL	11.2757 mL	22.5515 mL
	5 mM	0.4510 mL	2.2551 mL	4.5103 mL
	10 mM	0.2255 mL	1.1276 mL	2.2551 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: ≥ 0.62 mg/mL (1.40 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 0.62 mg/mL (1.40 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 0.62 mg/mL (1.40 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

LXE408 is an orally active, non-competitive and kinetoplastid-selective proteasome inhibitor. LXE408 has an IC_{50} of 0.04 μM for ***L. donovani*** proteasome and an EC_{50} of 0.04 μM for L. donovani. LXE408 has a low propensity to cross the blood brain barrier. LXE408 has the potential for visceral leishmaniasis (VL) research[1].

In Vitro

LXE408 (compound 1) can occupy the pocket as a ternary complex with the proteasome. LXE408 shows no inhibition of the hERG channel (IC_{50}>30 μM) in a manual patch clamp assay. LXE408 has a low propensity to cross the blood brain barrier (brain/plasma AUC ratio=0.03 in mice)[1].

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

In Vivo

LXE408 (compound 1; 0.3-10 mg/kg; PO; twice daily for 8 days) potently reduces the parasite burden in the liver in a dose-dependent manner[1].

LXE408 (1, 3, 10, 20 mg/kg; p.o.; b.i.d.; for 10 days) effects robust healing of parasite-induced skin lesions at the base of the tail in BALB/c mice infected with L. major[1].

LXE408 (5 mg/kg IV and 20 mg/kg PO) has a $T_{1/2}$ of 3.3 hours for mouse. LXE408 (3 mg/kg IV and 10 mg/kg PO) has a $T_{1/2}$ of 3.8 hours, a CL of 2.1 mL/min•kg, and a V_{ss} of 0.53 L/kg for male Sprague-Dawley rat[1].

LXE408 (0.3 mg/kg IV and 1.0 mg/kg PO) has a $T_{1/2}$ of 3.8 hours for male beagle dog. LXE408 (0.3 mg/kg IV and 10 mg/kg PO) has a $T_{1/2}$ of 9.7 hours for male cynomolgus monkey[1].

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

Animal Model:	Female BALB/c mice (6-8 weeks old) infected with L. donovani[1]
Dosage:	0.3, 1, 3, 10 mg/kg
Administration:	PO; twice daily for 8 days
Result:	Led to a 95% and >99.84% reduction of parasite burden in the liver at 1 mg/kg and 10 mg/kg.

Animal Model:	Balb/C mice[1]
Dosage:	5 mg/kg IV and 20 mg/kg PO (Pharmacokinetic Analysis)
Administration:	IV or PO
Result:	Had a $T_{1/2}$ of 3.3 hours, a CL of 2.3 mL/min•kg, and a V_{ss} of 0.63 L/kg for mouse.

REFERENCES

[1]. Advait Nagle, et al. Discovery and Characterization of Clinical Candidate LXE408 as a Kinetoplastid-Selective Proteasome Inhibitor for the Treatment of Leishmaniases. J Med Chem. 2020 Jul 15.

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