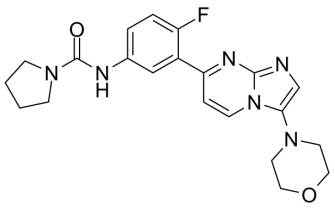
GSK3494245

Cat. No.:	HY-127102
CAS No.:	2080410-41-7
Molecular Formula:	$C_{21}H_{23}FN_6O_2$
Molecular Weight:	410.44
Target:	Parasite; Proteasome
Pathway:	Anti-infection; Metabolic Enzyme/Protease
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 : 100 mg/mL (243.64 mM; Need ultrasonic)

Preparing Stock Solutions	Mass / Solvent / Concentration	1 mg	5 mg	10 mg
	1 mM	2.4364 mL	12.1820 mL	24.3641 mL
	5 mM	0.4873 mL	2.4364 mL	4.8728 mL
	10 mM	0.2436 mL	1.2182 mL	2.4364 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 (6.09 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.5 mg/mL (6.09 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

GSK3494245 (DDD01305143) is a potent, orally active, and selective inhibitor of the chymotrypsin-like activity of the parasite proteasome binding in a site sandwiched between the β4 and β5 subunits (IC_{50}=0.16 μM for WT L. donovani proteasomes). GSK3494245 moderately inhibits chymotrypsin-like activity of human proteasome (IC_{50}: purified 26S=13 μM; enriched THP-1 extracts IC_{50}=40μM). GSK3494245 exhibits attractive biological and biosafety properties[1][2].

In Vitro

GSK3494245 shows EC_{50} value of 5.7 μM in L. donovani intramacrophage assay, where the amastigotes are cultured in differentiated THP-1 cells. GSK3494245 demonstrates good selectivity over mammalian cell growth inhibition (THP-1 cells; EC_{50} > 50 μM)[1].

GSK3494245 (DDD01305143) shows pEC_{50}s of 6.5 and 5.8 against axenic amastigote and ld InMac, respectively. Ld InMac is the intramacrophage assay carried out in THP-1 cells with L. donovani amastigote[2].

	MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	GSK3494245 (25 mg/kg; orally twice a day for 10 consecutive days) elicits a >95% reduction of parasite load in Infected mice (L. donovani, LV9)[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

REFERENCES

[1]. Wyllie S, et al. Preclinical candidate for the treatment of visceral leishmaniasis that acts through proteasome inhibition. Proc Natl Acad Sci U S A. 2019;116(19):9318-9323.

[2]. Thomas MG, et al. Identification of GSK3186899/DDD853651 as a Preclinical Development Candidate for the Treatment of Visceral Leishmaniasis. J Med Chem. 2019;62(3):1180-1202.

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