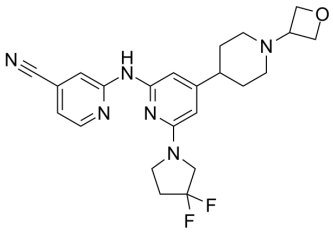
GNE-3511

Cat. No.:	HY-12947
CAS No.:	1496581-76-0
Molecular Formula:	$C_{23}H_{26}F_2N_6O$
Molecular Weight:	440.49
Target:	MAP3K
Pathway:	MAPK/ERK Pathway
Storage:	Powder -20°C 3 years 4°C 2 years In solvent -80°C 1 year -20°C 6 months



SOLVENT & SOLUBILITY

In Vitro

DMSO : 31.25 mg/mL (70.94 mM; Need ultrasonic)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	2.2702 mL	11.3510 mL	22.7020 mL
	5 mM	0.4540 mL	2.2702 mL	4.5404 mL
	10 mM	0.2270 mL	1.1351 mL	2.2702 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: ≥ 2.08 mg/mL (4.72 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

GNE-3511 is an orally active bioavailable and brain-penetrant dual leucine zipper kinase (DLK) inhibitor with a K_i of 0.5 nM. GNE-3511 can cross the blood-brain-barrier and can be used for the research of neurodegenerative diseases[1].

IC_{50} & Target

Ki: 0.5 nM (DLK); IC50: 30 nM (p-JNK), 107 nM (DRG); ⊠5000 nM (MKK4), ⊠5000 nM (MKK7), 129 nM (JNK1),514 nM (JNK2), 364 nM (JNK3), 67.8 nM (MLK1), 767 nM (MLK2) and 602 nM (MLK3)[1]

In Vitro

GNE-3511 has inhibitory activity for p-JNK and DRG with IC_{50} values of 30 nM and 107 nM, respectively[1].
GNE-3511 has kinase selectivity for MKK4, MKK7, JNK1, JNK2, JNK3, MLK1, MLK2 and MLK3 with IC_{50} values of ⊠5000 nM, ⊠ 5000 nM, 129 nM, 514 nM, 364 nM, 67.8 nM, 767 nM and 602 nM, respectively[1].
GNE-3511 displays concentration-dependent protection of neurons from degeneration in vitro[1].
MCE has not independently confirmed the accuracy of these methods. They are for reference only.

In Vivo

GNE-3511 (oral gavage; 75 mg/kg; single) suppresses CYP-induced nociceptive behavior by inhibiting DLK in mice[2].
GNE-3511 (oral gavage; 75 mg/kg; single) suppresses CYP-induced edema and hemorrhage in mouse bladder[2].
GNE-3511 (iv.; 1 mg/kg or po.; 5 mg/kg) exhibits moderate in vivo plasma clearances, moderate volumes of distribution, short half-lives, and brain penetration[2].
Pharmacokinetic Parameters of GNE-3511 (iv.; 1 mg/kg or po.; 5 mg/kg)[2].

species	CL_p (mL/min/kg	Vd_{ss} (L/kg	$t_{1/2}$ (h)	F (%)	B_u/P_u	CSF/P_u
mouse	56	2.5	0.6	45	0.24 at 6 h	
rat	30	3.7	1.8	63	0.7	0.4
dog	41	6.5	4	32		0.4
cynomolgous	16	3.1	2.4	19		0.6

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

Animal Model:	Cystitis mouse model[1]
Dosage:	75 mg/kg
Administration:	oral gavage;75 mg/kg; single
Result:	Significantly reduced the number of nociceptive behavior as well as nociceptive score. Had no impact on bladder weight, did not induce bladder edema or hemorrhage and significantly suppressed CYP-induced increase in bladder weight, bladder edema, and hemorrhage.

Animal Model:	mouse, rat, cynomolgus and dog[2]
Dosage:	1 mg/k, 5 mg/kg
Administration:	iv.; 1 mg/kg or po.; 5 mg/kg
Result:	Exhibited moderate in vivo plasma clearances, moderate volumes of distribution, short half-lives and brain penetration.

CUSTOMER VALIDATION

- Proc Natl Acad Sci U S A. 2018 Oct 16;115(42):E9899-E9908.
- Cell Rep. 2019 Sep 3;28(10):2581-2593.e5.
- Neurobiol Dis. 2021 Dec 16;105586.
- J Innate Immun. 2021 Jun 25;1-10.
- Patent. US20230014181.

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REFERENCES

[1]. Chen Jiang, et al. Neuronal Dual Leucine Zipper Kinase Mediates Inflammatory and Nociceptive Responses in Cyclophosphamide-Induced Cystitis. J Innate Immun

[2]. Patel S et al. Discovery of dual leucine zipper kinase (DLK, MAP3K12) inhibitors with activity in neurodegeneration models. J Med Chem. 2015 Jan 8;58(1):401-18.

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