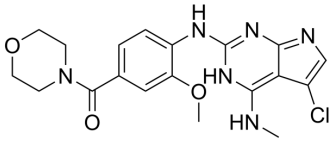
JH-II-127

Cat. No.:	HY-16936
CAS No.:	1700693-08-8
Molecular Formula:	$C_{19}H_{21}ClN_6O_3$
Molecular Weight:	416.86
Target:	LRRK2
Pathway:	Autophagy
Storage:	Powder -20°C 3 years 4°C 2 years In solvent -80°C 2 years -20°C 1 year



SOLVENT & SOLUBILITY

In Vitro

DMSO : 110 mg/mL (263.88 mM; Need ultrasonic)

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	2.3989 mL	11.9944 mL	23.9889 mL
5 mM	0.4798 mL	2.3989 mL	4.7978 mL
10 mM	0.2399 mL	1.1994 mL	2.3989 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: ≥ 2.75 mg/mL (6.60 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.75 mg/mL (6.60 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

JH-II-127 is an orally active, highly potent, selective and brain-permeable LRRK2 inhibitor, with IC_{50}s of 6, 2 and 48 nM for wild-type LRRK2 and LRRK2-G2019S and mutant LRRK2-A2016T. JH-II-127 inhibits Ser935 phosphorylation in all tissues of mice, including the brain. JH-II-127 can be used in the study of parkinson's syndrome[1].

In Vitro

JH-II-127 (0.03, 0.1, 0.3, 1, 3 μM; 90 min) inhibits LRRK2 in HEK293 cells[1].
JH-II-127 (0.3, 1, 3 μM; 90 min) inhibits endogenously expressed LRRK2 in mouse Swiss 3T3 cells[1].
MCE has not independently confirmed the accuracy of these methods. They are for reference only.

Western Blot Analysis[1]

Cell Line:	HEK293 cells (expressing GFP-LRRK2, GFP-LRRK2[G2019S], GFP-LRRK2[G2019S + A2016T], and GFP-LRRK2[A2016T], respectively)
Concentration:	0.03, 0.1, 0.3, 1, 3 μM
Incubation Time:	90 min
Result:	Induced a dose-dependent inhibition of Ser910 and Ser935 phosphorylation in both wild-type LRRK2 and LRRK2[G2019S] stably transfected into HEK293 cells. Inhibited phosphorylation of Ser910 and Ser935 at approximately 0.3 μM for wild-type LRRK2 and LRRK2[G2019S]. Induced dephosphorylation of Ser910 and Ser935 at a concentration of 0.3-1 μM in the drug-resistant LRRK2[A2016T + G2019S] and LRRK2[A2016T] mutants.

Western Blot Analysis[1]

Cell Line:	Mouse Swiss 3T3 cells
Concentration:	0.03, 0.1, 0.3, 1, 3 μM
Incubation Time:	90 min
Result:	Induced similar dose-dependent Ser935 dephosphorylation of endogenous LRRK2.

In Vivo

JH-II-127 (100 mg/kg; i.p.; single) results in near complete dephosphorylation of Ser935 of LRRK2 in all tissues including brain[1].

Pharmacokinetic Parameters of JH-II-127 in Wild type male C57BL/6 mice[1].

matrix	route	T_{max} (h)	C_0/C_{max} (ng/mL)	AUC_{Last} (h•ng/mL)	AUG_{INF} (h•ng/mL)	$T_{1/2}$ (h)	CL (mL/min/kg)	V_{ss} (L/kg)
plasma	IV (2 mg/kg)	-	1604.47	532.67	535.57	0.66	62.24	1.73
plasma	PO (10 mg/kg)	1	802.72	3094.58	3867.07	-	-	-
brain	IV (2 mg/kg)	-	1343.6	239.31	246.47	0.23	135.24	1.7
brain	PO (10 mg/kg)	1	247.35	688.21	762.38	-	-	-

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

Animal Model:	Wild type male C57BL/6 mice[1].
Dosage:	2 mg/kg (for i.v.); 10 mg/kg (for p.o.); 10, 30, 100 mg/kg (for i.p.)
Administration:	Intravenous and intraperitoneal injection; oral administration; single.
Result:	Led to near complete dephosphorylation of Ser935 of LRRK2 in all tissues including brain when at 100 mg/kg of i.p. and near complete inhibition in all tissues at 30 mg/kg but only partial inhibition in brain at the 10 mg/kg dose. Demonstrated good oral bioavailability.

REFERENCES

[1]. Hatcher JM, et al. Discovery of a Pyrrolopyrimidine (JH-II-127), a Highly Potent, Selective, and Brain Penetrant LRRK2 Inhibitor. ACS Med Chem Lett. 2015 Apr 7;6(5):584-9.

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