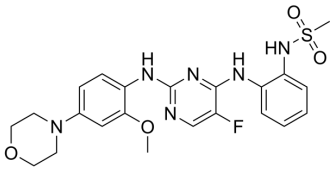
CZC-25146

Cat. No.:	HY-15800A
CAS No.:	1191911-26-8
Molecular Formula:	$C_{22}H_{25}FN_6O_4S$
Molecular Weight:	488.54
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 : ≥ 46 mg/mL (94.16 mM)

* "≥" means soluble, but saturation unknown.

Preparing Stock Solutions	Mass / Solvent / Concentration	1 mg	5 mg	10 mg
	1 mM	2.0469 mL	10.2346 mL	20.4692 mL
	5 mM	0.4094 mL	2.0469 mL	4.0938 mL
	10 mM	0.2047 mL	1.0235 mL	2.0469 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 (5.12 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (5.12 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

CZC-25146 is a potent and orally active LRRK2 inhibitor with IC_{50} values of 4.76 nM and 6.87 nM for wild-type LRRK2 and G2019S LRRK2, respectively. CZC-25146 inhibits PLK4, GAK, TNK1, CAMKK2 and PIP4K2C as well. CZC-25146 prevents mutant LRRK2-induced injury of neurons in vitro. CZC-25146 exhibits relatively favorable pharmacokinetic properties in mice. CZC-25146 can increase normal α-1-antitrypsin (AAT) secretion and reduce inflammatory cytokines. CZC-25146 can be used to research Parkinson's disease and liver diseases[1][2][3].

IC_{50} & Target

IC_{50}: 4.76 nM (wild-type LRRK2), 6.87 nM (G2019S LRRK2)[1]

In Vitro

CZC-25146 (0.01-5 μM; 7 days) does not cause cytotoxicity in human cortical neurons, nor blocking neuronal development[1].

CZC-25146 (0.01-5 μM; 2 days) potently attenuates G2019S LRRK2-mediated toxicity in primary rodent neurons in a concentration-dependent manner with an EC_{50} of ~100 nM[1].
CZC-25146 (0.06-1000 nM) rescues LRRK2 G2019S-induced neurite defects in primary human neurons in a dose-dependent manner[1].
CZC-25146 (14.3 and 28.6 μM; 48 h) markedly reduces The mutant AAT encoded by the Z allele (ATZ) polymer load and restores AAT secretion in iPSC-Hepatocyte, without compromising cell viability[3].
MCE has not independently confirmed the accuracy of these methods. They are for reference only.

Cell Cytotoxicity Assay[1]

Cell Line:	Human cortical neurons
Concentration:	0.01, 0.1, 1 and 5 μM
Incubation Time:	7 days
Result:	Did not cause cytotoxicity in human cortical neurons at concentrations below 5 μM over a seven-day treatment in culture, nor did it block neuronal development.

In Vivo

CZC-25146 (250 mg/kg; p.o.; 14 days) reduces the ATZ polymer levels in over expressing human polymeric ATZ mice[3].
CZC-25146 (1 mg/kg for i.v.; 5 mg/kg for p.o.; single dosage) exhibits relatively good pharmacokinetic properties and an extensive distribution throughout animal body following intravenous injection into mice[1].
MCE has not independently confirmed the accuracy of these methods. They are for reference only.

Animal Model:	Genetically modified male mice (6 weeks; over expressing human polymeric ATZ)[3]
Dosage:	250 mg/kg
Administration:	p.o.; 14 days
Result:	Dramatically and reproducibly reduced the ATZ polymer levels with an overall reduction from 60% in the control group to 37%.

Animal Model:	Male CD-1 mice[1]
Dosage:	1 mg/kg for i.v.; 5 mg/kg for p.o.
Administration:	i.v. and p.o.; single dosage
Result:	Pharmacokinetic Parameters of CZC-25146 in male CD-1 mice[1].

	i.v. (1 mg/kg)	p.o. (5 mg/kg)
CL (L/h/kg)	2.3	
V_{ss} (L/kg)	5.4	
$t_{1/2}$ (h)	1.6	1
t_{max} (h)	0	0.25
C_{max} (ng/mL)	154	1357

AUC_{last} (ng/mL·h)	419	2878
AUC_{inf} (ng/mL·h)	434	2894
F (%)		133

REFERENCES

[1]. Atashrazm F, et al. LRRK2 inhibitors and their potential in the treatment of Parkinson's disease: current perspectives. Clin Pharmacol. 2016 Oct 20;8:177-189.

[2]. Deniz Kent, et al. Small molecule screen employing patient-derived iPS hepatocytes identifies LRRK2 as a novel therapeutic target for Alpha1 Antitrypsin Deficiency.

[3]. Ramsden N, et al. Chemoproteomics-based design of potent LRRK2-selective lead compounds that attenuate Parkinson's disease-related toxicity in human neurons. ACS Chem Biol. 2011 Oct 21;6(10):1021-8.

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