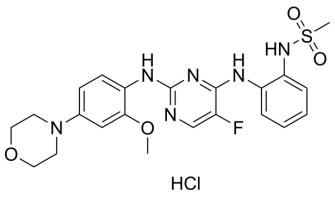
CZC-25146 hydrochloride

Cat. No.:	HY-15800
CAS No.:	1330003-04-7
Molecular Formula:	$C_{22}H_{26}ClFN_6O_4S$
Molecular Weight:	525
Target:	LRRK2
Pathway:	Autophagy
Storage:	Please store the product under the recommended conditions in the Certificate of Analysis.



BIOLOGICAL ACTIVITY

Description	CZC-25146 hydrochloride is a potent LRRK2 inhibitor with IC_{50} values of 4.76 nM and 6.87 nM for wild-type LRRK2 and G2019S LRRK2, respectively. CZC-25146 hydrochloride inhibits PLK4, GAK, TNK1, CAMKK2 and PIP4K2C as well. CZC-25146 hydrochloride prevents mutant LRRK2-induced injury of neurons in vitro. CZC-25146 hydrochloride exhibits relatively favorable pharmacokinetic properties in mice. CZC-25146 hydrochloride can increase normal α-1-antitrypsin (AAT) secretion and reduce inflammatory cytokines. CZC-25146 hydrochloride 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 (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]. CZC-25146 (250 mg/kg; p.o.; 14 days) reduces the ATZ polymer levels in over expressing human polymeric ATZ mice[3]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

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

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%

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.

Caution: Product has not been fully validated for medical applications. For research use only.

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