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SZABO-SCANDIC HandelsgmbH

Quellenstraße 110, A-1100 Wien

T. +43(0)1 489 3961-0

F. +43(0)1 489 3961-7

mail@szabo-scandic.com

www.szabo-scandic.com

linkedin.com/company/szaboscandic

LRRK2-IN-1

Cat. No.: HY-10875

CAS No.: 1234480-84-2

Molecular Formula: $C_{31}H_{38}N_8O_3$

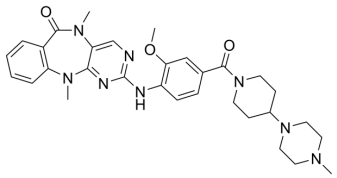
Molecular Weight: 570.69

Target: LRRK2; Apoptosis

Pathway: Autophagy; Apoptosis

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 : 30 mg/mL (52.57 mM; Need ultrasonic)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	1.7523 mL	8.7613 mL	17.5226 mL
	5 mM	0.3505 mL	1.7523 mL	3.5045 mL
	10 mM	0.1752 mL	0.8761 mL	1.7523 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 (4.38 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.5 mg/mL (4.38 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (4.38 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

LRRK2-IN-1 is a potent and selective LRRK2 inhibitor with IC_{50} of 6 nM and 13 nM for LRRK2 (G2019S) and LRRK2 (WT), respectively.

IC_{50} & Target

IC50: 13 nM (WT), 6 nM (G2019S)

In Vitro

Wild-type and G2019S transduction results in 2.5 fold higher TR-FRET signal which can be inhibited by LRRK2-IN-1 in a dose-dependent manner with IC_{50} values of 0.08 μM and 0.03 μM, respectively[1]. LRRK2-IN-1 possessed an IC_{50} of 45 nM for

	inhibition of DCLK2 and exhibits an IC_{50} of greater than 1 μM when evaluated in biochemical assays for AURKB, CHEK2, MKNK2, MYLK, NUAK1, and PLK1. LRRK2-IN-1 is confirmed to inhibit MAPK7 with an EC_{50} of 160 nM. LRRK2-IN-1 induces a dose dependent inhibition of Ser910 and Ser935 phosphorylation accompanied by loss of 14-3-3 binding to both wild type LRRK2 and LRRK2[G2019S] stably transfected into HEK293 cells[2]. LRRK2-IN-1 is moderately cytotoxic with IC_{50} of 49.3 μM in HepG2 cells. LRRK2-IN-1 exhibits genotoxicity in the presence and absence of S9 at 15.6 and 3.9 μM, respectively[3]. LRRK2-IN-1 inhibits proliferation, migration, and induces cell death with hallmarks of apoptosis of HCT116 and AsPC-1 cells[4]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	LRRK2-IN-1 (100 mg/kg, i.p.) induces dephosphorylation of LRRK2 in the kidney of the mice[2]. Peritumoral injection of LRRK2-IN-1 (100 mg/kg) results in a significant decrease in tumor volume and weight of AsPC-1 tumor xenografts[4]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Kinase Assay [2]	Active GST-LRRK2 (1326-2527), GST-LRRK2 [G2019S] (1326-2527), GST-LRRK2 [A2016T] (1326-2527) and GST-LRRK2 [A2016T+G2019S] (1326-2527) enzyme is purified with glutathione sepharose from HEK293 cell lysate 36 h following transient transfection of the appropriate cDNA constructs. Peptide kinase assays, performed in duplicate, are set up in a total volume of 40 μL containing 0.5 μg LRRK2 kinase (which at approximately 10% purity gives a final concentration of 8 nM) in 50 mM Tris/HCl, pH 7.5, 0.1 mM EGTA, 10 mM $MgCl_2$, 20 μM Nictide, 0.1 μM [γ-^{32}P]ATP (500 cpm/pmol) and the indicated concentrations of inhibitor dissolved in DMSO. After incubation for 15 min at 30°C, reactions are terminated by spotting 35 μL of the reaction mix onto P81 phosphocellulose paper and immersion in 50 mM phosphoric acid. Samples are washed extensively and the incorporation of [γ-^{32}P]ATP into Nictide is quantified by Cerenkov counting. IC_{50} values are calculated with GraphPad Prism using non-linear regression analysis. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Cell Assay [4]	Cells (10^4 cells per well) are seeded into a 96-well tissue culture plate in triplicate. The cells are cultured in the presence of LRRK2-IN-1 with DMSO as a vehicle at 0, 0.31, 0.63, 1, 2, and 5, 10, and 20 μM. 48 h post treatment, 10 μL of TACS MTT Reagent is added to each well and the cells are incubated at 37°C until dark crystalline precipitate become visible in the cells. 100 μL of 266 mM NH_4OH in DMSO is then added to the wells and placed on a plate shaker at low speed for 1 minute. After shaking, the plate is allowed to incubate for 10 minutes protected from light and the OD550 for each well is read using a microplate reader. The results are averaged and calculated as a percentage of the DMSO (vehicle) control +/- the standard error of the mean. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [2]	LRRK2-IN-1 is dissolved in Captisol and administered by intraperitoneal injection into wild type male C57BL/6 mice at a dose of 100 mg/kg. Control mice are injected with an equal volume of Captisol. At 1 and 2 h time points, mice are extinguwashed by cervical dislocation and kidney and brain tissue rapidly dissected and snap-frozen in liquid nitrogen. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Cells. 2024 Mar 23, 13(7), 565.
- iScience. 2023 Sep 30.
- Mol Pharm. 2018 Aug 6;15(8):3252-3259.
- Anticancer Res. 2018 Nov;38(11):6225-6230.
- bioRxiv. 2023 Jun 30.

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REFERENCES

[1]. Hermanson SB, et al. Screening for Novel LRRK2 Inhibitors Using a High-Throughput TR-FRET Cellular Assay for LRRK2 Ser935 Phosphorylation.PLoS One. 2012;7(8):e43580. Epub 2012 Aug 28.

[2]. Deng, Xianming., et al. Characterization of a selective inhibitor of the Parkinson's disease kinase LRRK2. Nature Chemical Biology (2011), 7(4), 203-205.

[3]. Koshibu K, et al. Alternative to LRRK2-IN-1 for Pharmacological Studies of Parkinson's Disease. Pharmacology. 2015;96(5-6):240-7.

[4]. Weygant N, et al. Small molecule kinase inhibitor LRRK2-IN-1 demonstrates potent activity against colorectal and pancreatic cancer through inhibition of doublecortin-like kinase 1. Mol Cancer. 2014 May 6;13:103.

Tel: 609-228-6898 Fax: 609-228-5909 E-mail: tech@MedChemExpress.com

Address: 1 Deer Park Dr, Suite Q, Monmouth Junction, NJ 08852, USA