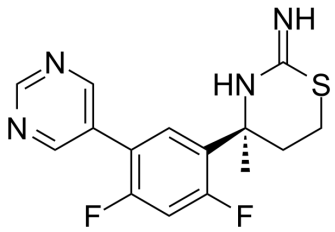
LY2811376

Cat. No.:	HY-10472
CAS No.:	1194044-20-6
Molecular Formula:	$C_{15}H_{14}F_2N_4S$
Molecular Weight:	320.36
Target:	Beta-secretase
Pathway:	Neuronal Signaling
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 : ≥ 31 mg/mL (96.77 mM)

* "≥" means soluble, but saturation unknown.

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	3.1215 mL	15.6074 mL	31.2149 mL
	5 mM	0.6243 mL	3.1215 mL	6.2430 mL
	10 mM	0.3121 mL	1.5607 mL	3.1215 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 (7.80 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.5 mg/mL (7.80 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (7.80 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

LY2811376 is the first orally available non-peptidic β-secretase (BACE1) inhibitor with IC_{50} of 239 nM-249 nM, that acts to decrease Aβ secretion with EC_{50} of 300 nM, and demonstrates to have 10-fold selectivity towards BACE1 over BACE2, and more than 50-fold inhibition over other aspartic proteases including cathepsin D, pepsin, or renin.

IC_{50} & Target

BACE1

In Vitro	In an APP-overexpressing human embryonic kidney cell line, LY2811376 treatment yields a concentration-dependent decrease in Aβ secretion with a half-maximal effective concentration (EC_{50}) of appr 300 nM. LY2811376 treatment of primary neuronal cultures of PDAPP transgenic mouse produces a concentration-dependent decrease in Aβ secretion with an EC_{50} of appr 100 nM[1]. LY2811376 has good ADME properties (BACE1 IC_{50}=240 nM, cellular potency IC_{50}=300 nM) and selectivity (BACE2 and cathepsin D selectivity: appr 10- and 65-fold, respectively)[3]. LY2811376 reduces the Aβ40 levels in cortex and plasma without change of health and weight in a dose-dependent manner[4]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	LY2811376 (10, 30, and 100 mg/kg, p.o.) results in dose-dependent, significant reductions in Aβ as well as sAPPβ and C99, the proximal cleavage products of APP proteolysis by BACE1. LY2811376 produces dose-dependent decreases in all APP-related PD markers of BACE1 inhibition in PDAPP mice. Low (30 mg) and high (90 mg) doses of LY2811376 investigated in the CSF sampling study are based on PK and plasma $Aβ^{1-40}$ PD observed in the SAD study[1]. LY2811376 (30 mg/kg, p.o.) can lead to a 60% decrease in the soluble Aβs in mouse cortex[2]. LY2811376 (100 mg/kg, p.o.) decreases the spine density and formation in mice. LY2811376 (100 mg/kg every 12 hours over 16 days) causes a reduction in the frequency of sEPSC and mEPSC, whereas the effects of LY2811376 on the amplitude of sEPSC fails to reach significance[4]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Animal Administration [1]	Sprague Dawley [Crl:CD(SD)] rats (10 per sex per group), appr 7 weeks of age, are given 0 (vehicle only), 10, 30, or 100 mg/kg LY2811376 by daily oral gavage. Vehicle consists of 1% (w/v) hydroxyethylcellulose, 0.25% (v/v) polysorbate 80, and 0.05% (v/v) Dow Corning Antifoam 1510-US in reverse osmosis water. At necropsy after 3 months of treatment, tissues are immersion fixed in 10% neutral-buffered formalin (brain) or modified Davidson's solution (eyes) and then processed by routine methods to paraffin block and hematoxylin-eosin (H&E)-stained histologic slides. From selected animals given 100 mg/kg on a subsequent investigative study, eyes are fixed in modified Karnovsky's solution, processed routinely into epoxy resin, and then ultrathin sections stained with uranyl acetate and Sato's lead citrate are examined in a transmission electron microscope. In a separate study, BACE1 knock-out mice (B6.129-Bace1tm1Pcw/J) are given 0 or 100 mg/kg LY2811376 by daily oral gavage for 9 weeks, and then necropsied tissues are collected and examined by light microscopy as described above for the rat toxicology study. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Sci Adv. 2017 Feb 24;3(2):e1601068.
- Genes Dis. 2020 Nov 21;8(6):867-881.
- J Agric Food Chem. 2022 Feb 9;70(5):1536-1546.
- FEBS J. 2017 Apr;284(7):1096-1109.
- Stem Cells. 2017 Feb;35(2):374-385.

See more customer validations on www.MedChemExpress.com

REFERENCES

[1]. May PC, et al. Robust central reduction of amyloid-β in humans with an orally available, non-peptidic β-secretase inhibitor. J Neurosci. 2011 Nov 16;31(46):16507-16516.

[2]. Zhang X, et al. Near-infrared fluorescence molecular imaging of amyloid beta species and monitoring therapy in animal models of Alzheimer's disease. Proc Natl Acad Sci U S A. 2015 Aug 4;112(31):9734-9.

[3]. Ghosh AK, et al. Prospects of β-Secretase Inhibitors for the Treatment of Alzheimer's Disease. ChemMedChem. 2015 Sep;10(9):1463-6

[4]. Filser S, et al. Pharmacological inhibition of BACE1 impairs synaptic plasticity and cognitive functions. Biol Psychiatry. 2015 Apr 15;77(8):729-39.

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