LY-411575

Cat. No.: HY-50752

CAS No.: 209984-57-6

Molecular Formula: $C_{26}H_{23}F_2N_3O_4$

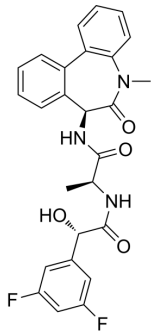
Molecular Weight: 479.48

Target: γ-secretase; Notch; Apoptosis; Organoid

Pathway: Neuronal Signaling; Stem Cell/Wnt; Apoptosis

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 : 33.33 mg/mL (69.51 mM; Need ultrasonic)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	2.0856 mL	10.4280 mL	20.8559 mL
	5 mM	0.4171 mL	2.0856 mL	4.1712 mL
	10 mM	0.2086 mL	1.0428 mL	2.0856 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 (5.21 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (5.21 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

LY-411575 is a potent γ-secretase inhibitor with IC_{50} of 0.078 nM/0.082 nM (membrane/cell-based), and also inhibits Notch S3 cleavage with IC_{50} of 0.39 nM.

IC_{50} & Target

IC50: 0.078 nM (γ-secretase in membrane), 0.082 nM (γ-secretase cell-based), 0.39 nM (Notch S3 cleavage cell-based)[1]

In Vitro

LY-411,575 blocks Notch activation, and results in apoptosis in primary and immortalized KS cells. LY-411,575 (500 μM) induces G2/M growth arrest SLK cells[2]. LY411575 treatment significantly decreases the amounts of intracellular HCV RNA with IC_{50} of 0.56 ± 0.20 μM and extracellular HCV particles. LY411575 (0-40 nM) alone or in combination with BMS-790052 (0-40 pM) decreases supernatant infectious titers in a dose-dependent manner, and is synergistic regarding production of infectious virus. LY411575 (10 μM) treatment impairs ROS production in HCVcc-infected cells[4]. LY411575 significantly

	attenuates EMT by inhibiting the Notch signaling activation in vitro[5]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	LY-411,575 (10 mg/kg) decreases brain and plasma Aβ40 and -42 robustly when chronically administered to TgCRND8 mice [1]. LY411,575 reduces cortical Aβ40 in young transgenic CRND8 mice (ED_{50} appr 0.6 mg/kg) and produces significant thymus atrophy and intestinal goblet cell hyperplasia at higher doses (>3 mg/kg). The extent of intestinal goblet cell hyperplasia induced by LY411,575 (10 mg/kg) is similar in young and aged mice[3]. LY411575 inhibits mouse proliferative vitreoretinopathy (PVR) formation in vivo[5]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Animal Administration [3]	Mice from the aged cohort (16-26 months old) are either retired breeders or experimentally naive mice. Before dosing begin and for the duration of the study, mice are singly housed with a plastic igloo and nesting material. Mice are sacrificed 2 to 4 h after their final dosing. For oral dosing, LY411,575 and LY-D are formulated as 10 mg/mL solutions and diluted 1:10 with 0.4% methycellulose. In the case of subcutaneous dosing, the 10 mg/mL stock solution is diluted 1:10 with 20% hydroxyl-propyl-β-cyclodextrin. If necessary, serial dilutions are made from the 1 mg/mL solution using the appropriate 1:10 vehicle. The dosing volume is 10 mL/kg. After oral administration of 10 mg/kg LY411,575, inhibition of plasma Aβ is still significant 24, but not 48, h after dosing, so in an effort to maintain continuous γ-secretase inhibition, LY411,575 and LY-D are dosed once per day in all studies. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Adv Sci (Weinh). 2022 Sep 18;e2203557.
- Cell Death Dis. 2022 Jan 17;13(1):60.
- Cell Rep. 2016 Dec 6;17(10):2687-2699.
- Oncoimmunology. 2018 Aug 23;7(11):e1461303.
- Int Immunopharmacol. 2022 Sep 28;112:109251.

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REFERENCES

[1]. Wong GT, et al. Chronic treatment with the gamma-secretase inhibitor LY-411,575 inhibits beta-amyloid peptide production and alters lymphopoiesis and intestinal cell differentiation. J Biol Chem. 2004 Mar 26;279(13):12876-82.

[2]. Curry CL, et al. Gamma secretase inhibitor blocks Notch activation and induces apoptosis in Kaposi's sarcoma tumor cells. Oncogene. 2005 Sep 22;24(42):6333-44.

[3]. Hyde LA, et al. Studies to investigate the in vivo therapeutic window of the gamma-secretase inhibitor N2-[(2S)-2-(3,5-difluorophenyl)-2-hydroxyethanoyl]-N1-[(7S)-5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl]-L-alaninamide (LY411,575) in the CRND8 mouse. J Pharmacol Exp Ther. 2006 Dec;319(3):1133-43.

[4]. Otoguro T, et al. Inhibitory effect of presenilin inhibitor LY411575 on maturation of hepatitis C virus core protein, production of the viral particle and expression of host proteins involved in pathogenicity. Microbiol Immunol. 2016 Nov;60(11):740-753

[5]. Zhang J, et al. Notch signaling modulates proliferative vitreoretinopathy via regulating retinal pigment epithelial-to-mesenchymal transition. Histochem Cell Biol. 2017 Mar;147(3):367-375.

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

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