Product Data Sheet

Product Name: LY-411575
Cat. No.: GC12191

Chemical Properties

Cas. No.	209984-57-6		
Chemical Name	(2S)-2-[[(2S)-2-(3,5-difluorophenyl)-2-hydroxyacetyl]amino]-N-[(7S)-5-methyl-6-oxo-7H-benzo[d][1]benzazepin-7-yl]propanamide		
SMILES	CC(C(=O)NC1C2=CC=CC=C2C3=CC=CC=C3N(C1=O)C)NC(=O)C(C4=CC(=CC(=C4)F)F)O		
Formula	$C_{26}H_{23}F_2N_3O_4$	M.Wt	479.48
Solubility	≥ 23.85 mg/mL in DMSO, ≥ 98.4 mg/mL in EtOH with ultrasonic	Storage	Store at -20°C
General tips	For obtaining a higher solubility , please warm the tube at 37 °C and shake it in the ultrasonic bath for a while.Stock solution can be stored below -20°C for several months.		
Shipping Condition	Evaluation sample solution : ship with blue ice All other available size: ship with RT , or blue ice upon request.		

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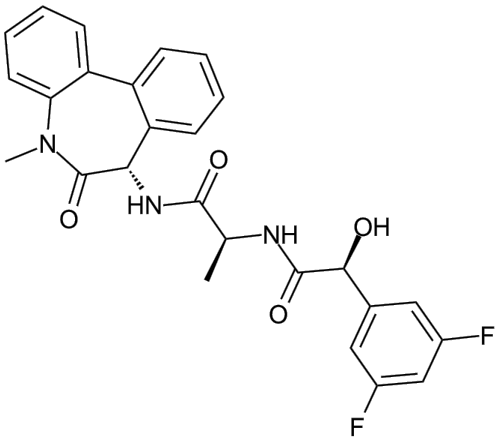
Structure



Protocol

Kinase experiment [1]:

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Inhibitory activities	Procedures for measuring γ-secretase activity in membranes prepared from HEK293 cells expressing APP. Intact HEK293 cells expressing either APP or N E were treated with various concentrations of LY-411,575 for 4 h at 37°C. In the case of cells expressing N E, cells were lysed, the cell lysates were separated on a 4-12% NuPAGE gel, and the processed NICD fragment was detected via Western blot with a cleavage site-specific antibody. The inhibition of NICD production was quantified by spot densitometric analysis using FluorChem. In the case of cells expressing APP, the conditioned medium was collected, centrifuged at 10,000×g for 5 min to remove cell debris, and stored at -20°C prior to the determination ofAβ levels. Aβ40 and -42 produced in HEK293 membrane- and cell-based assays, as well as plasma Aβ40 and cortex Aβ40 from TgCRND8 mice, were analyzed without pretreatment using an electrochemiluminescence detection-based immunoassay. Plasma Aβ42 was measured by enzyme-linked immunosorbent assay. A commercially available enzyme-linked immunosorbent assay kit was used to measure cortex Aβ42.

Cell experiment [1]:

Cell lines	HEK293 cells expressing human APP carrying both the Swedish and London mutations or N E.
Preparation method	Soluble in DMSO > 10 mM. General tips for obtaining a higher concentration: Please warm the tube at 37°C for 10 minutes and/or shake it in the ultrasonic bath for a while. Stock solution can be stored below -20°C for several months.
Reaction Conditions	4 h.
Applications	In HEK293 cells expressing human APP or N E, LY-411,575 inhibits Aβ40 and NICD production with IC50 values of 0.082 and 0.39 nM, respectively.

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Animal experiment [1]:

Animal models	Six-week-old female TgCRND8 or male C57BL/6 mice.
Dosage form	1-10 mg/kg; dosed orally once/day for 5 or 15 days.
Preparation method	Formulated as 10 mg/ml solutions in 50% polyethylene glycol, 30% propylene glycol, 10% ethanol and diluted in 0.4% methylcellulose for dosing.
Applications	In TgCRND8 mice, LY-411,575 decreases brain and plasma Aβ40 and Aβ42. LY-411,575 (10 mg/kg) reduces weight of mice by 2 g. LY-411,575 induces a marked atrophy of the cortical zone of the thymus and reduces the amount of thymocyte cells.
Other notes	Please test the solubility of all compounds indoor, and the actual solubility may slightly differ with the theoretical value. This is caused by an experimental system error and it is normal.

References:

[1]. Wong GT, Manfra D, Poulet FM, 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, 279(13): 12876-12882.

Background

LY-411575 is a potent inhibitor of γ-secretase with IC50 value of 0.078 nM in membrane assay.[1] γ-Secertase is one of intramenbrane-cleaving aspartyl protease which cleaves many type-I membrane proteins and many of them have important biological functions. γ-Secretase is a multi-subunit protease and it contains presenilin, nicastrin, APH-1(Anterior Pharynx- defective 1) and PEN-2. Presenilin contains Asp258 and Asp385 embedded in the sixth and seventh transmembrane

domain and forms the active site. The feature of being a membrane integrated protease complex makes it difficult to be purified as well as studying its mechanism.γ-secretase is responsible for the generation Aβfrom the amyloid precursor protein.γ-Secertase has been considered as an important drug target for Alzheimer's disease.γ-Secertase also is responsible for Notch processing which is related to cancer such as leukemia.[2]

LY-411,575 significantly inhibits theγ-secretase activity in vitro. LY-411,575 inhibits the production of Aβproduction with IC50 value of 0.078 nM in membrane-assay and 0.082 nM in cell-basedγ-secretase assays, respectively. LY-411,575 also affects the Notch pathway by inhibiting Notch S3 cleavage with IC50 value of 0.39 nM.[1] LY-411,575 treatment also significantly inhibited the Notch pathway by inhibiting the γ-secretase activity luciferase activity in primary KS cells. LY-411,575 also induced the apoptosis though Notch pathway inhibition in primary and immortalized Kaposi's sarcoma (KS) tumor cells.[2]

LY-411,575 decreases the levels of brain and plasma Aβ40 and -42 at 10 mg/kg oral doses.[1] LY-411,575 also decreases cortical Aβ40 levels in transgenic CRND8 mice with ED50 ≈ 0.6 mg/kg. LY-411,575 also induced significantly intestinal goblet cell hyperplasia and thymus atrophy by inhibiting Notch signaling pathway at higher doses in vivo.[3]

References:

1.Wong GT, Manfra D, Poulet FM, Zhang Q, Josien H, Bara T, Engstrom L, Pinzon-Ortiz M, Fine JS, Lee HJ 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, 279(13):12876-12882.

2.Curry CL, Reed LL, Golde TE, Miele L, Nickoloff BJ, Foreman KE: Gamma secretase inhibitor blocks Notch activation and induces apoptosis in Kaposi's sarcoma tumor cells. Oncogene 2005, 24(42):6333-6344.

3.Hyde LA, McHugh NA, Chen J, Zhang Q, Manfra D, Nomeir AA, Josien H, Bara T, Clader JW, Zhang L 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-di hydro-5H-dibenzo[b,d]azepin-7-yl]-L-alaninamide (LY411,575) in the CRND8 mouse. J Pharmacol Exp Ther 2006, 319(3):1133-1143.