产品名称：**LY-411575**
产品别名：**LY-411575**

生物活性：

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 IC50 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].
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 (ED50 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].
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

*请根据产品在不同溶剂中的溶解度选择合适的溶剂配制储备液；一旦配成溶液，请分装保存，避免反复冻融造成的产品失效。

储备液的保存方式和期限：-80°C, 6 months; -20°C, 1 month。-80°C 储存时，请在 6 个月内使用，-20°C 储存时，请在 1 个月内使用。

In Vivo:

请根据您的实验动物和给药方式选择适当的溶解方案。以下溶解方案都请先按照 **In Vitro** 方式配制澄清的储备液，再依次添加助溶剂：

——为保证实验结果的可靠性，澄清的储备液可以根据储存条件，适当保存；体内实验的工作液，建议您现用现配，当天使用； 以下溶剂前显示的百分比是指该溶剂在您配制终溶液中的体积占比；如在配制过程中出现沉淀、析出现象，可以通过加热和/或超声的方式助溶

1.请依序添加每种溶剂： 10% DMSO→40% PEG300 →5% Tween-80 → 45% saline

Solubility: ≥ 2.5 mg/mL (5.21 mM); Clear solution

此方案可获得 ≥ 2.5 mg/mL (5.21 mM，饱和度未知) 的澄清溶液。

以 1 mL 工作液为例，取 100 μL 25.0 mg/mL 的澄清 DMSO 储备液加到 400 μL PEG300 中，混合均匀；向上述体系中加入 50 μL Tween-80，混合均匀；然后继续加入 450 μL 生理盐水定容至 1 mL。

2.请依序添加每种溶剂： 10% DMSO →90% corn oil

	Solubility: ≥ 2.5 mg/mL (5.21 mM); Clear solution 此方案可获得 ≥ 2.5 mg/mL (5.21 mM，饱和度未知) 的澄清溶液，此方案不适用于实验周期在半个月以上的实验。 以 1 mL 工作液为例，取 100 μL 25.0 mg/mL 的澄清 DMSO 储备液加到 900 μL 玉米油中，混合均匀。
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]. 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 [3]. 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. [4]. 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. [5]. 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.

实验参考：

Animal Administration	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. [3]
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]. 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 [3]. 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. [4]. 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. [5]. 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-dibenz

	o[b,d]azepin-7-yl]-L-alaninamide (LY411,575) in the CRND8 mouse. J Pharmacol Exp Ther. 2006 Dec;319(3):1133-43.