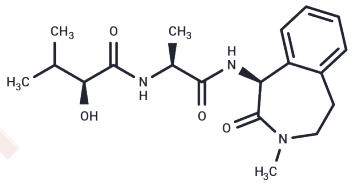
Data Sheet (Cat.No.T6125)

TargetMol

Semagacestat

Chemical Properties



CAS No. : 425386-60-3

Formula: C19H27N3O4

Molecular Weight: 361.44

Storage: Powder: -20°C for 3 years | In solvent: -80°C for 1 year
Actual storage temperature shall be subject to the COA.

Biological Description

Description	Semagacestat (LY450139) (LY450139) is a γ-secretase blocker for Aβ42/Aβ40/Aβ38 (IC50: 10.9/12.1/12.0 nM) and also inhibits Notch signaling (IC50: 14.1 nM).
Targets(IC50)	Beta Amyloid,Gamma-secretase
In vitro	Semagacestat reduces the secretion of Aβ42, Aβ40 and Aβ38 from H4 human glioma cells stably overexpressing human wild-type APP into the culture medium, with IC50 of 10.9 nM, 12.1 nM and 12.0 nM, respectively, without affecting cell viability. Semagacestat also increases β-CTF in cell lysates with ECmax of 16.0 nM, and the increase can be unexpectedly attenuated at high concentrations. Semagacestat inhibits Notch signaling with IC50 of 14.1 nM, and shows minimal Notch-sparing selectivity with Notch IC50/Aβ42 IC50 only 1.3. [1] Semagacestat causes a concentration-dependent decrease in Aβ40 secreted into the medium with IC50 of 111 nM from murine CTX expressing endogenous murine APP, but murine Aβ42 formation in CTX is roughly 12-fold less than Aβ40 in accordance with data for neurons from wild type mice. [2]
In vivo	Oral administration of Semagacestat (1 mg/kg) to 5.5-month old APP-transgenic Tg2576 mice significantly ameliorates memory deficits on spatial working memory using the Y-maze task, which disappears after 8 days subchronic dosing. LY450139 decreases hippocampal levels of both Aβ42 and Aβ40 at 10 mg/kg (22-23% reduction) and 30 mg/kg (36-41% reduction) and increases β-CTF at 0.3-10 mg/kg in a dose dependent manner with no inhibition on the processing of other γ-secretase substrates, such as Notch, N-cadherin or EphA4, in the brain, but impairs normal cognition in wild-type mice and 3-month-old Tg2576 mice failing to restore cognitive deficits in the Y-maze test. [1]
Kinase Assay	Cellular APP processing assay and Notch signaling assay: H4 human glioma cells stably overexpressing human wild-type APP695 are treated with Semagacestat at various concentrations for 24 hours. Levels of Aβ42, Aβ40, and Aβ38 in the media are measured using separate ELISA kits. The expression vector of the constitutively active form of Notch (NotchΔE), encoding bases 1-60 and 5193-6657 of the human Notch1 coding region (NM_017617), is constructed into a pcDNA3.1 vector with a sequence modification from mouse to human. Notch signaling activity is evaluated using Cignal RBP-Jk Reporter Assay kit. RBP-Jk protein [CSL/CBF1/Su(H)/Lag1] is a transcription factor activated with Notch intracellular domain produced by γ-secretase. H4 cells are transiently transfected with the human NotchΔE expression vector and the RBP-Jk-responsive luciferase

Kinase Assay	construct using Lipofectamine 2000, and then exposed to various concentrations of Semagacestat for 16 hours. Notch signaling is measured based on luciferase activity in the cell lysate using the Dual-Glo Luciferase Assay System.
Cell Research	Cells are incubated with Semagacestat for 24 hours. For detection of cell viability, the percentage of viable cells is quantified by their capacity to reduce 3-(4,5-dimethylthiazole-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) following incubation with 0.5 mg/mL MTT for 60 minutes. For the detection of sAPP species, cells are lysed and analysed by western blotting.(Only for Reference)

Solubility Information

Solubility	H2O: < 1 mg/mL (insoluble or slightly soluble), DMSO: 67 mg/mL (185.37 mM),Sonication is recommended. Ethanol: 39 mg/mL (107.9 mM),Sonication is recommended. (< 1 mg/ml refers to the product slightly soluble or insoluble)
In vivo Formulation	10% DMSO+40% PEG300+5% Tween 80+45% Saline: 2.5 mg/mL (6.92 mM),Sonication is recommended. *Please add the solvents sequentially, clarifying the solution as much as possible before adding the next one. Dissolve by heating and/or sonication if necessary. Working solution is recommended to be prepared and used immediately. The formulation provided above is for reference purposes only. In vivo formulations may vary and should be modified based on specific experimental conditions.*

Preparing Stock Solutions

	1mg	5mg	10mg
1 mM	2.7667 mL	13.8336 mL	27.6671 mL
5 mM	0.5533 mL	2.7667 mL	5.5334 mL
10 mM	0.2767 mL	1.3834 mL	2.7667 mL
50 mM	0.0553 mL	0.2767 mL	0.5533 mL

Please select the appropriate solvent to prepare the stock solution, according to the solubility of the product in different solvents. Please use it as soon as possible.

Note: The dilution table applies only to solid products. For liquid products, please calculate the stock solution based on the stated concentration and/or density.

Reference

Mitani Y, et al. J Neurosci, 2012, 32(6), 2037-2050.
Elvang AB, et al. J Neurochem, 2009, 110(5), 1377-1387.