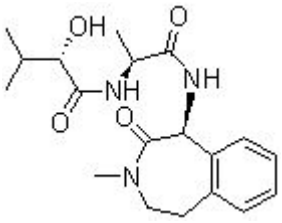
Biochempartner
瀚香生物科技

Product Introduction

Semagacestat (LY450139)

Semagacestat (LY450139) is a γ-secretase blocker for **Aβ42**, **Aβ40** and **Aβ38** with **IC50** of 10.9 nM, 12.1 nM and 12.0 nM, also inhibits **Notch** signaling with **IC50** of 14.1 nM. Phase 3.

Technical Data:

Molecular Weight (MW):	361.44	
Formula:	$C_{19}H_{27}N_3O_4$	
Solubility (25°C) * <1 mg/ml means slightly soluble or insoluble:	DMSO 72 mg/mL	
	Water <1 mg/mL	
	Ethanol 41 mg/mL	
Purity:	>98%	
Storage:	3 years -20℃Powder	
	6 months-80℃in DMSO	
CAS No.:	425386-60-3	

Biological Activity

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 EC_{max} 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]

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]

The best characterized γ-secretase inhibitor that has reached the clinic.

References

[1] Mitani Y, et al. J Neurosci, 2012, 32(6), 2037-2050.

[2] Elvang AB, et al. J Neurochem, 2009, 110(5), 1377-1387.

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