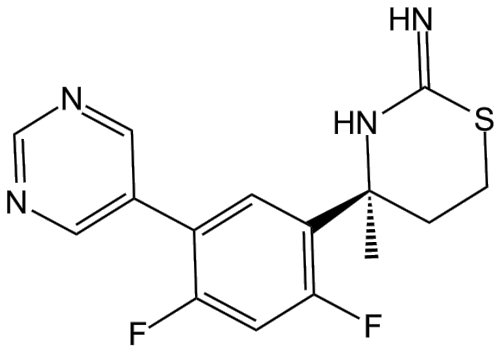
Product Data Sheet

Product Name: LY2811376
Cat. No.: GC17791

Chemical Properties

Cas. No.	1194044-20-6		
Chemical Name	(4S)-4-(2,4-difluoro-5-pyrimidin-5-ylphenyl)-4-methyl-5,6-dihydro-1,3-thiazin-2-amine		
SMILES	CC1(CCSC(=N1)N)C2=C(C=C(C(=C2)C3=CN=CN=C3)F)F		
Formula	$C_{15}H_{14}F_2N_4S$	M.Wt	320.4
Solubility	DMF: 30 mg/ml,DMSO: 30 mg/ml,DMSO:PBS(pH7.2) (1:1): 0.5 mg/ml,Ethanol: 25 mg/ml	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.		

Structure



Protocol

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Animal experiment: Sprague Dawley [Crl:CD(SD)] rats (10 per sex per group), appr 7 weeks of age, are given 0 (vehicle only), 10, 30, or 100 mg/kg LY2811376 by daily oral gavage. Vehicle consists of 1% (w/v) hydroxyethylcellulose, 0.25% (v/v) polysorbate 80, and 0.05% (v/v) Dow Corning Antifoam 1510-US in reverse osmosis water. At necropsy after 3 months of treatment, tissues are immersion fixed in 10% neutral-buffered formalin (brain) or modified Davidson's solution (eyes) and then processed by routine methods to paraffin block and hematoxylin-eosin (H&E)-stained histologic slides. From selected animals given 100 mg/kg on a subsequent investigative study, eyes are fixed in modified Karnovsky's solution, processed routinely into epoxy resin, and then ultrathin sections stained with uranyl acetate and Sato's lead citrate are examined in a transmission electron microscope. In a separate study, BACE1 knock-out mice (B6.129-Bace1tm1Pcw/J) are given 0 or 100 mg/kg LY2811376 by daily oral gavage for 9 weeks, and then necropsied tissues are collected and examined by light microscopy as described above for the rat toxicology study.

References:

[1]. May PC, et al. Robust central reduction of amyloid-β in humans with an orally available, non-peptidic β-secretase inhibitor. J Neurosci. 2011 Nov 16;31(46):16507-16516.
[2]. Zhang X, et al. Near-infrared fluorescence molecular imaging of amyloid beta species and monitoring therapy in animal models of Alzheimer's disease. Proc Natl Acad Sci U S A. 2015 Aug 4;112(31):9734-9.
[3]. Ghosh AK, et al. Prospects of β-Secretase Inhibitors for the Treatment of Alzheimer's Disease. ChemMedChem. 2015 Sep;10(9):1463-6.
[4]. Filser S, et al. Pharmacological inhibition of BACE1 impairs synaptic plasticity and cognitive functions. Biol Psychiatry. 2015 Apr 15;77(8):729-39.

Background

LY2811376 is a non-peptidic inhibitor of BACE1.
Beta-secretase 1 (BACE1) is an aspartic-acid protease that cleaves the amyloid precursor protein (APP) into amyloid-βpeptide (Aβ), which plays a critical role in Alzheimer's disease (AD).

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In recombinant enzyme assays, LY2811376 inhibited hBACE1 with IC50 values of 249 nM and 239 nM against a larger chimeric protein substrate and a small synthetic peptide, respectively. In a human embryonic kidney cell line overexpressed APP, LY2811376 decreased Aβ secretion with EC50 value of 300 nM in a concentration-dependant way [1]. In SH-SY5Y cells, LY2811376 reduced Aβ1-40 and Aβ1-42 secreted to the cell medium while increased the level of Aβ5-40 [2].
In the APPV717F mouse, LY2811376 significantly reduced Aβ, as well as sAPP and C99, the cleavage products of APP by BACE1 [1]. In a healthy population (n =18), LY2811376 (30 mg, 90 mg) increased Aβ5-40 and Aβ5-X in a dose-dependant way, while Aβ1-34 reduced in a same way. These results suggested that LY2811376 inhibited N-terminally truncated Aβ peptides in a BACE1-independent pathway [2].

References:

[1]. May PC, Dean RA, Lowe SL, et al. Robust Central Reduction of Amyloid- in Humans with an Orally Available, Non-Peptidic -Secretase Inhibitor. J Neurosci, 2011, 31(46): 16507-16516.
[2]. Portelius E, Dean RA, Andreasson U, et al. β-site amyloid precursor protein-cleaving enzyme 1 (BACE1) inhibitor treatment induces Aβ5-X peptides through alternative amyloid precursor protein cleavage. Alzheimers Res Ther, 2014, 6(5-8): 75.

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