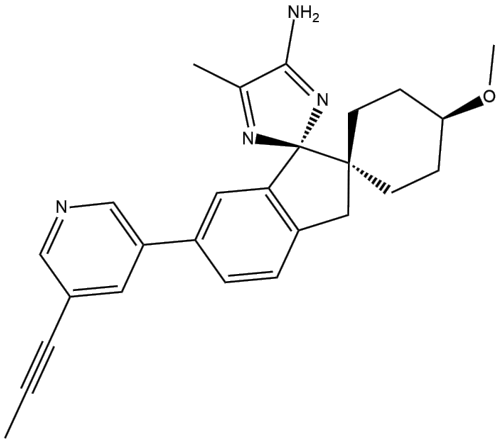
Product Data Sheet

Product Name: Lanabecestat
Cat. No.: GC19217

Chemical Properties

Cas. No.	1383982-64-6		
SMILES	CC#CC1=CC(C2=CC([C@@]34N=C(C)C(N)=N4)=C(C[C@@]53CC[C@@H](OC)CC5)C=C2)=CN=C1		
Formula	$C_{26}H_{28}N_4O$	M.Wt	412.53
Solubility	DMSO : ≥ 100 mg/mL (242.41 mM)	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

Cell experiment: Cells are incubated with different lanabecestat concentrations for 5 to 16 h, and the release of sAβPPβ, Aβ1-40, Aβ1-42, or sAβPPα into the medium is analyzed using kits. Cytotoxic effect of lanabecestat is evaluated in the cell plates using cell proliferation/cytotoxicity kit[1].

Caution: Product has not been fully validated for medical applications. For research use only.
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Animal experiment: Female 7- to 14-week-old C57BL/6 mice (n=6 per treatment group and timepoint) receive vehicle or lanabecestat solution at 50, 100, or 200 μmol/kg (20, 41, or 82 mg/kg) as a single dose via oral gavage. Mice and guinea pigs are anesthetized 1.5, 2, 3, 4, 6, 8, 16, 24, or 48 h after the (last) administration of vehicle or drug and are then kept under isoflurane anesthesia. Cerebrospinal fluid (CSF) is aspirated from the cisterna magna, and plasma is isolated from blood collected by cardiac puncture into EDTA tubes. The animals are then sacrificed by decapitation, and the brains are dissected into hemispheres[1].

References:

[1]. Eketj ll S, et al. AZD3293: A Novel, Orally Active BACE1 Inhibitor with High Potency and Permeability and Markedly Slow Off-Rate Kinetics. J Alzheimers Dis. 2016;50(4):1109-23.

Background

Lanabecestat (AZD3293) is a potent, highly permeable, orally active and blood-brain barrier penetrating BACE1 inhibitor with a Ki of 0.4 nM.

Lanabecestat acts as a full inhibitor of BACE1 in vitro, with a competitive and reversible mechanism of action towards the hBACE1 active site. Lanabecestat displays a very high target affinity and a markedly slow target off-rate. The off-rate of lanabecestat has an estimated t1/2 of approximately 9 h. Lanabecestat displays pM potency in primary neuron cultures from mice and guinea pigs and in SH-SY5Y cells over-expressing AβPP (IC50=610 pM, 310 pM, and 80 pM, respectively). The in vitro plasma protein binding of lanabecestat is determined by equilibrium dialysis using mouse, rat, guinea pig, dog, and human plasma. The compound is stable in the plasma of these species for at least the duration of the in vitro incubation period. The unbound fractions are 1.3% to 1.8% for mice, 4.2% to 5.9% for rats, 8.3% to 10.3% for guinea pigs, 9.4% to 10.3% for dogs, and 7.7% to 9.4% for human plasma. The mean blood:plasma ratio of 0.7 in human blood indicates no significant association with red blood cells. The free fraction in the brain tissue binding assay is 4.5%[1].

In mice, guinea pigs, and dogs, lanabecestat displays significant dose- and time-dependent reductions in plasma, cerebrospinal fluid, and brain concentrations of Aβ40, Aβ42, and sAβPPβ[1].

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