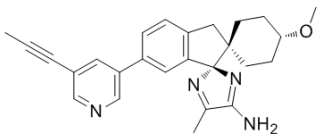
Lanabecestat

Cat. No.:	HY-100740
CAS No.:	1383982-64-6
Molecular Formula:	$C_{26}H_{28}N_4O$
Molecular Weight:	412.53
Target:	Beta-secretase
Pathway:	Neuronal Signaling

Storage:

Powder	-20°C	3 years
	4°C	2 years
In solvent	-80°C	6 months
	-20°C	1 month



SOLVENT & SOLUBILITY

In Vitro

DMSO : ≥ 100 mg/mL (242.41 mM)

* "≥" means soluble, but saturation unknown.

Preparing Stock Solutions	Concentration \ Solvent \ Mass	1 mg	5 mg	10 mg
	1 mM	2.4241 mL	12.1203 mL	24.2407 mL
	5 mM	0.4848 mL	2.4241 mL	4.8481 mL
	10 mM	0.2424 mL	1.2120 mL	2.4241 mL

Please refer to the solubility information to select the appropriate solvent.

BIOLOGICAL ACTIVITY

Description

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

IC_{50} & Target

Ki: 0.4 nM (BACE1)[1]

In Vitro

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 (IC_{50}=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 Vivo	In mice, guinea pigs, and dogs, lanabecestat displays significant dose- and time-dependent reductions in plasma, cerebrospinal fluid, and brain concentrations of $A\beta_{40}$, $A\beta_{42}$, and sAβPPβ[1].

PROTOCOL

Cell Assay [1]	Cells are incubated with different lanabecestat concentrations for 5 to 16 h, and the release of sAβPPβ, $A\beta_{1-40}$, $A\beta_{1-42}$, 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]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [1]	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]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

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.

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