Verubecestat

Cat. No.: HY-16759

CAS No.: 1286770-55-5

Molecular Formula: $C_{17}H_{17}F_2N_5O_3S$

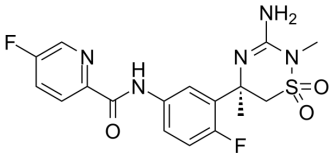
Molecular Weight: 409.41

Target: Beta-secretase

Pathway: Neuronal Signaling

Storage:

Powder	-20°C	3 years
	4°C	2 years
In solvent	-80°C	2 years
	-20°C	1 year



SOLVENT & SOLUBILITY

In Vitro

DMSO : ≥ 35 mg/mL (85.49 mM)

* "≥" means soluble, but saturation unknown.

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	2.4425 mL	12.2127 mL	24.4254 mL
5 mM	0.4885 mL	2.4425 mL	4.8851 mL
10 mM	0.2443 mL	1.2213 mL	2.4425 mL

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

In Vivo

1. Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
   Solubility: ≥ 2.5 mg/mL (6.11 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.5 mg/mL (6.11 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (6.11 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Verubecestat (MK-8931) is an orally active, high-affinity BACE1 and BACE2 inhibitor with K_i values of 2.2 nM and 0.38 nM. Verubecestat effectively reduces Aβ40 and has the potential for Alzheimer's Disease[1][2].

IC_{50} & Target	BACE1	BACE2

In Vitro

Verubecestat (MK-8931) is a β-site amyloid precursor protein cleaving enzyme 1/2 (BACE1/2) inhibitor. Verubecestat does

not significantly inhibit human CYP isoforms 1A2, 2C9, 2C19, 2D6, and 3A4 (all IC_{50}>40 μM), indicating that the compound is unlikely to be a perpetrator of CYP-mediated drug-drug interactions[1].
Verubecestat has IC_{50}s of 2.1 nM, 0.7 nM, 4.4 nM for Aβ1-40, Aβ1-42, sAPPβ in HEK293 $APP^{Swe/Lon}$ cells[1].
MCE has not independently confirmed the accuracy of these methods. They are for reference only.

In Vivo

Verubecestat (MK-8931; 3 mg/kg; IV or oral) has a $T_{1/2}$ of 1.9 hours, a CL of 46 mL/min/kg, a V_{ss} of 5.4 L/kg, a C_{max} of 0.27 μM and a AUC of 1.1 μM•h for Sprague-Dawley (SD) rats[1].
Verubecestat (1 mg/kg; IV) has a $T_{1/2}$ of 4.9 hours, a CL of 21 mL/min/kg, a V_{ss} of 7.5 L/kg for cynomolgus monkeys[1].
Verubecestat (1 mg/kg; IV) has a $T_{1/2}$ of 9.7 hours, a CL of 4.3 mL/min/kg, a V_{ss} of 2.7 L/kg for beagle dogs[1].
Verubecestat (30 mg/kg; orally; BID for 5 days) causes a modest (1.4-fold) induction of CYP 3A1 activity but does not significantly alter the expression of CYPs 1A1, 1A2, 2B, 3A2, or 4A in rats[1].
Verubecestat dose-dependently reduces CSF and cortex Aβ40 with ED_{50} values of 5 and 8 mg/kg, respectively, corresponding to unbound plasma EC_{50} values of 48 and 81 nM, respectively[1].
Verubecestat (3 and 10 mg/kg; orally) reduces profound, sustained of CSF Aβ40 levels and has peak effects on CSF Aβ lowering (72 and 81% reduction at 3 and 10 mg/kg, respectively) 12 h after dosing[1].
MCE has not independently confirmed the accuracy of these methods. They are for reference only.

Animal Model:	Sprague-Dawley (SD) rats[1]
Dosage:	3 mg/kg (Pharmacokinetic Analysis)
Administration:	IV or oral
Result:	Had a $T_{1/2}$ of 1.9 hours, a CL of 46 mL/min/kg, a V_{ss} of 5.4 L/kg, a C_{max} of 0.27 μM and a AUC of 1.1 μM•h.

CUSTOMER VALIDATION

- Cell Death Differ. 2022 Jun 22.
- Microorganisms. 2023 Jun 18, 11(6), 1608.

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REFERENCES

[1]. Yan R, et al. Stepping closer to treating Alzheimer's disease patients with BACE1 inhibitor drugs. Transl Neurodegener. 2016 Jul 14;5:13.

[2]. Scott JD, et al. Discovery of the 3-Imino-1,2,4-thiadiazinane 1,1-Dioxide Derivative Verubecestat (MK-8931)-A β-Site Amyloid Precursor Protein Cleaving Enzyme 1 Inhibitor for the Treatment of Alzheimer'sDisease. Med Chem. 2016 Dec 8;59(23):10435-10450.

Tel: 609-228-6898 Fax: 609-228-5909 E-mail: tech@MedChemExpress.com
Address: 1 Deer Park Dr, Suite Q, Monmouth Junction, NJ 08852, USA