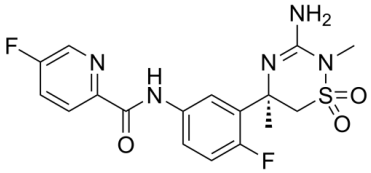
Data Sheet

Product Name:	Verubecestat
Cat. No.:	CS-5823
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
Solubility:	DMSO : ≥ 35 mg/mL



BIOLOGICAL ACTIVITY:

Verubecestat (MK-8931) is an orally active, high-affinity **BACE1** and **BACE2** inhibitor with $\mathbf{K_i}$ values of 2.2 nM and 0.38 nM. Verubecestat effectively reduces Aβ40 and has the potential for Alzheimer's Disease[1][2]. IC50 & Target:Ki: 2.2 nM (BACE1) and 0.38 nM (BACE2)[1] ***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].

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].

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.

CAIndexNames:

2-Pyridinecarboxamide, N-[3-[(5R)-3-amino-5,6-dihydro-2,5-dimethyl-1,1-dioxido-2H-1,2,4-thiadiazin-5-yl]-4-fluorophenyl]-5-fluoro-

SMILES:

O=C(C1=NC=C(F)C=C1)NC2=CC=C(F)C([C@@](C3)(C)N=C(N)N(C)S3(=O)=O)=C2

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

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