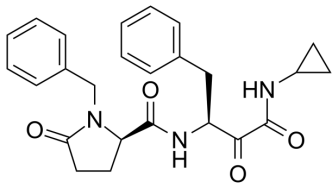
(1S,2R)-Alicapistat

Cat. No.:	HY-109001A
CAS No.:	2221010-57-5
Molecular Formula:	$C_{25}H_{27}N_3O_4$
Molecular Weight:	433.5
Target:	Proteasome
Pathway:	Metabolic Enzyme/Protease
Storage:	Powder -20°C 3 years 4°C 2 years In solvent -80°C 6 months -20°C 1 month



BIOLOGICAL ACTIVITY

Description	(1S,2R)-Alicapistat ((1S,2R)-ABT-957) is an orally active selective inhibitor of human calpains 1 and 2 for the potential application of Alzheimer's disease (AD)[1]. (1S,2R)-Alicapistat mitigates the metabolic liability of carbonyl reduction and inhibits calpain 1 with an IC_{50} value of 395 nM[2].
IC_{50} & Target	IC50: 395 nM (human calpain 1)[1]
In Vitro	(1S,2R)-Alicapistat exihibits inadequate CNS-penetration concentrations to obtain a pharmacodynamic effect[1]. Calpain 1 (μ-calpain) and 2 (m-calpain) expression in a calcium-dependent manner with μ-molar or m-molar calcium concentrations required for their respective activation, respectively. (1S,2R)-Alicapistat (compound 22) (100 nM) prevents Aβ oligomer-induced deficits in synaptic transmission in rat[2]. (1S,2R)-Alicapistat (compound 22) (385 nM) diplays efficacy with respect to prevention of NMDA-induced neurodegeneration and A-induced synaptic dysfunction[2]. (1S,2R)-Alicapistat (9-21 nM) has the CSF concentrations without reaching the IC_{50} for calpain inhibition and shows no dose-limiting toxicities (DLTs) in the broad populations studies[3]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	(1S,2R)-Alicapistat (compound 22) (iv or po; 1-3 mg/kg) shows moderate mean plasma clearance values (CLp) in mouse, rat, and dog (0.13-1.04 L/hr.kg), while high in monkey (1.98 L/hr.kg). Mean steady-state volume of distribution values (Vss) were moderate in mouse, dog, and monkey (0.64-1.8 L/kg), but higher in rat (3.4 L/kg). The plasma elimination half-life ($t_{1/2}$) was shortest in dog (1.7 hours), followed by 2.3 hours in monkey and approximately 6.0 hours in mouse and rat. Oral bioavailability (F) values were high in mouse, rat, and dog (>80%), while moderate in monkey (14%)[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

REFERENCES

[1]. Lon HK, et al. Pharmacokinetics, Safety, Tolerability, and Pharmacodynamics of Alicapistat, a Selective Inhibitor of Human Calpains 1 and 2 for the Treatment of Alzheimer Disease: An Overview of Phase 1 Studies. Clin Pharmacol Drug Dev. 2019 Apr. 8(3):290

[2]. Jantos K, et al. Discovery of ABT-957: 1-Benzyl-5-oxopyrrolidine-2-carboxamides as selective calpain inhibitors with enhanced metabolic stability. Bioorg Med Chem Lett. 2019 Aug 1. 29(15):1968-1973.

[3]. Jastaniah A, Gaisina IN, Knopp RC, Thatcher GRJ. Synthesis of α-Ketoamide-Based Stereoselective Calpain-1 Inhibitors as Neuroprotective Agents. ChemMedChem. 2020 Dec 3. 15(23):2280-2285.

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