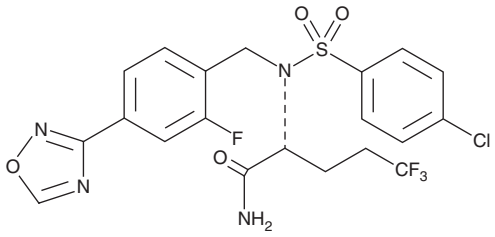
PRODUCT INFORMATION

Avagacestat

Item No. 16711

CAS Registry No.: 1146699-66-2
Formal Name: (2R)-2-[[(4-chlorophenyl)sulfonyl][[2-fluoro-4-(1,2,4-oxadiazol-3-yl)phenyl]methyl]amino]-5,5,5-trifluoro-pentanamide
Synonym: BMS 708163
MF: $C_{20}H_{17}ClF_4N_4O_4S$
FW: 520.9
Purity: ≥98%
UV/Vis.: λ_{max}: 244 nm
Supplied as: A crystalline solid
Storage: -20°C
Stability: ≥4 years



Information represents the product specifications. Batch specific analytical results are provided on each certificate of analysis.

Laboratory Procedures

Avagacestat is supplied as a crystalline solid. A stock solution may be made by dissolving the avagacestat in the solvent of choice, which should be purged with an inert gas. Avagacestat is soluble in organic solvents such as ethanol, DMSO, and dimethyl formamide. The solubility of avagacestat in these solvents is approximately 5, 15, and 2 mg/ml, respectively.

Avagacestat is sparingly soluble in aqueous buffers. For maximum solubility in aqueous buffers, avagacestat should first be dissolved in DMSO and then diluted with the aqueous buffer of choice. DMSO has a solubility of approximately 0.3 mg/ml in a 1:2 solution of DMSO:PBS (pH 7.2) using this method. We do not recommend storing the aqueous solution for more than one day.

Description

γ-Secretase is a protease complex that cleaves single-pass transmembrane proteins, such as Notch receptors and β-amyloid precursor protein (APP), within the transmembrane domain.[1,2] Avagacestat is a potent, orally bioavailable inhibitor of γ-secretase that more potently inhibits the cleavage of APP to Aβ40 than signaling through Notch (IC_{50}s = 0.30 and 58 nM, respectively).[3] It shows good pharmacokinetics in rats, dogs, and humans and passes the blood-brain barrier, reducing plasma, brain, and cerebrospinal fluid Aβ40 levels.[3,4] While suppressing the production of Aβ38, Aβ40, and Aβ42, γ-secretase inhibitors, including avagacestat, increase the level of APP β-C-terminal fragment, both *in vitro* and *in vivo*, altering cell function.[5] Avagacestat may impact Notch signaling *in vivo*, although it is generally considered a "Notch-sparing" γ-secretase inhibitor.[6]

References

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2. Jurisch-Yaksi, N., Sannerud, R., and Annaert, W. *Biochim Biophys. Acta.* **1828(12)**, 2815-2827 (2013).
3. Gillman, K.W., Starrett, J.E., Jr., Parker, M.F., *et al. ACS Med. Chem. Lett.* **1(3)**, 120-124 (2010).
4. Albright, C.F., Dockens, R.C., Meredith, J.E., Jr., *et al. J. Pharmacol. Exp. Ther.* **344(3)**, 686-695 (2013).
5. Mitani, Y., Yarimizu, J., Saita, K., *et al. J. Neurosci.* **32(6)**, 2037-2050 (2012).
6. Crump, C.J., Castro, S.V., Wang, F., *et al. Biochemistry* **51(37)**, 7209-7211 (2012).

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