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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

BMS 708163 Synonym: MF: C20H17ClF4N4O4S

FW: 520.9 **Purity:** ≥98%

≥2 years at -20°C Stability: Supplied as: A crystalline solid λ_{max} : 244 nm UV/Vis.:

$\dot{N}H_{2}$

Laboratory Procedures

For long term storage, we suggest that avagacestat be stored as supplied at -20°C. It should be stable for at least two years. Avagacestat is supplied as a crystalline solid. A stock solution may be made by dissolving the avagacestat in the solvent of choice. Avagacestat is soluble in organic solvents such as ethanol, DMSO, and dimethyl formamide, which should be purged with an inert gas. 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. Avagacestat 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.

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 A β 40 than signaling through Notch (IC₅₀s = 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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- 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).
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