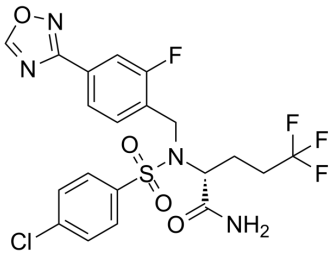
Avagacestat

Cat. No.:	HY-50845
CAS No.:	1146699-66-2
Molecular Formula:	$C_{20}H_{17}ClF_4N_4O_4S$
Molecular Weight:	520.89
Target:	γ-secretase; Notch
Pathway:	Neuronal Signaling; Stem Cell/Wnt
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 : ≥ 100 mg/mL (191.98 mM)

* "≥" means soluble, but saturation unknown.

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	1.9198 mL	9.5990 mL	19.1979 mL
5 mM	0.3840 mL	1.9198 mL	3.8396 mL
10 mM	0.1920 mL	0.9599 mL	1.9198 mL

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

In Vivo

1. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 3 mg/mL (5.76 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Avagacestat (BMS-708163) is a potent inhibitor of γ-secretase, with IC_{50}s of 0.27 nM and 0.30 nM for Aβ42 and Aβ40 inhibition; Avagacestat (BMS-708163) also inhibits NICD (Notch IntraCellular Domain) with IC_{50} of 0.84 nM and shows weak inhibition of CYP2C19, with IC_{50} of 20 μM. Avagacestat can be used for Alzheimer disease research.

IC_{50} & Target

IC50: 0.27 nM (γ-secretase, Aβ42), 0.30 nM (γ-secretase, Aβ40), 20 μM (CYP2C19)[1], 0.84 nM (NICD)[2]

In Vitro

Avagacestat (BMS-708163) exhibits weaker potency for inhibition of Notch processing, IC_{50}=58±23 nM, as compared to its inhibition potency for APP cleavage[1]. Avagacestat (BMS-708163) (10 μM) combined with gefitinib significantly attenuates the colony growth of PC9/AB2 cells, increases the expression of active caspase 3 and PARP and reduces the expression of Ki-67 in PC9/AB2 cells. Avagacestat (BMS-708163) induces apoptosis and enhances cell cycle arrest at the G1 phase in PC9/AB2 cells. Avagacestat (BMS-708163) treatment effectively downregulates the expression of Notch1, HES1, PI3K and Akt in

	PC9/AB2 cells[3]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	Avagacestat (BMS-708163) significantly reduces both plasma and brain Aβ40 levels relative to control at 10 and 100 mg/kg for the entire dosing interval, demonstrates significant Aβ40 lowering for 8 h after an oral dose of 1 mg/kg, and significantly lowers CSF Aβ40 levels in rats, when measured 5 h after single oral doses ranging from 3 to 100 mg/kg[1]. Avagacestat (BMS-708163) (10 mg/kg) monotherapy has a minor inhibitory effect on PC9/AB2 tumor growth compared with gefitinib alone. BMS-708163 monotherapy results in a slight increase in caspase 3 expression as well as a mild decrease in Ki-67 expression in vivo. In the xenograft lung cancer samples treated with Avagacestat (BMS-708163) plus gefitinib, there are a marked increase in caspase 3 expression and a reduction in Ki-67 staining[3]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Cell Assay [3]	The cell viability is assessed using a tetrazolium salt (WST-8)-based colorimetric assay from the Cell Counting Kit 8 (CCK-8). The cells are seeded into 96-well plates at an initial density of 5×10^3 cells/well and cultured for 24 h, after which the cells are cultured with DMSO, increased concentrations of gefitinib or Avagacestat (BMS-708163) , BIBW2992, or the combination of Avagacestat (BMS-708163) and BIBW2992 for an additional 48 h. The A450 is measured in a microplate reader after 10 μL of CCK-8 solution is added and incubated for 1 h. The percentage of growth is shown relative to untreated controls. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [3]	Four- to six-week-old female Balb/c athymic (nu + /nu +) mice are anesthetized with ether. The mice are acclimatized for one week before being injected with 1.5×10^6 PC9/AB2 cells that have been resuspended in 200 μL of matrigel. When established tumors of approximately 150-300 mm^3 in diameter are detected, the mice are randomly divided into groups and fed orally by gavage with either vehicle (1% methylcellulose, 0.2% Tween 80 in sterilized water), gefitinib (3 mg/kg diluted in vehicle), Avagacestat (BMS-708163) (10 mg/kg diluted in vehicle), or a combination of gefitinib (3 mg/kg) and Avagacestat (BMS-708163) (10 mg/kg) for 5 days/week. Each treatment group consists of eight mice. The tumor volume are measured and calculated every five days using the following formula: $\pi/6\times(\text{larger diameter})\times(\text{smaller diameter})^2$. After 30 days, mice are killed by cervical dislocation. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- EMBO J. 2012 May 16;31(10):2261-74.
- J Alzheimers Dis. 2012;28(4):809-22.

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REFERENCES

[1]. Gillman KW, et al. Letter Discovery and Evaluation of BMS-708163, a Potent, Selective and Orally Bioavailable γ-Secretase Inhibitor. Med Chem Lett, 2010, 1 (3), 120-124.

[2]. Crump CJ, et al. BMS-708,163 targets presenilin and lacks notch-sparing activity. Biochemistry. 2012 Sep 18;51(37):7209-11.

[3]. Xie M, et al. γ Secretase inhibitor BMS-708163 reverses resistance to EGFR inhibitor via the PI3K/Akt pathway in lung cancer. J Cell Biochem. 2015 Jun;116(6):1019-27.

[4]. Borghys H, et al. A canine model to evaluate efficacy and safety of γ-secretase inhibitors and modulators. J Alzheimers Dis. 2012;28(4):809-22.

[5]. Vladimir Coric, et al. Safety and tolerability of the γ-secretase inhibitor avagacestat in a phase 2 study of mild to moderate Alzheimer disease. Arch Neurol. 2012

Nov;69(11):1430-40.

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