产品名称：Avagacestat (BMS-708163)
产品别名：Avagacestat

生物活性：

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.
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, IC50=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].
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].
Solvent&Solubility	***In Vitro:*** **DMSO : ≥ 100 mg/mL** (**191.98 mM**) **H_2O : < 0.1 mg/mL** (insoluble) * "≥" 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

*请根据产品在不同溶剂中的溶解度选择合适的溶剂配制储备液；一旦配成溶液，请分装保存，避免反复冻融造成的产品失效。

储备液的保存方式和期限：-80°C, 6 months; -20°C, 1 month。-80°C 储存时，请在 6 个月内使用，-20°C 储存时，请在 1 个月内使用。

In Vivo:

请根据您的实验动物和给药方式选择适当的溶解方案。以下溶解方案都请先按照 **In Vitro** 方式配制澄清的储备液，再依次添加助溶剂：

——为保证实验结果的可靠性，澄清的储备液可以根据储存条件，适当保存；体内实验的工作液，建议您现用现配，当天使用； 以下溶剂前显示的百分比是指该溶剂在您配制终溶液中的体积占比；如在配制过程中出现沉淀、析出现象，可以通过加热和/或超声的方式助溶

1.请依序添加每种溶剂： 10% DMSO→40% PEG300 →5% Tween-80 → 45% saline

	Solubility: ≥ 3 mg/mL (5.76 mM); Clear solution 此方案可获得 ≥ 3 mg/mL (5.76 mM，饱和度未知) 的澄清溶液。 以 1 mL 工作液为例，取 100 μL 30.0 mg/mL 的澄清 DMSO 储备液加到 400 μL PEG300 中，混合均匀向上述体系中加入 50 μL Tween-80，混合均匀；然后继续加入 450 μL 生理盐水定容至 1 mL。 2.请依序添加每种溶剂： 10% DMSO →90% corn oil Solubility: ≥ 3 mg/mL (5.76 mM); Clear solution 此方案可获得 ≥ 3 mg/mL (5.76 mM，饱和度未知) 的澄清溶液，此方案不适用于实验周期在半个月以上的实验。 以 1 mL 工作液为例，取 100 μL 30.0 mg/mL 的澄清 DMSO 储备液加到 900 μL 玉米油中，混合均匀。
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]. 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. [3]. Crump CJ, et al. BMS-708,163 targets presenilin and lacks notch-sparing activity. Biochemistry. 2012 Sep 18;51(37):7209-11. [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.

实验参考：

Cell Assay	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. [3]
Animal Administration	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: π/6×(larger diameter)×(smaller diameter)^2. After 30 days, mice are killed by cervical dislocation. [3]
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]. 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. [3]. Crump CJ, et al. BMS-708,163 targets presenilin and lacks notch-sparing activity. Biochemistry. 2012 Sep 18;51(37):7209-11.

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