产品名称：PF-3084014
产品别名：Nirogacestat

生物活性：

Description	Nirogacestat (PF-3084014) is a reversible, noncompetitive, and selective γ-secretase inhibitor with IC50 of 6.2 nM.
IC_{50} & Target	IC50: 6.2 nM (γ-secretase)[1]
In Vitro	The IC50 of Nirogacestat (PF-03084014) for γ-secretase enzyme inhibition in cell-free assay for Aβ production using detergent solubilized membranes derived from HeLa cells is determined to be 6.2 nM. When tested for inhibition of Notch receptor cleavage in cellular assays using HPB-ALL cells that harbor mutations in both the heterodimerization and PEST domains in Notch1, the cell IC50 is determined to be 13.3 nM. Nirogacestat (PF-03084014) causes a significant increase in caspase-3 activities in HPB-ALL and TALL-1 cells as well as an induction of cleaved PARP and cleaved caspase-3 after a 7-day treatment[1].
In Vivo	Nirogacestat (PF-03084014) shows robust antitumor activity in this model on 14-day twice daily dosing. Tumor growth inhibition is dose dependent, with maximal tumor growth inhibition of ~92% obtained at high dose levels (150 mg/kg). In tumor growth inhibition studies where mice receive repetitive twice daily dosing for more than a week, Nirogacestat (PF-03084014) is well tolerated at dose levels below 100 mg/kg as no significant weight loss, morbidity, or mortality is observed. When the dose is increased to 150 mg/kg, however, mice have diarrhea and show weight loss (10-15%) approximately 10 days after compound administration. The body weight of treated animals usually returns to normal if dosing holidays are given, suggesting that the toxicity of Nirogacestat (PF-03084014) is reversible[1].
Solvent&Solubility	***In Vitro:*** **DMSO : ≥ 50 mg/mL (102.12 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	2.0423 mL	10.2116 mL	20.4232 mL
	5 mM	0.4085 mL	2.0423 mL	4.0846 mL
	10 mM	0.2042 mL	1.0212 mL	2.0423 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: 2.5 mg/mL (5.11 mM); Suspended solution; Need ultrasonic and warming

此方案可获得 2.5 mg/mL (5.11 mM)的均匀悬浊液，悬浊液可用于口服和腹腔注射。

以 1 mL 工作液为例，取 100 μL 25.0 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% (20% SBE-β-CD in saline) Solubility: 2.5 mg/mL (5.11 mM); Suspended solution; Need ultrasonic 此方案可获得 2.5 mg/mL (5.11 mM)的均匀悬浊液，悬浊液可用于口服和腹腔注射。 以 1 mL 工作液为例，取 100 μL 25.0 mg/mL 的澄清 DMSO 储备液加到 900 μL 20% 的 SBE-β-CD 生理盐水水溶液中，混合均匀。 3.请依序添加每种溶剂： 10% DMSO →90% corn oil Solubility: ≥ 2.5 mg/mL (5.11 mM); Clear solution 此方案可获得 ≥ 2.5 mg/mL (5.11 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 25.0 mg/mL 的澄清 DMSO 储备液加到 900 μL 玉米油中，混合均匀。
References	[1]. Wei P, et al. Evaluation of selective gamma-secretase inhibitor PF-03084014 for its antitumor efficacy and gastrointestinal safety to guide optimal clinical trial design. Mol Cancer Ther. 2010 Jun;9(6):1618-28.

实验参考：

Cell Assay	Cells are seeded in 96-well plates at 2,000 (Sup-T1, Jurkat, and DND-41) or 10,000 (HPB-ALL or TALL-1) cells/well in growth media supplemented with 10% fetal bovine serum. Serial dilutions of Nirogacestat (PF-03084014) are done in DMSO, appropriate controls or designated concentrations of Nirogacestat (PF-03084014) are added to each well, and cells are incubated at 37°C for 7 days (final DMSO content 0.1%). Resazurin at a final concentration of 0.1 mg/mL is added to the cells and plates are incubated for 2 to 4 hours. Fluorescent signals are read as emission at 590 nm after excitation at 560 nm. IC50 values are calculated by using the sigmoidal dose-response (variable slope) in GraphPad Prism[1].
Animal Administration	Mice[1] Athymic female mice (*nu/nu*, 6-8 weeks) are used. For antitumor efficacy, animals bearing tumors of 150 to 300 mm^3 in size are randomly divided into groups that received either vehicle (0.5% methylcellulose) or Nirogacestat (PF-03084014) (150 mg/kg, diluted in vehicle), and dosed by oral gavage. Animal body weight and tumor measurements are obtained every 2 to 3 days. Tumor volume (mm^3) is measured with Vernier calipers and calculated. Percent (%) inhibition values are measured on the final day of study for drug-treated compared with vehicle-treated mice and are calculated. For all tumor growth inhibition experiments, 8 to 10 mice per dose group are used. Student's t test is used to determine the P value.
References	[1]. Wei P, et al. Evaluation of selective gamma-secretase inhibitor PF-03084014 for its antitumor efficacy and gastrointestinal safety to guide optimal clinical trial design. Mol Cancer Ther. 2010 Jun;9(6):1618-28.