Nirogacestat

Cat. No.: HY-15185

CAS No.: 1290543-63-3

Molecular Formula: $C_{27}H_{41}F_2N_5O$

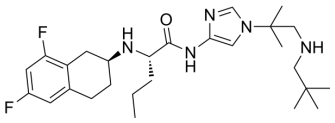
Molecular Weight: 489.64

Target: γ-secretase; Apoptosis

Pathway: Neuronal Signaling; Stem Cell/Wnt; Apoptosis

Storage:

Powder	-20°C	3 years
	4°C	2 years
In solvent	-80°C	6 months
	-20°C	1 month



SOLVENT & SOLUBILITY

In Vitro

DMSO : 28.57 mg/mL (58.35 mM; Need ultrasonic)

H_2O : < 0.1 mg/mL (ultrasonic;warming;heat to 60°C) (insoluble)

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

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

In Vivo

1. Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
   Solubility: 2.5 mg/mL (5.11 mM); Suspended solution; Need ultrasonic and warming
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: 2.5 mg/mL (5.11 mM); Suspended solution; Need ultrasonic
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (5.11 mM); Clear solution
4. Add each solvent one by one: 5% DMSO >> 40% PEG300 >> 5% Tween-80 >> 50% saline
   Solubility: 1.43 mg/mL (2.92 mM); Suspended solution; Need ultrasonic

BIOLOGICAL ACTIVITY

Description

Nirogacestat (PF-3084014) is a reversible, orally bioavailable, noncompetitive, and selective γ-secretase inhibitor with an IC_{50} of 6.2 nM. Inhibition of Notch signaling by Nirogacestat while minimizing gastrointestinal toxicity presents a promising approach for research of Notch receptor-dependent cancers[1].

IC_{50} & Target	IC50: 6.2 nM (γ-secretase)[1]
In Vitro	The IC_{50} 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 IC_{50} 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]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
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]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Cell Assay [1]	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. IC_{50} values are calculated by using the sigmoidal dose-response (variable slope) in GraphPad Prism[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [1][2]	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. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Cancer Cell. 2021 Mar 8;39(3):380-393.e8.
- Neuron. 2023 Apr 4;S0896-6273(23)00220-9.
- J Clin Invest. 2020 Feb 3;130(2):612-624.
- EMBO Mol Med. 2017 Jul;9(7):950-966.
- Int J Oncol. 2018 Jul;53(1):99-112.

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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.

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