Nirogacestat dihydrobromide

Cat. No.: HY-15185B

CAS No.: 1962925-29-6

Molecular Formula: $C_{27}H_{43}Br_2F_2N_5O$

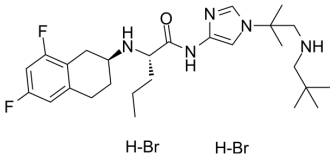
Molecular Weight: 651.47

Target: γ-secretase; Apoptosis

Pathway: Neuronal Signaling; Stem Cell/Wnt; Apoptosis

Storage: 4°C, sealed storage, away from moisture

* In solvent : -80°C, 6 months; -20°C, 1 month (sealed storage, away from moisture)



SOLVENT & SOLUBILITY

In Vitro

DMSO : 80 mg/mL (122.80 mM; Need ultrasonic)

Preparing Stock Solutions	Mass / Solvent / Concentration	1 mg	5 mg	10 mg
	1 mM	1.5350 mL	7.6750 mL	15.3499 mL
	5 mM	0.3070 mL	1.5350 mL	3.0700 mL
	10 mM	0.1535 mL	0.7675 mL	1.5350 mL

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

BIOLOGICAL ACTIVITY

Description

Nirogacestat dihydrobromide (PF-3084014 dihydrobromide) 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 dihydrobromide while minimizing gastrointestinal toxicity presents a promising approach for research of Notch receptor-dependent cancers[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 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 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 is reversible[1].

MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Nat Med. 2023 Sep;29(9):2295-2306.
- 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.

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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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