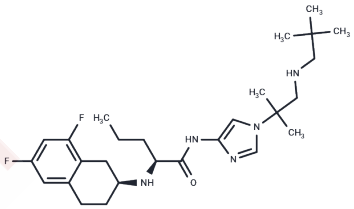
Data Sheet (Cat.No.T6935)

TargetMol

Nirogacestat

Chemical Properties



CAS No. : 1290543-63-3

Formula: C27H41F2N5O

Molecular Weight: 489.64

Storage: Keep away from moisture,Keep away from direct sunlight
Powder: -20°C for 3 years | In solvent: -80°C for 1 year
Actual storage temperature shall be subject to the COA.

Biological Description

Description	Nirogacestat (PF 03084014) is a specific γ-secretase inhibitor (IC50: 6.2 nM, in a cell-free assay).
Targets(IC50)	Apoptosis,Gamma-secretase
In vitro	Nirogacestatinhibits Notch receptor cleavage in HPB-ALL cells that harbor mutations in both the heterodimerization and PEST domains in Notch1 (IC50: 13.3 nM). Nirogacestatdownregulates Notch target genes Hes-1 (IC50<1 nM) and cMyc expression (IC50:10 nM) in HPB-ALL cells, respectively. Nirogacestatinhibits cell growth of a subset of human T-ALL cell lines (HPB-ALL, DND-41, TALL-1, and Sup-T1) through induction of cell cycle arrest and apoptosis (IC50s: 30-100 nM). Nirogacestatreduces proliferation of HUVECs (IC50: 0.5 μM) and decreases the lumen formation (IC50: 50 nM). Nirogacestat(1 μM) has no antiproliferative effect in MX1 cells; however, it inhibits migration by 95%.
In vivo	Nirogacestat(200 mg/kg, p.o.) causes maximal NICD inhibition for ~80% in xenograft HPB-ALL tumors. Nirogacestatshows robust antitumor activity in this mode with a maximal tumor growth inhibition of 92% at the dose of 150 mg/kg, accompanied by a significant reduction of NICD/Notch1, tumor mitotic index (Ki67), and apoptosis (activated caspase-3) staining. Nirogacestat(120 mg/kg) induces apoptosis, antiproliferation, reduces tumor cell self-renewal ability, impairs tumor vasculature, and decreases metastasis activity in breast cancer HCC1599 tumor-bearing mice. In various types of the breast xenograft models, Nirogacestathas significant antitumor activity (TGI>50%).
Kinase Assay	γ-secretase assay:A DNA fragment encoding amino acids 596 - 695 of the 695-aa isoform of APP (APP695) and the Flag sequence (DYKDDDDK) at the C terminus is generated by PCR amplification with suitably designed oligonucleotides and the APP695 cDNA. The Met that serves as the translation start site is residue 596 of APP695 (the P1 residue with respect to theβ-secretase cleavage site). This DNA fragment is inserted into the prokaryotic expression vector pET2-21b. The recombinant protein, C100Flag, is overproduced in Escherichia coli [strain BL21(DE3)] and purified by Mono-Q column chromatography. C100Flag (1.7 μM) is incubated with cell membranes (0.5 mg/mL) in the presence of CHAPSO, CHAPS (3-[(3-cholamidopropyl)dim-ethylammonio]-1-propanesulfonate), or Triton X-100 (0, 0.125, 0.25, 0.5, or 1%) in buffer B (50 mM Pipes,

Kinase Assay	pH 7.0y 5 mM MgCl2/5 mM CaCl2/150 mM KCl) at 37°C. The reactions are stopped by adding RIPA (150 mM NaCl/1.0% NP-40/0.5% sodium deoxycholate 0.1% SDS/50 mM Tris HCl, pH 8.0) and boiling for 5 min. The samples ae centrifuged and the supernatant solutions are assayed for the Aβ peptides by ECL. The Aβ40- and Aβ42-related products from γ-secretase-mediated processing of C100Flag possess a Met at the N terminus and are thus defined as M-Aβ40 and M-Aβ42, respectively. Likewise, supernatant solution (0.125 mg/mL) from CHAPSO-extracted HeLa cell membranes (solubilized γ-secretase) is incubated with C100Flag (1.7 μM) in buffer B containing 0.25% CHAPSO and subsequently assayed for M-Aβ40 and M-Aβ42 by using ECL.
Cell Research	Cell lines: Human T-ALL cell lines HPB-ALL. Concentrations: ~1 μM. Method: Cells are seeded in 96-well plates at 10,000 cells/well in growth media supplemented with 10% fetal bovine serum.Serial dilutions of PF-03084014 are done in DMSO,appropriate controls or designated concentrations of PF-03084014 are added to each well,and cells are incubated at 37℃ 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.
Animal Research	Animal Models: Human T-cell acute lymphoblastic leukemia xenografts HPB-ALL. Formulation: 0.5% methylcellulose. Dosages: 150 mg/kg,b.i.d. Administration: p.o.

Solubility Information

Solubility	DMSO: 61.25 mg/mL (125.09 mM),Sonication is recommended. H2O: < 1 mg/mL (insoluble or slightly soluble), Ethanol: 90 mg/mL (183.81 mM),Sonication is recommended. (< 1 mg/ml refers to the product slightly soluble or insoluble)
In vivo Formulation	10% DMSO+90% Corn Oil: 3.3 mg/mL (6.74 mM),Sonication is recommended. *Please add the solvents sequentially, clarifying the solution as much as possible before adding the next one. Dissolve by heating and/or sonication if necessary. Working solution is recommended to be prepared and used immediately. The formulation provided above is for reference purposes only. In vivo formulations may vary and should be modified based on specific experimental conditions.*

Preparing Stock Solutions

	1mg	5mg	10mg
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
50 mM	0.0408 mL	0.2042 mL	0.4085 mL

Please select the appropriate solvent to prepare the stock solution, according to the solubility of the product in different solvents. Please use it as soon as possible.

Note: The dilution table applies only to solid products. For liquid products, please calculate the stock solution based on the stated concentration and/or density.

Reference

Wei P, et al. Mol Cancer Ther, 2010, 9(6), 1618-1628.
Machine learning-enabled virtual screening indicates the anti-tuberculosis activity of aldoxorubicin and quarfloxin with verification by molecular docking, molecular dynamics simulations, and biological evaluations
Zhang CC, et al. Clin Cancer Res, 2012, 18(18), 52008-52019.
Li YM, et al. Proc Natl Acad Sci USA, 2000, 97(11), 6138-6143.

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