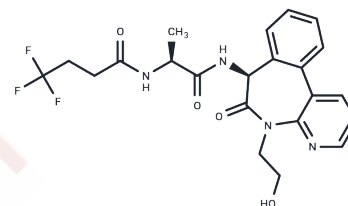


Crenigacestat

Chemical Properties

CAS No. :	1421438-81-4
Formula:	C22H23F3N4O4
Molecular Weight:	464.44
Storage:	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	Crenigacestat (LY3039478) is an orally bioavailable Notch inhibitor with an IC50 of ~1 nM in most tumor cell lines tested. It effectively inhibits mutant Notch receptor activity and, in a xenograft tumor model, inhibits the expression of Notch-regulated genes and N1ICD cleavage in the tumor microenvironment.
Targets(IC50)	Gamma-secretase
In vitro	Crenigacestat is a novel small molecule that is an exquisitely potent inhibitor of Notch-1 intracellular domain (N1ICD) cleavage with an IC50 of ~1 nM in most of the tumor cell lines tested. Crenigacestat also potently inhibits mutant Notch receptor activity[2]. Treatment with a gamma secretase inhibitor, Crenigacestat, significantly inhibited the growth of 2 CCRCC(Clear cell renal cell carcinoma) cell lines in a concentration dependent manner. Crenigacestat treatment also led to decreased expression of Myc and Cyclin A1, two genes that were part of the NOTCH driven proliferative signature in murine and human model systems. Crenigacestat treatment also led to G0/G1 cell cycle arrest in CCRCC cells[3].
In vivo	In mice, its oral bioavailability(%F) is 65%, clearance(CL)=41 mL/min/kg, VDss = 3.8 L/kg. In Rats, its oral bioavailability(%F) is 65%, CL=98 mL/min/kg, VDss=4.9 L/kg. In Dogs, its oral bioavailability (%F) is 67%, CL=3.8 mL/min/kg, VDss=1.4 L/kg[1]. In a xenograft tumor model, Crenigacestat inhibited N1ICD cleavage and expression of Notch-regulated genes in the tumor microenvironment. The inhibition of Notch cleavage also resulted in the induction of apoptosis in a Notch-dependent xenograft model[2]. In immunodeficient NSG mice xenografted with 769-P CCRCC cells, Crenigacestat treatment resulted in significantly increased survival and delayed tumor growth in independent cohorts of mice demonstrating in vivo efficacy in CCRCC[3].
Cell Research	K07074 cells were plated to 24-well plates at 10 ⁵ cell/well. Viability of cells was assessed in quadruplicates at indicated timepoints using the CellTiter-Glo luminescent cell viability assay. To study the effect of the small molecular compounds on K07074 cell growth the compounds or DMSO were added to the growth media 24 h after seeding. The cells were incubated with inhibitors and DMSO as indicated. Cell viability was assessed as described above. Each experiment was carried out in triplicate and at least 3 independent experiments were performed. (Only for Reference)

Solubility Information

A DRUG SCREENING EXPERT

Solubility	DMSO: 150 mg/mL (322.97 mM),Sonication is recommended. H2O: < 1 mg/mL (insoluble or slightly soluble), (< 1 mg/ml refers to the product slightly soluble or insoluble)
In vivo Formulation	10% DMSO+40% PEG300+5% Tween 80+45% Saline: 10 mg/mL (21.53 mM),Solution. 10% DMSO+90% Saline: < 10 mg/mL (21.53 mM),Lower concentrations may be soluble, but exact solubility limit is unknown. <i>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.</i>

Preparing Stock Solutions

	1mg	5mg	10mg
1 mM	2.1531 mL	10.7657 mL	21.5313 mL
5 mM	0.4306 mL	2.1531 mL	4.3063 mL
10 mM	0.2153 mL	1.0766 mL	2.1531 mL
50 mM	0.0431 mL	0.2153 mL	0.4306 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

Eli Lilly Company. The 8th SCI-RSC Symposium on Proteinase Inhibitor Design. 2013.

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