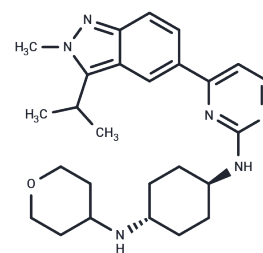


LY2857785

Chemical Properties

CAS No. : 1619903-54-6
 Formula: C₂₆H₃₆N₆O
 Molecular Weight: 448.6
 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	LY2857785 is a type I competitive and reversible ATP kinase inhibitor against CDK7/CDK8/CDK9 (IC ₅₀ s: 246 nM/16 nM/11 nM).
Targets(IC ₅₀)	Apoptosis,CDK
In vitro	At the cellular level, LY2857785 inhibits CTD P-Ser2 and CTD P-Ser5 in U2OS cells (IC ₅₀ s: 0.089 and 0.042 μM). However, LY2857785 only induces a moderate G2-M DNA content increase, from 35% to 55%, with EC ₅₀ 0.135 μM. LY2857785 shows potent compound exposure- and time-dependent cell proliferation inhibition in MV-4-11, RPMI8226, and L363 cells. When incubated between 4 to 24 hours, the cell growth inhibition potency reaches a maximal effect at 8 hours for MV-4-11, RPMI8226, and L363 cells (IC ₅₀ s: 0.04, 0.2, and 0.5 μM). LY2857785-induced cancer cell apoptosis is also time-dependent, reaching maximal potency at 8 hours with IC ₅₀ 0.5 μM in L363 cells.
In vivo	In HCT116 xenograft tumor-bearing mice, LY2857785 potently demonstrates dose-dependent RNAP II CTD P-Ser2 inhibition (TED ₅₀ : 4.4 mg/kg; TEC ₅₀ : 0.36 μM), with a significant duration of inhibition for 3 to 6 hours at TED ₇₀ (8 mg/kg) in both HCT116 and MV-4-11 nude mice xenograft models. In the nude rat MV-4-11 xenograft model, LY2857785 similarly shows dose-dependent CTD P-Ser2 inhibition for 8 hours at TED ₇₀ (7 mg/kg) and TED ₉₀ (10 mg/kg).
Kinase Assay	CDK7 and CDK9 reaction mixtures contain 10 mM Tris-HCl (pH 7.4), 10 mM HEPES, 5 mM DTT, 10 μM ATP, 0.5 μCi 33p-ATP, 10 mM MnCl ₂ , 150 mM NaCl, 0.01% Triton X-100, 2% DMSO, 0.05 mM CDK7/9ptide, and 2 nM CDK7/Mat1/cyclin H, or 2 nM CDK9/cyclin T1, respectively. CDK8/cyclin C reaction is performed in HEPES 30 mM, DTT 2 mM, MgCl ₂ 5 mM, 0.015% Triton X-100, 5 μM ATP, and 400 nM of RBER-CHKStide containing 20 nM of enzyme. LY2857785 in DMSO is diluted serially 1:3 for dose-response. Reactions are carried out in 96-well polystyrene plates. The reactions are incubated at room temperature for 60 minutes and followed by termination with 10% H ₃ PO ₄ or 10% trichloroacetic acid (TCA). For the filter binding assay, reactions are transferred to 96-well filter plates and measured by Microbeta scintillation counter. For ADP Transcreener Fluorescent Polarization Assays, reactions are quenched with ADP detection mix, incubated 2 hours at room temperature and then FP is measured at λ _{ex} =610 nm, λ _{em} =670 nm on a Tecan Ultra 384 plate reader. The concentration of ADP product is calculated from millipolarization (μP) using a prepared ADP/ATP dilution series as a standard curve. Kinase profiling are carried out in 96-well polystyrene plates. Briefly, in

Kinase Assay	a final volume of 25 μ L the enzyme is incubated with the appropriate buffer, peptide substrate, and the diluted LY2857785. Reactions are initiated by the addition of ATP/[33P] and the ATP mix is incubated at room temperature for 40 minutes. Reactions are quenched with the addition of 5 μ L of 3% phosphoric acid, 10 μ L of the reaction are spotted onto a filter mat, washed 3 times for 5 minutes in 75 mM phosphoric acid and once in methanol. Once the filters are dry, they are submitted to scintillation counting.
Cell Research	Solid tumor cells are plated in poly-D-lysine coated and hematologic cell lines are seeded in noncoated 96-well plates overnight before being treated with LY2857785. Solid tumor cells are fixed with Prefer for 20 minutes at room temperature and permeated with 0.1% Triton X-100 in PBS for 15 minutes. Caspase-3 expression is measured by immunofluorescence with anti-activated caspase-3. Terminal deoxynucleotidyl transferase-mediated dUTP nick end labeling (TUNEL) activity is measured with In Situ Cell Death Detection Kit. Both assays are analyzed on Acumen Explorer laser-scanning fluorescence microplate cytometer. Hematologic tumor cells are assayed for cell viability with CellTiter-Glo Luminescent Cell Viability Assay.
Animal Research	For xenograft models, human cancer cells A375, U87MG, MV-4-11, and HCT116 are implanted into female nude rats or athymic nude female mice. The animals are dosed with saline, Rapamycin, or LY2857785, respectively. MV-4-11 xenografts in nude mice are treated by LY2857785 (4, 8, and 18 mg/kg) i.v. bolus. MV-4-11 xenografts in nude rats are treated with LY2857785 (3, 6, and 9 mg/kg) 4-hour i.v. infusion. An untreated vehicle control group is administered saline i.v. every 3 days. Flow cytometry analysis is conducted using Beckman Coulter's CXP software. Statistical significance of the effect of LY2857785 and/or control compounds is assessed by the Dunnett method, one-way ANOVA.

Solubility Information

Solubility	DMSO: 10 mg/mL (22.29 mM),Sonication is recommended. (< 1 mg/ml refers to the product slightly soluble or insoluble)
In vivo Formulation	10% DMSO+40% PEG300+5% Tween 80+45% Saline: 1 mg/mL (2.23 mM),Sonication is recommended. <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	2.2292 mL	11.1458 mL	22.2916 mL
5 mM	0.4458 mL	2.2292 mL	4.4583 mL
10 mM	0.2229 mL	1.1146 mL	2.2292 mL
50 mM	0.0446 mL	0.2229 mL	0.4458 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

Yin T, et al. A novel CDK9 inhibitor shows potent antitumor efficacy in preclinical hematologic tumor models. Mol Cancer Ther. 2014 Jun;13(6):1442-56. Mol Cancer Ther. 2014 Jun;13(6):1442-56.

Inhibitor · Natural Compounds · Compound Libraries · Recombinant Proteins

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