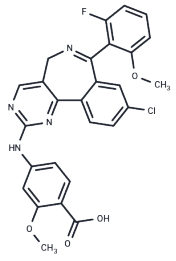
Data Sheet (Cat.No.T2241)

TargetMol

Alisertib

Chemical Properties



CAS No. : 1028486-01-2

Formula: C27H20ClFN4O4

Molecular Weight: 518.92

Appearance: no data available

Storage: Powder: -20°C for 3 years | In solvent: -80°C for 1 year

Biological Description

Description	Alisertib (MLN 8237) is a specific Aurora A inhibitor (IC50: 1.2 nM). The selectivity of Alisertib(MLN 8237) is >200-fold higher for Aurora A than Aurora B.
Targets(IC50)	Apoptosis,Aurora Kinase,Autophagy
In vitro	Treatment of cultured MM cells with Alisertib (MLN8237) results in mitotic spindle abnormalities, mitotic accumulation, as well as inhibition of cell proliferation through apoptosis and senescence. In addition, MLN8237 up-regulates p53 and tumor suppressor genes p21 and p27. Combining MLN8237 with dexamethasone, doxorubicin, or bortezomib induces synergistic/additive anti-MM activity in vitro [1]. Alisertib inhibited AAK over ABK with a selectivity of more than 200-fold in cells. Alisertib inhibited proliferation of human tumor cell lines in vitro [2]. A T217D/W277E double mutant exhibits superior levels of resistance to MLN8237, with the I50 value increasing approximately 20-fold from 30 to 650 nM in the presence of TPX2 [3].
In vivo	Tumor burden was significantly reduced and overall survival was significantly increased in animals treated with 30 mg/kg MLN8237 for 21 days. Induction of apoptosis and cell death by MLN8237 were confirmed in tumor cells excised from treated animals by TdT-mediated dUTP nick end labeling assay [1]. Alisertib produced a dose-dependent decrease in bipolar and aligned chromosomes in the HCT-116 xenograft model. Alisertib produced tumor growth inhibition in solid tumor xenograft models and regressions in in vivo lymphoma models. In addition, a dose of alisertib that caused tumor stasis, as measured by volume, resulted in a decrease in FLT uptake [2]. Nude mice bearing human tumor xenografts treated with a single oral dose of alisertib (20 mg/kg) displayed a phenotype consistent with inhibition of Aurora A [4].
Kinase Assay	Recombinant murine Aurora A and Aurora B protein were expressed in Sf9 cells and purified with GST affinity chromatography. The peptide substrate for Aurora A was conjugated with biotin (Biotin-GLRRASLG). Aurora A kinase (5 nM) was assayed in 50 mM Hepes (pH 7.5)/10 mM MgCl2/5 mM DTT/0.05% Tween 20/2 μM peptide substrate/3.3 μCi/ml [γ-33P]ATP at 2 μM by using Image FlashPlates. Aurora B kinase (2 nM) was assayed with 10 μM biotinylated peptide Biotin-TKQTARKSTGGKAPR in 50 mM Tricine (pH 8.0)/2.5 mM MgCl2/5 mM DTT/10% glycerol/2% BSA/40 μCi/ml [γ-33P]ATP at 250 μM. The conditions for all other in vitro kinase assays are available upon request. MLN8054 was run in a 226 kinase screen at a 1 μM compound concentration with an ATP concentration of 10 μM for all assays [2].

Cell Research	HCT-116 colorectal carcinoma cells were plated on 6-well dishes (2 × 10^5 per well) and propagated in McCoy's 5A media supplemented with 10% FBS. After 18 hours, alisertib at a final concentration of 0.050, 0.250, or 1.000 μmol/L was added, and the cells were grown for an additional 24 hours. Cells treated with dimethyl sulfoxide (DMSO; 0.2%) served as the untreated vehicle control. The cells were harvested with trypsin EDTA 1×, washed once with PBS, fixed in 70% ethanol, and stored at 4°C for 1 hour. The cells were resuspended in propidium iodide (1:40) and RNAse A (1:5,000) in PBS for 30 minutes at 4°C. Cell-cycle distributions were determined by measuring DNA content using flow cytometry, and samples were analyzed using Winlist 5.0 software [2].
Animal Research	Mice were irradiated (200 cGy), and then 5 × 106 MM1.S cells were inoculated subcutaneously in the right flank. When tumor growth was measurable (~ 2 weeks after the injection), mice were assigned into 4 groups (10 mice each) receiving vehicle orally (100 μL of 10% 2-hydroxypropyl-β-cyclodextrin/1% sodium bicarbonate) or MLN8237 (7.5 mg/kg, 15 mg/kg, and 30 mg/kg in a final formulation in 10% 2-hydroxypropyl-β-cyclodextrin/1% sodium bicarbonate) for 21 consecutive days. The maximal tolerated dose of MLN8237 in most mouse strains (continuous dosing for 21 days) is approximately 20 mg/kg twice a day (40 mg/kg per day). Tumor volumes were measured by a Vernier caliper every alternate day and calculated using the following formula: length × width2 × 0.5. Tumor growth inhibition (TGI) was calculated using the formula (Δcontrol average volume ? Δtreated average volume) × 100/(Δcontrol average volume). Mice were killed at the end of the treatment, 2 hours after the last treatment, or when tumor reached 2 cm^3; tumors were immediately collected from mice and evaluated for induction of apoptosis and cell death by TdT-mediated dUTP nick end labeling (TUNEL) assay [1].

Solubility Information

Solubility	10% DMSO+40% PEG300+5% Tween 80+45% Saline: 5 mg/mL (9.64 mM),Suspension. DMSO: 50 mg/mL (96.35 mM),Sonication is recommended. H2O: < 1 mg/mL (insoluble or slightly soluble), Ethanol: < 1 mg/mL (insoluble or slightly soluble), (< 1 mg/ml refers to the product slightly soluble or insoluble)

Preparing Stock Solutions

	1mg	5mg	10mg
1 mM	1.9271 mL	9.6354 mL	19.2708 mL
5 mM	0.3854 mL	1.9271 mL	3.8542 mL
10 mM	0.1927 mL	0.9635 mL	1.9271 mL
50 mM	0.0385 mL	0.1927 mL	0.3854 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.

Reference

Görgün G, et al. A novel Aurora-A kinase inhibitor MLN8237 induces cytotoxicity and cell-cycle arrest in multiple myeloma. Blood. 2010 Jun 24;115(25):5202-13.
Sun Y, Gao Y, Chen J, et al. CREBBP cooperates with the cell cycle machinery to attenuate chidamide sensitivity in relapsed/refractory diffuse large B-cell lymphoma. Cancer Letters. 2021
Qi J, Gao X, Zhong X, et al. Selective inhibition of Aurora A and B kinases effectively induces cell cycle arrest in t(8; 21) acute myeloid leukemia. Biomedicine & Pharmacotherapy. 2019, 117: 109113.
Manfredi MG, et al. Characterization of Alisertib (MLN8237), an investigational small-molecule inhibitor of aurora A kinase using novel in vivo pharmacodynamic assays. Clin Cancer Res. 2011 Dec 15;17(24):7614-24.
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Wang D, Wang Y, Di X, et al.Cortical tension drug screen links mitotic spindle integrity to Rho pathway.Current Biology.2023
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Huang Y, Mu K, Teng X, et al. Identification and mechanistic analysis of an inhibitor of the CorC Mg2+ transporter[J]. iScience. 2021