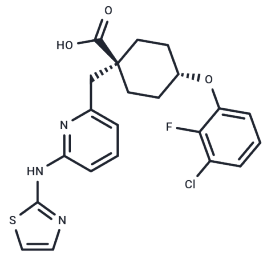
Data Sheet (Cat.No.T6068)

TargetMol

MK-5108

Chemical Properties



CAS No. : 1010085-13-8

Formula: C22H21ClFN3O3S

Molecular Weight: 461.94

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	MK-5108 (VX-689) is a highly potent and specific Aurora-A kinase inhibitor with an IC50 value of 0.064 nM.
Targets(IC50)	Aurora Kinase,Autophagy
In vitro	MK-5108 inhibits Aurora-A activity in an ATP-competitive manner. MK-5108 shows robust selectivity against the other family kinases Aurora-B (220-fold) and Aurora-C (190-fold) in the biochemical assay. MK-5108 also reveals high selectivity for Aurora-A over other protein kinases. MK-5108 inhibits only one kinase (TrkA) with <100-fold selectivity. MK-5108 may be more Aurora-A selective than MLN8054. Consistent with the induction of pHH3-positive cells, MK-5108 induces accumulation of cells in the G2-M phase. MK-5108 inhibits the proliferation of tumor cells including HCC1143, AU565, MCF-7, HCC1806 and CAL85-1 with an IC50 of 0.42 μM, 0.45 μM, 0.52 μM, 0.56 μM and 0.74 μM, respectively. [1] MK-5108 decreases cell viability in a dose-dependent fashion in all three cell lines including LEIO285, LEIO505 and SK-LSM1 cells with an IC50 of approximately 100 nM. Incubation with MK-5108 in LEIO285 increases the proportion of cells in G2/M at 48 and 72 hours post-treatment. MK-5108 significant increases in Caspase 3/7 activity when compared to DMSO-treated control cultures at both time points. In LEIO505 cells, MK-5108 leads to more cells accumulating at G2/M phases at 24 hours but not 48 hours or 72 hours. MK-5108 arrests ULMS cell lines at M phase MK-5108 decreases the IC50 of gemcitabine in LEIO285 cells, but increases IC50 of gemcitabine in LEIO505 and SK-LMS1 cells. [2]
In vivo	MK-5108 induces pHH3-positive cells at doses of 16 mg/kg and 32 mg/kg. Plasma concentration of MK-5108 at 8 mg/kg and 16 mg/kg are 1.7 μM and 4.4 μM, respectively. MK-5108 treatment results in the induction of pHH3 in tumor and skin tissues, which starts at 2 hours and reachs a maximum at 4 hours. MK-5108 treatments at 15 mg/kg and 30 mg/kg results in significant tumor growth inhibition with the change in mean tumor volume for the treatment group as a percentage of the mean change in the control group (%T/C) of 10% and ?6% at day 11, and 17% and 5% at day 18, respectively. MK-5108 is well tolerated at both doses, with minimal reduction in body weight. MK-5108 also exhibits significant antitumor activity through intermittent dosing in nude rats bearing SW48 tumors, MK-5108 at 15 mg/kg and 45 mg/kg causes dose-dependent tumor growth inhibition with a %T/C of 35% and 7% at day 10, and 58% and 32% at day 27, respectively. [1]

Kinase Assay	Biochemical kinase assays: Recombinant His-tagged human Aurora-A protein is expressed in Escherichia coli and is purified with HisTrap HP column. Purified recombinant human Aurora-B and Aurora-C protein are purchased. Experiments are done in quintuplicate in 96-well plates. The Aurora-A assay reaction is conducted in the presence of 20 μM ATP, 25 μM Tetra-Kemptide [RRR(GLRRASLG)4R-NH2], 1.0 μCi per well [γ-33P]-ATP, 0.1 ng per well Aurora-A in 50 mM Tris-HCl (pH 7.4), 15 mM Mg(OAc)2, and 0.2 mM EDTA at 30°C for 40 minutes. To investigate the inhibition mode of MK-5108 for Aurora-A, the IC50 values of MK-5108 are determined in the presence of different concentrations of ATP. Then, the IC50 value is plotted as a function of ATP concentration to analyze the effect of ATP concentration on the IC50 value of MK-5108. The Aurora-B assay reaction is conducted in the presence of 15 μM ATP, 100 μM Kemptide (GLRRASLG-NH2), 1.0 μCi per well [γ-33P]-ATP, 5.0 ng per well Aurora-B in 50 mM Tris-HCl (pH 7.4), 15 mM Mg(OAc)2, and 0.2 mM EDTA at 30 °C for 20 minuts. The Aurora-C assay reaction is conducted in the presence of 40 μM ATP, 100 μM Kemptide, 1.0 μCi per well [γ-33P]-ATP, 15 ng per well Aurora-C in 10 mM MOPS-NaOH (pH 7.4), 5 mM Mg(OAc)2, 1 mM (±) DTT, and 1 mM EGTA at 30 °C for 20 minutes. After kinase reactions are terminated by adding 2.0% phosphoric acid, Tetra-Kemptide or Kemptide is trapped on the MultiScreen-PH plate. Wells are washed five times with 0.64% phosphoric acid and then monitored for radioactivity in a liquid scintillation counter.
Cell Research	HeLa-S3 cells are synchronized at the G1-S phase boundary by double thymidine block with 2 mM thymidine. Cells are washed and seeded to 96-well cell culture plates. After 4 hours, an equal volume of medium containing MK-5108 is added to each well. Nocodazole (300 nM) is used as a 100% control. The cells are fixed overnight with cold methanol 12 hours after seeding. Then, the cells are stained with rabbit anti-phospho-histone H3 Ser28 antibody and then with anti-rabbit IgG-Cy5. Total nuclei are stained with 10 mg/mL 4′,6-diamidino-2-phenylindole. Immunostained images are acquired using the IN Cell Analyzer1000 with ×10 objective lens. After acquisition of images, data are analyzed. The %pHH3-positive index is determined by measuring the %pHH3-positive cell counts per total nuclei counts for each sample, then by normalizing with respect to nocodazole-treated cells. (Only for Reference)

Solubility Information

Solubility	Ethanol: < 1 mg/mL (insoluble or slightly soluble), H2O: < 1 mg/mL (insoluble or slightly soluble), DMSO: 50 mg/mL (108.24 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: 2 mg/mL (4.33 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	2.1648 mL	10.8239 mL	21.6478 mL
5 mM	0.433 mL	2.1648 mL	4.3296 mL
10 mM	0.2165 mL	1.0824 mL	2.1648 mL
50 mM	0.0433 mL	0.2165 mL	0.433 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

Shimomura T, et al. Mol Cancer Ther. 2010, 9(1), 157-166.
Shan W, et al. Clin Cancer Res. 2012, 18(12), 3352-3365.

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