AT9283

Cat. No.: HY-50514

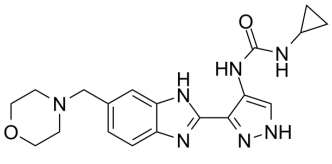
CAS No.: 896466-04-9

Molecular Formula: $C_{19}H_{23}N_7O_2$

Molecular Weight: 381.43

Target: JAK; Aurora Kinase; Bcr-Abl; FLT3; Apoptosis; Autophagy

Pathway: Epigenetics; JAK/STAT Signaling; Protein Tyrosine Kinase/RTK; Stem Cell/Wnt; Cell Cycle/DNA Damage; Apoptosis; Autophagy



Storage:

Powder	-20°C	3 years
	4°C	2 years
In solvent	-80°C	2 years
	-20°C	1 year

SOLVENT & SOLUBILITY

In Vitro

DMSO : ≥ 100 mg/mL (262.17 mM)

* "≥" means soluble, but saturation unknown.

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	2.6217 mL	13.1086 mL	26.2171 mL
	5 mM	0.5243 mL	2.6217 mL	5.2434 mL
	10 mM	0.2622 mL	1.3109 mL	2.6217 mL

Please refer to the solubility information to select the appropriate solvent.

In Vivo

1. Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
   Solubility: ≥ 2.5 mg/mL (6.55 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.5 mg/mL (6.55 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (6.55 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

AT9283 is a multi-targeted kinase inhibitor with potent activity against Aurora A/B, JAK2/3, Abl (T315I) and Flt3 (IC_{50}s ranging from 1 to 30 nM). AT9283 inhibits growth and survival of multiple solid tumors in vitro and in vivo[1][2].

IC_{50} & Target

Aurora A	Aurora B	JAK3	JAK2
3 nM (IC_{50})	3 nM (IC_{50})	1.1 nM (IC_{50})	1.2 nM (IC_{50})

	ABL(T315I) 4 nM (IC_{50})	Flt-3

In Vitro	AT9283 leads to a clear polyploid phenotype by inhibiting the activity of Aurora B kinase in HCT116 cells with IC_{50} of 30 nM. Furthermore, AT9283 also produces the potent inhibition on HCT116 colony formation[1]. AT9283 induces apoptosis in a dose and time dependent manner and inhibits cell proliferation with an IC_{50} < 1 μM in B-NHL cell lines[2]. AT9283 inhibits growth, induces dose dependent cytotoxicity, and inhibits STAT3 signaling pathway in MM cell lines. T9283 inhibits phospho Histone H3 and phospho Aurora A at Thr 288. AT9283 increases G2/M phase and induces apoptosis of MM cells in a time-dependent manner[3]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	In HCT116 human colon carcinoma xenograft bearing mice, AT9283 treatment (15 mg/kg and 20 mg/kg) for 16 days results in a significant tumor growth inhibition of 67% and 76%, respectively. In addition, AT9283 also exhibits a significantly longer half-life in tumors (2.5 hours) compared with plasma (0.5 hour) and modest oral bioavailability in mice[1]. AT9283 (15 mg/kg) and docetaxel (10 mg/kg) alone has modest anti-tumor activity. T9283 at 20 mg/kg and AT9283 (15 or 20 mg/kg) plus docetaxel (10 mg/kg) demonstrate a statistically significant tumor growth inhibition and enhance survival inmouse xenograft model of mantle cell lymphoma[2]. AT9283 (45 mg/kg, i.p.) inhibits tumor growth in mice. Two cycles of AT9283 45 mg/kg 14 hours after drug administration confirm decreased expression of phospho-Histone H3 and Aurora B in treated animals[3]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Cell Assay [2]	Lymphoma cells are seeded at 8,000 per well in 96-well culture plates and allowed to grow for 24 hr followed by the desired treatment with increasing concentrations of the indicated agents for 4 days. Viable cell densities are determined using a CellTiter 96 Cell Proliferation Assay. The IC_{50} values are estimated by Calcusyn software. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [2]	SCID mice are injected with 1×10^7 Granta-519 MCL cells subcutaneously into the right hind flank. When tumors reached a volume of appr 60-100 mm^3, mice are divided randomly (pair-matched) into six test groups with 12 mice per cohort: control group (saline), AT9283 (15 mg/kg IP Q1D, 5 days a week × 3 weeks) group, AT9283 (20 mg/kg IP Q1D, 5 days a week × 3 weeks) group, docetaxel (10 mg/kg IV Q1W × 3 weeks) group, AT9283 (15 mg/kg IP Q1D, 5 days a week × 3 weeks) + docetaxel (10 mg/kg IV Q1W × 3 weeks) group and AT9283 (20 mg/kg IP Q1D, 5 days a week × 3 weeks) + docetaxel (10 mg/kg IV Q1W × 3 weeks) group. The length (L) and width (W) of the subcutaneous tumors are measured by calipers and the tumor volume (TV) is calculated as: $TV=(L\times W^2)/2$. Mice are sacrificed at the end of study and overall survival for each cohort is analyzed by Kaplan–Meier method. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Sci Transl Med. 2018 Jul 18;10(450):eaaq1093.
- J Adv Res. 2023 Mar 7;S2090-1232(23)00070-X.
- Cancers (Basel). 2022 Mar 19;14(6):1575.
- Patent. US20180263995A1.
- Harvard Medical School LINCS LIBRARY

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REFERENCES

[1]. Howard S, et al. Fragment-Based Discovery of the Pyrazol-4-yl Urea (AT9283), a Multitargeted Kinase Inhibitor with Potent Aurora Kinase Activity. Journal of Medicinal Chemistry (2009), 52(2), 379-388.

[2]. Qi W, et al. AT9283, a novel aurora kinase inhibitor, suppresses tumor growth in aggressive B-cell lymphomas. Int J Cancer. 2012 Jun 15;130(12):2997-3005.

[3]. Santo L, et al. Antimyeloma activity of a multitargeted kinase inhibitor, AT9283, via potent Aurora kinase and STAT3 inhibition either alone or in combination with lenalidomide. Clin Cancer Res. 2011 May 15;17(10):3259-71

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