产品名称：**AT9283**
产品别名：**AT9283**

生物活性：

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	ABL(T315I)	Flt-3
	3 nM (IC_{50})	1.1 nM (IC_{50})	1.2 nM (IC_{50})	4 nM (IC_{50})	
3 nM (IC_{50})					

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].

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].

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

*请根据产品在不同溶剂中的溶解度选择合适的溶剂配制储备液；一旦配成溶液，请分装保存，避免反复冻融造成的产品失效。

储备液的保存方式和期限：-80°C, 6 months; -20°C, 1 month。-80°C 储存时，请在 6 个月内使用，-20°C 储存时，请在 1 个月内使用。

In Vivo:

请根据您的实验动物和给药方式选择适当的溶解方案。以下溶解方案都请先按照 **In Vitro** 方式配制澄清的储备液，再依次添加助溶剂：

源叶生物

Solvent&Solubility	——为保证实验结果的可靠性，澄清的储备液可以根据储存条件，适当保存；体内实验的工作液，建议您现用现配，当天使用； 以下溶剂前显示的百分比是指该溶剂在您配制终溶液中的体积占比；如在配制过程中出现沉淀、析出现象，可以通过加热和/或超声的方式助溶 1.请依序添加每种溶剂： 10% DMSO→40% PEG300 →5% Tween-80 → 45% saline Solubility: ≥ 2.5 mg/mL (6.55 mM); Clear solution 此方案可获得 ≥ 2.5 mg/mL (6.55 mM，饱和度未知) 的澄清溶液。 以 1 mL 工作液为例，取 100 μL 25.0 mg/mL 的澄清 DMSO 储备液加到 400 μL PEG300 中，混合均匀；向上述体系中加入 50 μL Tween-80，混合均匀；然后继续加入 450 μL 生理盐水定容至 1 mL。 2.请依序添加每种溶剂： 10% DMSO→ 90% (20% SBE-β-CD in saline) Solubility: ≥ 2.5 mg/mL (6.55 mM); Clear solution 此方案可获得 ≥ 2.5 mg/mL (6.55 mM，饱和度未知) 的澄清溶液。 以 1 mL 工作液为例，取 100 μL 25.0 mg/mL 的澄清 DMSO 储备液加到 900 μL 20% 的 SBE-β-CD 生理盐水水溶液中，混合均匀。 3.请依序添加每种溶剂： 10% DMSO →90% corn oil Solubility: ≥ 2.5 mg/mL (6.55 mM); Clear solution 此方案可获得 ≥ 2.5 mg/mL (6.55 mM，饱和度未知) 的澄清溶液，此方案不适用于实验周期在半个月以上的实验。 以 1 mL 工作液为例，取 100 μL 25.0 mg/mL 的澄清 DMSO 储备液加到 900 μL 玉米油中，混合均匀。
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

实验参考：

Cell Assay	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. [2]
Animal Administration	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. [2]

源叶生物

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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