AT9283

Cat. No.: HY-50514
CAS No.: 896466-04-9
Molecular Formula: C₁₉H₂₃N₇O₂
Molecular Weight: 381.43
Target: JAK; Aurora Kinase; Autophagy
Pathway: Epigenetics; JAK/STAT Signaling; Stem Cell/Wnt; Cell Cycle/DNA Damage; Autophagy
Storage: Powder
-20°C 3 years
4°C 2 years
In solvent
-80°C 6 months
-20°C 1 month

SOLVENT & SOLUBILITY

In Vitro
DMSO : ≥ 100 mg/mL (262.17 mM)
* "≥" means soluble, but saturation unknown.

Preparing Stock Solutions

<table>
<thead>
<tr>
<th>Solvent Concentration</th>
<th>Mass of 1 mg</th>
<th>Mass of 5 mg</th>
<th>Mass of 10 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 mM</td>
<td>2.6217 mL</td>
<td>13.1086 mL</td>
<td>26.2171 mL</td>
</tr>
<tr>
<td>5 mM</td>
<td>0.5243 mL</td>
<td>2.6217 mL</td>
<td>5.2434 mL</td>
</tr>
<tr>
<td>10 mM</td>
<td>0.2622 mL</td>
<td>1.3109 mL</td>
<td>2.6217 mL</td>
</tr>
</tbody>
</table>

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 multitargeted kinase inhibitor which potently inhibits aurora kinase A/B, JAK2/3 (IC₅₀=1.2 nM, 1.1 nM).

IC₅₀ & Target

<table>
<thead>
<tr>
<th></th>
<th>JAK3</th>
<th>JAK2</th>
<th>Aurora A</th>
<th>Aurora B</th>
</tr>
</thead>
<tbody>
<tr>
<td>IC₅₀</td>
<td>1.1 nM (IC₅₀)</td>
<td>1.2 nM (IC₅₀)</td>
<td>3 nM (IC₅₀)</td>
<td>3 nM (IC₅₀)</td>
</tr>
</tbody>
</table>
Abl (T315I) 
4 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[3]. 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 in mouse 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].

**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 mm³, 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 × W²)/2. Mice are sacrificed at the end of study and overall survival for each cohort is analyzed by Kaplan–Meier method.

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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.
