JNJ-7706621

Cat. No.: HY-10329
CAS No.: 443797-96-4
Molecular Formula: C₁₅H₁₂F₂N₆O₃S
Molecular Weight: 394.36
Target: Aurora Kinase; CDK; Apoptosis
Pathway: Cell Cycle/DNA Damage; Epigenetics; Apoptosis
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 : ≥ 125 mg/mL (316.97 mM)
* "≥" means soluble, but saturation unknown.

<table>
<thead>
<tr>
<th>Preparing Stock Solutions</th>
<th>Concentration</th>
<th>Mass</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 mM</td>
<td>2.5358 mL</td>
</tr>
<tr>
<td></td>
<td>5 mM</td>
<td>0.5072 mL</td>
</tr>
<tr>
<td></td>
<td>10 mM</td>
<td>0.2536 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: ≥ 2.08 mg/mL (5.27 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.08 mg/mL (5.27 mM); Clear solution

BIOLOGICAL ACTIVITY

Description
JNJ-7706621 is a potent aurora kinase inhibitor, and also inhibits CDK1 and CDK2, with IC₅₀ of 9, 3, 11, and 15 nM for CDK1, CDK2, Aurora-A and Aurora-B, respectively.

<table>
<thead>
<tr>
<th>IC₅₀ &amp; Target</th>
<th>CDK2/cyclinE 3 nM (IC₅₀)</th>
<th>cdk2/cyclin A 4 nM (IC₅₀)</th>
<th>Cdk1/cyclin B 9 nM (IC₅₀)</th>
<th>CDK3/Cyclin E 58 nM (IC₅₀)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDK6/cyclinD1</td>
<td>175 nM (IC₅₀)</td>
<td>Cdk4/cyclin D1 253 nM (IC₅₀)</td>
<td>Aurora A 11 nM (IC₅₀)</td>
<td>Aurora B 15 nM (IC₅₀)</td>
</tr>
<tr>
<td>Kinase</td>
<td>IC₅₀ (nM)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>--------</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VEGF-R1</td>
<td>6400</td>
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<tr>
<td>VEGF-R2</td>
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<tr>
<td>VEGF-R3</td>
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<tr>
<td>FGF-R1</td>
<td>575</td>
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<tr>
<td>FGF-R2</td>
<td>226</td>
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<tr>
<td>GSK3β</td>
<td>254</td>
<td></td>
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</tr>
</tbody>
</table>

**In Vitro**

JNJ-7706621 shows antiproliferative activity against various human tumor cells with IC₅₀s of 284, 254, and 447 nM for HeLa, HCT116, and A375, respectively[1]. JNJ-7706621 inhibits other centrosomal proteins such as TOG, Nek2, and TACC3 in early mitotic phase, but does not prevent localization of Aurora A to the spindle poles. Treatment of nocodazole-synchronized cells with JNJ-7706621 can override mitotic arrest by preventing spindle checkpoint signaling, resulting in failure of chromosome alignment and segregation[2]. JNJ-7706621 suspensions inhibits cell viability of HeLa cells with IC₅₀s of 2.1 and 0.9 μg/mL at 24 and 48 h. The IC₅₀ of the JNJ-7706621-loaded nanoparticles are 35 and 2.7 μg/mL and the IC₅₀ of the JNJ-7706621-loaded micelles are 6.3 and 1.6 μg/mL[3]. JNJ-7706621 shows inhibition of Aurora-A and Aurora-B but has no activity at the highest concentration tested on the Plk1 or Wee1 serine/threonine kinases. JNJ-7706621 also shows potent growth inhibition in vitro on all human cancer cell types with IC₅₀ values ranging from 112 to 514 nM[4].

**In Vivo**

JNJ-7706621 (100 mg/kg, i.p.) exhibits 95% tumor growth inhibition in A375 (human melanoma) tumor xenograft model[1]. JNJ-7706621-loaded micelles inhibit tumor growth, and delay the tumor growth more efficiently than the control JNJ-7706621 suspension[3]. JNJ-7706621 (100 and 125 mg/kg) is efficacious in a human tumor xenograft model under intermittent dosing regimens[4].

**PROTOCOL**

**Kinase Assay [4]**

To identify compounds that inhibit CDK1 kinase activity, a screening method is developed using the CDK1/cyclin B complex to phosphorylate a biotinylated peptide substrate containing the consensus phosphorylation site for histone H1, which is phosphorylated in vivo by CDK1. Inhibition of CDK1 activity is measured by observing a reduced amount of ³²P-g-ATP incorporation into the immobilized substrate in streptavidin-coated 96-well scintillating microplates. CDK1 enzyme is diluted in 50 mM Tris-HCl (pH 8), 10 mM MgCl₂, 0.1 mM Na₃VO₄, 1 mM DTT, 1% DMSO, 0.25 AM peptide, 0.1 ACi per well ³²P-g-ATP (2,000-3,000 Ci/mmol), and 5 AM ATP in the presence or absence of various concentrations of test compound and incubated at 30°C for 1 hour. The reaction is terminated by washing with PBS containing 100 mM EDTA and plates are counted in a scintillation counter. Linear regression analysis of the percent inhibition by test compound is used to determine IC₅₀ values. The Aurora kinase assays are done with 10 AM ATP and a peptide containing a dual repeat of the kemptide phosphorylation motif. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

**Cell Assay [3]**

HeLa cells are seeded in 96-well plates at the density of 2500 viable cells per well. The cells are then incubated with a suspension of JNJ-7706621, JNJ-7706621-loaded micelles and nanoparticles (JNJ-7706621 concentrations of 0.011, 0.022, 0.11, 0.22, 1.1, 2.2, 11 and 22 μg/mL; dilutions are made in the medium) and drug-free polymeric micelles (polymers concentrations 0.3 mg/mL) and drug-free polymeric micelles (polymers concentrations 0.3 mg/mL) and nanoparticles (polymers concentration 5 mg/mL) for 4, 24 and 48 h. The cytotoxicity is assessed using the MTT test. Absorbance is measured at 570 nm using a microplate reader. Untreated cells are taken as control with 100% viability and Triton X-100 1% is used as positive control of cytotoxicity. The results are expressed as mean values ± standard deviations of five measurements. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

**Animal Administration [4]**

Briefly, animals are implanted s.c. with 1 mm³ A375 tumor fragments in the hindflank. After tumors reach 62 to 126 mg, groups are pair matched. Animals are given JNJ-7706621 or vehicle control starting on day 1. The tumor growth delay method is followed where each animal is euthanized when its neoplasm reached a predetermined size of 2.0 g. All statistical analyses are conducted using unpaired t tests at a P level of 0.05 (two tailed). MCE has not independently confirmed the accuracy of these methods. They are for reference only.
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REFERENCES


