JNJ-7706621

Cat. No.: HY-10329

CAS No.: 443797-96-4

Molecular Formula: $C_{15}H_{12}F_2N_6O_3S$

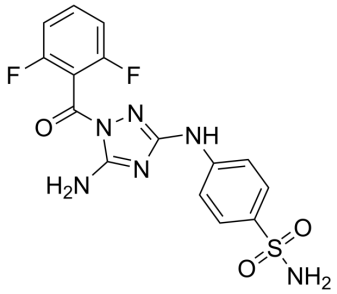
Molecular Weight: 394.36

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.

Preparing Stock Solutions

Concentration \ Solvent, Mass	1 mg	5 mg	10 mg
1 mM	2.5358 mL	12.6788 mL	25.3575 mL
5 mM	0.5072 mL	2.5358 mL	5.0715 mL
10 mM	0.2536 mL	1.2679 mL	2.5358 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: ≥ 2.08 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 IC_{50}s of 9 nM, 3 nM, 11 nM, and 15 nM for CDK1, CDK2, aurora-A and aurora-B, respectively[1][2][3].

IC_{50} & Target

CDK6/cyclinD1 175 nM (IC_{50})	CDK2/cyclinE 3 nM (IC_{50})	Cdk4/cyclin D1 253 nM (IC_{50})	Cdk1/cyclin B 9 nM (IC_{50})
cdk2/cyclin A 4 nM (IC_{50})	CDK3/Cyclin E 58 nM (IC_{50})	Aurora A 11 nM (IC_{50})	Aurora B 15 nM (IC_{50})

	VEGF-R2 154 nM (IC_{50})	VEGF-R1 6400 nM (IC_{50})	VEGF-R3 735 nM (IC_{50})	FGF-R1 575 nM (IC_{50})
	FGF-R2 226 nM (IC_{50})	GSK3β 254 nM (IC_{50})		

In Vitro

JNJ-7706621 shows antiproliferative activity against various human tumor cells with IC_{50}s 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 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 IC_{50} values ranging from 112 to 514 nM[3]. JNJ-7706621 suspensions inhibits cell viability of HeLa cells with IC_{50}s of 2.1 and 0.9 μg/mL at 24 and 48 h. The IC_{50} of the JNJ-7706621-loaded nanoparticles are 35 and 2.7 μg/mL and the IC_{50} of the JNJ-7706621-loaded micelles are 6.3 and 1.6 μg/mL[4].

MCE has not independently confirmed the accuracy of these methods. They are for reference only.

In Vivo

JNJ-7706621 (100 and 125 mg/kg) is efficacious in a human tumor xenograft model under intermittent dosing regimens[3]. 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[4].

MCE has not independently confirmed the accuracy of these methods. They are for reference only.

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 phosphorylatedin vivo by CDK1. Inhibition of CDK1 activity is measured by observing a reduced amount of ^{33}P-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 $MgCl_2$, 0.1 mM Na_3VO_4, 1 mM DTT, 1% DMSO, 0.25 AM peptide, 0.1 ACi per well ^{33}P-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 IC_{50} values. The Aurora kinase assays are done with 10 AM ATP and a peptide containing a dual repeat of the kemptide phosphorylation motif.

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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 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.

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Animal Administration [4]

Briefly, animals are implanted s.c. with 1 mm^3 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.

CUSTOMER VALIDATION

- Cell Chem Biol. 2019 Sep 19;26(9):1263-1273.e5.
- BMC Cancer. 2022 Nov 24;22(1):1211.

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REFERENCES

[1]. Huang S, et al. Synthesis and evaluation of N-acyl sulfonamides as potential prodrugs of cyclin-dependent kinase inhibitor JNJ-7706621. Bioorg Med Chem Lett. 2006 Jul 15;16(14):3639-41. Epub 2006 May 6.

[2]. Matsuhashi A, et al. Growth suppression and mitotic defect induced by JNJ-7706621, an inhibitor of cyclin-dependent kinases and aurora kinases. Curr Cancer Drug Targets. 2012 Jul;12(6):625-39.

[3]. Danhier F, et al. Active and passive tumor targeting of a novel poorly soluble cyclin dependent kinase inhibitor, JNJ-7706621. Int J Pharm. 2010 Jun 15;392(1-2):20-8.

[4]. Emanuel S, et al. The in vitro and in vivo effects of JNJ-7706621: a dual inhibitor of cyclin-dependent kinases and aurora kinases. Cancer Res. 2005 Oct 1;65(19):9038-46.

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