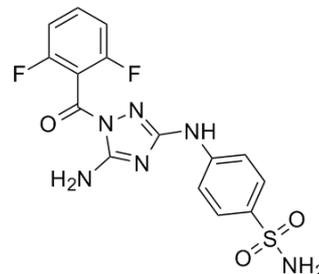


## Data Sheet

Product Name:	JNJ-7706621
Cat. No.:	HY-10329
CAS No.:	443797-96-4
Molecular Formula:	C <sub>15</sub> H <sub>12</sub> F <sub>2</sub> N <sub>6</sub> O <sub>3</sub> S
Molecular Weight:	394.36
Target:	Aurora Kinase; CDK
Pathway:	Cell Cycle/DNA Damage; Epigenetics
Solubility:	10 mM in DMSO



### BIOLOGICAL ACTIVITY:

JNJ-7706621 is a potent **aurora kinase** inhibitor, and also inhibits **CDK1** and **CDK2**, with **IC<sub>50</sub>s** of 9, 3, 11, and 15 nM for CDK1, CDK2, Aurora-A and Aurora-B, respectively.

IC<sub>50</sub> & Target: IC<sub>50</sub>: 3 nM (CDK2), 9 nM (CDK1), 11 nM (Aurora-A), 15 nM (Aurora-B)<sup>[4]</sup>

**In Vitro:** JNJ-7706621 shows antiproliferative activity against various human tumor cells with IC<sub>50</sub>s of 284, 254, and 447 nM for HeLa, HCT116, and A375, respectively<sup>[1]</sup>. 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<sup>[2]</sup>. JNJ-7706621 suspensions inhibits cell viability of HeLa cells with IC<sub>50</sub>s of 2.1 and 0.9 μg/mL at 24 and 48 h. The IC<sub>50</sub> of the JNJ-7706621-loaded nanoparticles are 35 and 2.7 μg/mL and the IC<sub>50</sub> of the JNJ-7706621-loaded micelles are 6.3 and 1.6 μg/mL<sup>[3]</sup>. 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<sub>50</sub> values ranging from 112 to 514 nM<sup>[4]</sup>.

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

### PROTOCOL (Extracted from published papers and Only for reference)

**Kinase Assay:** <sup>[4]</sup>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 <sup>33</sup>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<sub>2</sub>, 0.1 mM Na<sub>2</sub>VO<sub>4</sub>, 1 mM DTT, 1% DMSO, 0.25 AM peptide, 0.1 ACi per well <sup>33</sup>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<sub>50</sub> values. The Aurora kinase assays are done with 10 AM ATP and a peptide containing a dual repeat of the kemptide phosphorylation motif.

**Cell Assay:** <sup>[3]</sup>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  $\pm$  standard deviations of five measurements.

**Animal Administration:** JNJ-7706621 formulated as a nanocrystal suspension in 1.5% pluronic acid F108.<sup>[4]</sup> Briefly, animals are implanted s.c. with 1 mm<sup>3</sup> 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).

## 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]. Matsushashi 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.

**Caution: Product has not been fully validated for medical applications. For research use only.**

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