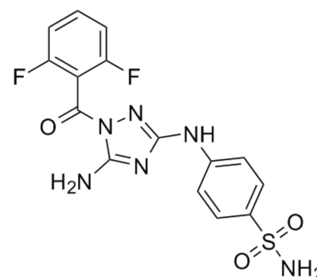
Data Sheet

Product Name: 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
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 **IC50**s of 9, 3, 11, and 15 nM for CDK1, CDK2, Aurora–A and Aurora–B, respectively.
IC50 & Target: IC50: 3 nM (CDK2), 9 nM (CDK1), 11 nM (Aurora–A), 15 nM (Aurora–B)[4]
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 (Extracted from published papers and Only for reference)

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 IC50 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: [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.

Animal Administration: JNJ–7706621 formulated as a nanocrystal suspension in 1.5% pluronic acid F108.[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).

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.

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

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