

产品名称: JNJ-7706621
产品别名: JNJ-7706621

生物活性:					
Description	JNJ-7706621 is a potent aurora kinase inhibitor, and also inhibits CDK1 and CDK2, with IC ₅₀ s of 9, 3, 11, and 15 nM for CDK1, CDK2, Aurora-A and Aurora-B, respectively.				
IC ₅₀ & Target [4]	CDK2/cyclinE	cdk2/cyclin A	Cdk1/cyclin B	CDK3/Cyclin E	CDK6/cyclinD1
	3 nM (IC ₅₀)	4 nM (IC ₅₀)	9 nM (IC ₅₀)	58 nM (IC ₅₀)	175 nM (IC ₅₀)
	Cdk4/cyclin D1	Aurora A	Aurora B	VEGF-R1	VEGF-R2
	253 nM (IC ₅₀)	11 nM (IC ₅₀)	15 nM (IC ₅₀)	6400 nM (IC ₅₀)	154 nM (IC ₅₀)
	VEGF-R3	FGF-R1	FGF-R2	GSK3β	
	735 nM (IC ₅₀)	575 nM (IC ₅₀)	226 nM (IC ₅₀)	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 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[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 IC ₅₀ 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].				
Solvent&Solubility	In Vitro: DMSO : ≥ 125 mg/mL (316.97 mM) * "≥" means soluble, but saturation unknown.				
	<div>Preparing Stock Solutions</div>	<div>Solvent / Mass / Concentration</div>	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
	*请根据产品在不同溶剂中的溶解度选择合适的溶剂配制储备液 一旦配成溶液，请分装保存，避免反复冻融造成的产品失效。 储备液的保存方式和期限 -80℃, 6 months; -20℃, 1 month。 -80℃ 储存时，请在 6 个月内使用，-20℃ 储存时，请在 1 个月内使用。 In Vivo: 请根据您的实验动物和给药方式选择适当的溶解方案。以下溶解方案都请先按照 In Vitro 方式配制澄清的储备液，再依次添加助溶剂： ——为保证实验结果的可靠性，澄清的储备液可以根据储存条件，适当保存；体内实验的工作液，建议您现				

	<p>用现配，当天使用； 以下溶剂前显示的百分比是指该溶剂在您配制终溶液中的体积占比；如在配制过程中出现沉淀、析出现象，可以通过加热和/或超声的方式助溶</p> <p>1.请依序添加每种溶剂： 10% DMSO→40% PEG300 →5% Tween-80 → 45% saline Solubility: ≥ 2.08 mg/mL (5.27 mM); Clear solution</p> <p>此方案可获得 ≥ 2.08 mg/mL (5.27 mM, 饱和度未知) 的澄清溶液。</p> <p>以 1 mL 工作液为例，取 100 μL 20.8 mg/mL 的澄清 DMSO 储备液加到 400 μL PEG300 中，混合均匀向上述体系中加入 50 μL Tween-80，混合均匀；然后继续加入 450 μL 生理盐水定容至 1 mL。</p> <p>2.请依序添加每种溶剂： 10% DMSO →90% corn oil Solubility: ≥ 2.08 mg/mL (5.27 mM); Clear solution</p> <p>此方案可获得 ≥ 2.08 mg/mL (5.27 mM, 饱和度未知) 的澄清溶液，此方案不适用于实验周期在半个月以上的实验。</p> <p>以 1 mL 工作液为例，取 100 μL 20.8 mg/mL 的澄清 DMSO 储备液加到 900 μL 玉米油中，混合均匀。</p>
References	<p>[1]. Huang S, et al. Synthesis and evaluation of N-acyl sulfonamides as potential prodrugs of cyclin-dependent kinase inhibitor JNJ-7706621. <i>Bioorg Med Chem Lett</i>. 2006 Jul 15;16(14):3639-41. Epub 2006 May 6.</p> <p>[2]. Matsuhashi A, et al. Growth suppression and mitotic defect induced by JNJ-7706621, an inhibitor of cyclin-dependent kinases and aurora kinases. <i>Curr Cancer Drug Targets</i>. 2012 Jul;12(6):625-39.</p> <p>[3]. Danhier F, et al. Active and passive tumor targeting of a novel poorly soluble cyclin dependent kinase inhibitor, JNJ-7706621. <i>Int J Pharm</i>. 2010 Jun 15;392(1-2):20-8.</p> <p>[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. <i>Cancer Res</i>. 2005 Oct 1;65(19):9038-46.</p>
实验参考：	
Cell Assay	<p>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. [3]</p>
Animal Administration	<p>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). [4]</p>
	<p>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 ³³P-g-ATP incorporation into the immobilized substrate in streptavidin-coated 96-well scintillating microplates. CDK1 enzyme is diluted in 50 mM</p>

Kinase Assay	<p>Tris-HCl (pH 8), 10 mM MgCl₂, 0.1 mM Na₃VO₄, 1 mM DTT, 1% DMSO, 0.25 AM peptide, 0.1 ACl per well ³³P-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. [4]</p>
References	<p>[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.</p> <p>[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.</p> <p>[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.</p> <p>[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.</p>

源叶生物