

产品名称: **NU7441 (KU-57788)**

产品别名: **KU-57788**

生物活性:

Description	KU-57788 is a potent and selective inhibitor of DNA-PK with an IC ₅₀ of 13 nM, with selectivity over a range of kinases including mTOR, PI 3-K, ATM and ATR.			
IC ₅₀ & Target [1]	DNA-PK	CRISPR/Cas9		
	13 nM (IC ₅₀)			
In Vitro	NU7441 at non-toxic concentration of 0.3 μM induces radio-sensitization in non-small cell lung cancer cells irradiated with low-LET and high-LET radiation, and does not show double strand break-repair inhibition in irradiated cells. NU7441 (3 μM) shows significantly increased persistent γ-H2AX signals. NU7441 (0.3 μM) causes significant G2/M arrest and a remarkable increase of DNA fragmentation and enhances cellular senescence in irradiated H1299 cells[1]. NU7441 (0.5 to 10 μM) inhibits the growth of liver cancer HepG2 cells dose- and time-dependently. NU7441 reduces pDNA-PKcs (S2056) protein expression in liver cancer cells. Furthermore, double treatment of NU7441 and 60Coy IR affects DNA damage repair[2]. NU7441 is solvent-exposed in BRD4, this inhibitor can be classified as a Type I BRD inhibitor[4]. NU7441 reduces the frequency of NHEJ while increasing the rate of HDR following Cas9-mediated DNA cleavage[5].			
In Vivo	lung cancer cells irradiated with low-LET and high-LET radiation, and does not show double strand break-repair inhibition in irradiated cells. KU-57788 (3 μM) shows significantly increased persistent γ-H2AX signals. KU-57788 (0.3 μM) causes significant G2/M arrest and a remarkable increase of DNA fragmentation and enhances cellular senescence in irradiated H1299 cells[1]. KU-57788 (0.5 to 10 μM) inhibits the growth of liver cancer HepG2 cells dose- and time-dependently. KU-57788 reduces pDNA-PKcs (S2056) protein expression in liver cancer cells. Furthermore, double treatment of KU-57788 and 60Coy IR affects DNA damage repair[2]. KU-57788 weakly inhibits BRD4 and BRDT with IC50s of 1 μM and 3.5 μM, respectively. KU-57788 is solvent-exposed in BRD4, this inhibitor can be classified as a Type I BRD inhibitor[4]. KU-57788 reduces the frequency of NHEJ while increasing the rate of HDR following Cas9-mediated DNA cleavage[5].			
Solvent&Solubility	In Vitro: DMSO : 14.29 mg/mL (34.56 mM; Need ultrasonic)			
	Preparing <			

	<p>1.请依序添加每种溶剂： 10% DMSO→40% PEG300 →5% Tween-80 → 45% saline Solubility: ≥ 1.43 mg/mL (3.46 mM); Clear solution</p> <p>此方案可获得 ≥ 1.43 mg/mL (3.46 mM, 饱和度未知) 的澄清溶液。</p> <p>以 1 mL 工作液为例, 取 100 μL 14.299999 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% (20% SBE-β-CD in saline) Solubility: ≥ 1.43 mg/mL (3.46 mM); Clear solution</p> <p>此方案可获得 ≥ 1.43 mg/mL (3.46 mM, 饱和度未知) 的澄清溶液。</p> <p>以 1 mL 工作液为例, 取 100 μL 14.299999 mg/mL 的澄清 DMSO 储备液加到 900 μL 20% 的 SBE-β-CD 生理盐水水溶液中, 混合均匀。</p> <p>3.请依序添加每种溶剂： 10% DMSO →90% corn oil Solubility: ≥ 1.43 mg/mL (3.46 mM); Clear solution</p> <p>此方案可获得 ≥ 1.43 mg/mL (3.46 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 14.299999 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]. Sunada S, et al. Nontoxic concentration of DNA-PK inhibitor NU7441 radio-sensitizes lung tumor cells with little effect on double strand break repair. <i>Cancer Sci.</i> 2016 Sep;107(9):1250-5</p> <p>[2]. Yang C, et al. NU7441 Enhances the Radiosensitivity of Liver Cancer Cells. <i>Cell Physiol Biochem.</i> 2016;38(5):1897-905</p> <p>[3]. Hardcastle IR, et al. Discovery of potent chromen-4-one inhibitors of the DNA-dependent protein kinase (DNA-PK) using a small-molecule library approach. <i>J Med Chem.</i> 2005 Dec 1;48(24):7829-46</p> <p>[4]. Ember SW, et al. The acetyl-lysine binding site of bromodomain-containing protein 4 (BRD4) interacts with diverse kinase inhibitors. <i>ACS Chem Biol.</i> 2014 Feb 25.</p> <p>[5]. Robert F, et al. Pharmacological inhibition of DNA-PK stimulates Cas9-mediated genome editing. <i>Genome Med.</i> 2015 Aug 27;7:93</p>
实验参考:	
Cell Assay	<p>HepG2 cells (4000 per well) are cultured in a 96-well plate for 24 h. Once the cells complete the attachment, 0.1 μM, 1 μM, 5 μM, and 10 μM of KU-57788 are added to the culture media. After 12 h of KU-57788 treatment, 10% CCK-8 solution is added into the culture media, and the incubation continued for two h. OD450 values are determined by a spectrometer, and the results are analyzed to measure the cell growth. [2]</p>
Kinase Assay	<p>The inhibitory activities of compounds against BRD4-1 and BRDT-1 are assessed by DSF using a StepOnePlus Real-Time PCR system. Purified BRD4-1 (4 μM final concentration; 10 mM HEPES (pH7.5), 100 mM NaCl, and 1 mM DTT), and BRDT-1 (4 μM final concentration; 50 mM phosphate (pH7.4), 100 mM NaCl, and 1 mM DTT) are assayed, in quadruplicates, in a 96-well plate. Inhibitors are added to a final concentration of 100 μM and 2% DMSO. Protein Thermal Shift Dye (1:8000) is used as the fluorescent probe, and fluorescence is measured using the ROX Reporter channel (620 nm). Protein stability is investigated by programing the thermocycler to increase the temperature from 25 to 99°C using 0.2°C increments and 10 s incubations per increment. The inflection point of</p>

	<p>the transition curve/melting temperature (T_m) is calculated using the Boltzmann equation within the Protein Thermal Shift Software (v.1.1). JQ1(+) and dinaciclib are used as controls for strong and weak binders of BRD4-1, respectively. The ΔT_m is calculated by using DMSO control wells as a reference. [4]</p>
References	<p>[1]. Sunada S, et al. Nontoxic concentration of DNA-PK inhibitor NU7441 radio-sensitizes lung tumor cells with little effect on double strand break repair. Cancer Sci. 2016 Sep;107(9):1250-5</p> <p>[2]. Yang C, et al. NU7441 Enhances the Radiosensitivity of Liver Cancer Cells. Cell Physiol Biochem. 2016;38(5):1897-905</p> <p>[3]. Hardcastle IR, et al. Discovery of potent chromen-4-one inhibitors of the DNA-dependent protein kinase (DNA-PK) using a small-molecule library approach. J Med Chem. 2005 Dec 1;48(24):7829-46</p> <p>[4]. Ember SW, et al. The acetyl-lysine binding site of bromodomain-containing protein 4 (BRD4) interacts with diverse kinase inhibitors. ACS Chem Biol. 2014 Feb 25.</p> <p>[5]. Robert F, et al. Pharmacological inhibition of DNA-PK stimulates Cas9-mediated genome editing. Genome Med. 2015 Aug 27;7:93</p>



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