

产品名称: **MK-4827 (tosylate)**

产品别名: **Niraparib tosylate**

生物活性:

Description	Niraparib tosylate (MK-4827 tosylate) is a highly potent and orally bioavailable PARP1 and PARP2 inhibitor with an IC ₅₀ of 3.8 and 2.1 nM, respectively. Niraparib tosylate (MK-4827 tosylate) leads to inhibition of repair of DNA damage and shows anti-tumor activity[1][2][3].				
IC₅₀ & Target	PARP-2	PARP-1	V-PARP	TANK-1	PARP-3
	2.1 nM (IC ₅₀)	3.8 nM (IC ₅₀)	330 nM (IC ₅₀)	570 nM (IC ₅₀)	1300 nM (IC ₅₀)
In Vitro	Niraparib (MK-4827) inhibits PARP activity with EC ₅₀ =4 nM and EC ₉₀ =45 nM in a whole cell assay. MK-4827 inhibits proliferation of cancer cells with mutant BRCA-1 and BRCA-2 with CC ₅₀ in the 10–100 nM range. MK-4827 displays excellent PARP 1 and 2 inhibition with IC ₅₀ =3.8 and 2.1 nM, respectively, and in a whole cell assay ^[1] . To validate that Niraparib (MK-4827) inhibits PARP in these cell lines, A549 and H1299 cells are treated with 1 μM Niraparib (MK-4827) for various times and measured PARP enzymatic activity using a chemiluminescent assay. The results show that Niraparib (MK-4827) inhibits PARP within 15 minutes of treatment reaching about 85% inhibition in the A549 cells at 1 h and about 55% inhibition at 1 h for the H1299 cells ^[2] .				
In Vivo	Niraparib (MK-4827) is well tolerated and demonstrates efficacy as a single agent in a xenograft model of BRCA-1 deficient cancer. Niraparib (MK-4827) is well tolerated in vivo and demonstrates efficacy as a single agent in a xenograft model of BRCA-1 deficient cancer. Niraparib (MK-4827) is characterized by acceptable pharmacokinetics in rats with plasma clearance of 28 (mL/min)/kg, very high volume of distribution (V _{dss} =6.9 L/kg), long terminal half-life (t _{1/2} =3.4 h), and excellent bioavailability, F=65% ^[1] . Niraparib (MK-4827) enhances radiation response of p53 mutant Calu-6 tumor in both cases, with the single daily dose of 50 mg/kg being more effective than 25 mg/kg given twice daily ^[3] .				
Solvent&Solubility	<i>In Vitro:</i> DMSO : ≥ 490 mg/mL (994.74 mM) H₂O : 1 mg/mL (2.03 mM; heat to 50°C) * "≥" means soluble, but saturation unknown.				
	Preparing Stock Solutions	Solvent	Mass	1 mg	5 mg
		Concentration			
		1 mM	2.0301 mL	10.1504 mL	20.3009 mL
		5 mM	0.4060 mL	2.0301 mL	4.0602 mL
		10 mM	0.2030 mL	1.0150 mL	2.0301 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°C, 6 months; -20°C, 1 month。 -80°C 储存时，请在 6 个月内使用， -20°C 储存时，请在 1 个月内使用。					
References	[1]. Jones P, et al. Discovery of 2-{4-[(3S)-piperidin-3-yl]phenyl}-2H-indazole-7-carboxamide (MK-4827): a novel oral poly(ADP-ribose)polymerase (PARP) inhibitor efficacious in BRCA-1 and -2 mutant tumors. <u>J Med Chem.</u> 2009 Nov 26;52(22):7170-85. [2]. Bridges KA, et al. Niraparib (MK-4827), a novel poly(ADP-Ribose) polymerase inhibitor, radiosensitizes human lung and breast cancer cells. <u>Oncotarget.</u> 2014 Jul 15;5(13):5076-86.				

	<p>[3]. Wang L, et al. MK-4827, a PARP-1/-2 inhibitor, strongly enhances response of human lung and breast cancer xenografts to radiation. <i>Invest New Drugs</i>. 2012 Dec;30(6):2113-20.</p> <p>[4]. Mirza MR, et al. Niraparib Maintenance Therapy in Platinum-Sensitive, Recurrent Ovarian Cancer. <i>N Engl J Med</i>. 2016 Dec 1;375(22):2154-2164.</p>
实验参考:	
Cell Assay	<p>The inhibition of PARP is analyzed in A549 and H1299 cells using the HT Universal Chemiluminescent PARP Assay Kit. Briefly, cells are treated with DMSO or 1 μM Niraparib (MK-4827) for 15, 30, 60, or 120 minutes, trypsinized, and transferred to a pre-chilled tube. The cells are washed twice with ice cold PBS and resuspended in cold PARP extraction buffer. The cell suspensions are incubated on ice for 30 minutes with periodic vortexing to disrupt the cell membrane. The suspensions are centrifuged and the supernatant transferred to a pre-chilled tube on ice. The histone coated wells of the 96-well plate are rehydrated with 1X PARP buffer and incubated at room temperature for 30 minutes. The PARP buffer is removed and 20 μg of protein as determined by the Bio-Rad Protein Assay is added to each well followed by diluted PARP-HSA enzyme and 1X PARP buffer. The strip wells are then incubated at room temperature for 60 minutes, washed twice with PBS containing 0.1% Triton X-100, and then washed with PBS. Diluted Strep-HRP is added to the strip wells and incubated for 60 minutes at room temperature. The wells are washed again as before. Equal volumes of PeroxyGlow A and B are combined and added to the wells and chemiluminescent readings are obtained immediately using a plate-reader[2]</p>
Animal Administration	<p>Mice^[3]</p> <p>Female nude mice (Ncr Nu/Nu) are randomly assigned to treatment groups consisting of 5 to 8 mice each when tumors grew to 6.0 mm in diameter at which time treatment with MK-4827 is initiated. MK-4827 is given at a dose of 25 mg/kg twice daily or 50 mg/kg once daily for either 21 days or is discontinued at 9 days from the time tumors reached 8 mm in diameter. Fractionated local tumor irradiation (XRT) is given when tumors reach 8.0 mm in diameter (7.7-8.2 mm). Radiation (2 Gy per fraction) is delivered to the tumor-bearing leg of mice once daily for 14 consecutive days or twice daily for 7 consecutive days using a small-animal irradiator consisting of two parallel-opposed ¹³⁷Cs sources, at a dose rate of 5 Gy/min. During irradiation un-anesthetized mice are mechanically immobilized in a jig so that the tumor is centered within a 3.0 cm diameter radiation field and the animal's body shielded from radiation exposure. On the day when both MK-4827 and radiation are given, drug is administered 1 h before the first radiation dose of the day.</p>
References	<p>[1]. Jones P, et al. Discovery of 2-{4-[(3S)-piperidin-3-yl]phenyl}-2H-indazole-7-carboxamide (MK-4827): a novel oral poly(ADP-ribose)polymerase (PARP) inhibitor efficacious in BRCA-1 and -2 mutant tumors. <i>J Med Chem</i>. 2009 Nov 26;52(22):7170-85.</p> <p>[2]. Bridges KA, et al. Niraparib (MK-4827), a novel poly(ADP-Ribose) polymerase inhibitor, radiosensitizes human lung and breast cancer cells. <i>Oncotarget</i>. 2014 Jul 15;5(13):5076-86.</p> <p>[3]. Wang L, et al. MK-4827, a PARP-1/-2 inhibitor, strongly enhances response of human lung and breast cancer xenografts to radiation. <i>Invest New Drugs</i>. 2012 Dec;30(6):2113-20.</p> <p>[4]. Mirza MR, et al. Niraparib Maintenance Therapy in Platinum-Sensitive, Recurrent Ovarian Cancer. <i>N Engl J Med</i>. 2016 Dec 1;375(22):2154-2164.</p>