产品名称：**2-[4-((3S)-3-哌啶基)苯基]-2H-吲唑-7-甲酰胺**
产品别名：**Niraparib ；MK-4827；尼拉帕尼**

生物活性：

Description

Niraparib (MK-4827) is a highly potent and orally bioavailable PARP1 and PARP2 inhibitor with IC_{50}s of 3.8 and 2.1 nM, respectively. Niraparib (MK-4827) leads to inhibition of repair of DNA damage and shows anti-tumor activity[1][2][3].

IC_{50} & 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 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 (Vd_{ss}=6.9 L/kg), long terminal half-life (t1/2=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

In Vitro:

DMSO : 25 mg/mL (**78.03 mM;** Need ultrasonic)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	3.1212 mL	15.6060 mL	31.2120 mL
	5 mM	0.6242 mL	3.1212 mL	6.2424 mL
	10 mM	0.3121 mL	1.5606 mL	3.1212 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。

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

1.请依序添加每种溶剂： 10% DMSO→40% PEG300 →5% Tween-80 → 45% saline

Solubility: ≥ 2.08 mg/mL (6.49 mM); Clear solution

	此方案可获得 ≥ 2.08 mg/mL (6.49 mM，饱和度未知) 的澄清溶液。 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。 2.请依序添加每种溶剂： 10% DMSO→ 90% (20% SBE-β-CD in saline) Solubility: ≥ 2.08 mg/mL (6.49 mM); Clear solution 此方案可获得 ≥ 2.08 mg/mL (6.49 mM，饱和度未知) 的澄清溶液。 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 20% 的 SBE-β-CD 生理盐水水溶液中，混合均匀。 3.请依序添加每种溶剂： 10% DMSO →90% corn oil Solubility: ≥ 2.08 mg/mL (6.49 mM); Clear solution 此方案可获得 ≥ 2.08 mg/mL (6.49 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。 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。
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. J Med Chem. 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. Oncotarget. 2014 Jul 15;5(13):5076-86. [3]. Wang L, et al. MK-4827, a PARP-1/-2 inhibitor, strongly enhances response of human lung and breast cancer xenografts to radiation. Invest New Drugs. 2012 Dec;30(6):2113-20. [4]. Mirza MR, et al. Niraparib Maintenance Therapy in Platinum-Sensitive, Recurrent Ovarian Cancer. N Engl J Med. 2016 Dec 1;375(22):2154-2164.

实验参考：

Cell Assay	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].
	Mice[3] 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 Niraparib (MK-4827) is

Animal Administration	initiated. Niraparib (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 Niraparib and radiation are given, drug is administered 1 h before the first radiation dose of the day.
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. J Med Chem. 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. Oncotarget. 2014 Jul 15;5(13):5076-86. [3]. Wang L, et al. MK-4827, a PARP-1/-2 inhibitor, strongly enhances response of human lung and breast cancer xenografts to radiation. Invest New Drugs. 2012 Dec;30(6):2113-20. [4]. Mirza MR, et al. Niraparib Maintenance Therapy in Platinum-Sensitive, Recurrent Ovarian Cancer. N Engl J Med. 2016 Dec 1;375(22):2154-2164.