产品名称：

3-[3-[4-[(Methylamino)methyl]phenyl]-5-isoxazolyl]-5-[4-[(1-methylethyl)sulfonyl]phenyl]-2-pyrazinam

产品别名：**Berzosertib**

生物活性：

Description	Berzosertib (VE-822) is an **ATR** inhibitor with a K_i value of less than 0.2 nM. It also inhibits **ATM** with a K_i of 34 nM.

IC_{50} & Target	ATR	ATM	PI3Kγ
	0.2 nM (Ki)	34 nM (Ki)	220 nM (Ki)

In Vitro	Berzosertib (VE-822) also inhibits DNK-PA, mTOR, PI3Kγ with IC50 of >4, >1, and 0.22 μM, respectively. In PSN-1 and MiaPaCa-2 cells, Berzosertib (VE-822) inhibits ATR and ATM with IC50 of 19 nM and 2.6 μM, respectively. VE-822 (80 nM) reduces phospho-Ser345-Chk1 after NSC 613327 (100 nM), radiation (XRT) (6 Gy) or both in PDAC. Additionally, Berzosertib (VE-822) does not inhibit ATM, Chk2 or DNA-PK phosphorylation in response to radiation, which further supports the selectivity of Berzosertib (VE-822) for ATR. VE-822 decreases survival of irradiated PDAC (all lines used are p53-mutant; K-Ras mutant). Knock down of Chk1 by siRNA sensitizes PSN-1 and MiaPaCa-2 cells to radiation but the radiosensitising effect is less profound compare with Berzosertib (VE-822). Adding Berzosertib (VE-822) to NSC 613327 reduces survival ~2-3-fold and dramatically more after chemoradiotherapy[1].
In Vivo	PSN-1 xenografts are treated with Berzosertib (VE-822) (60 mk/kg; d0, 1), NSC 613327 (100 mg/kg; d0) and/or XRT (6 Gy; d1). Tumors are then harvested 2 h post-XRT. Berzosertib (VE-822) inhibits p-Ser-345-Chk1 in xenografts after DNA-damaging agents, establishing VE-822 as a potent inhibitor of ATR in vivo. Besides, Berzosertib (VE-822) enhances the therapeutic efficacy of radiation (XRT) in MiaPaCa-2 and PSN-1 xenograft models[1].

Solvent&Solubility

In Vitro:

DMSO : ≥ 35 mg/mL (75.50 mM)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	2.1573 mL	10.7863 mL	21.5726 mL
	5 mM	0.4315 mL	2.1573 mL	4.3145 mL
	10 mM	0.2157 mL	1.0786 mL	2.1573 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: ≥ 2.5 mg/mL (5.39 mM); Clear solution

	此方案可获得 ≥ 2.5 mg/mL (5.39 mM，饱和度未知) 的澄清溶液。 以 1 mL 工作液为例，取 100 μL 25.0 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: ≥ 2.5 mg/mL (5.39 mM); Clear solution 此方案可获得 ≥ 2.5 mg/mL (5.39 mM，饱和度未知) 的澄清溶液。 以 1 mL 工作液为例，取 100 μL 25.0 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。
References	[1]. Fokas E, et al. Targeting ATR in vivo using the novel inhibitor VE-822 results in selective sensitization of pancreatic tumors to radiation. Cell Death Dis. 2012 Dec 6;3:e441.

实验参考：

Cell Assay	NSC 613327 (10 nM) is added 24 h pre-XRT and is replaced with fresh medium before addition of Berzosertib (VE-822). PSN-1 cells are treated with Berzosertib (VE-822) (80 nM) for 1 h before, through to 18 h after, XRT (6 Gy). Apoptosis is analyzed 48 h after XRT by flow cytometry using an Annexin V-FITC kit with PI[1].
Animal Administration	Mice[1] MiaPaCa-2 cells and PSN-1 cells (106 in 50 μL serum-free medium mixed with 50 μL of Matrigel) are inoculated subcutaneously in female Balb/c nude mice. When the xenograft tumors reach 80 mm3, the mice are randomized. Berzosertib (VE-822) (60 mg/kg) is administered by oral gavage on one of three alternate schedules; either daily on days 0-5 (total of six days dosing), daily on days 0 through to 3 (total of 4 days dosing) or on days 1, 3 and 5. XRT (6 Gy) is given either on days 0 or 1 or days 1-5 (total of 5 days dosing; 2 Gy). NSC 613327 is dosed at 100 mg/kg by intraperitoneal injection on day 0. XRT to the tumor is given 2 h after initiation of Berzosertib (VE-822) treatment.
References	[1]. Fokas E, et al. Targeting ATR in vivo using the novel inhibitor VE-822 results in selective sensitization of pancreatic tumors to radiation. Cell Death Dis. 2012 Dec 6;3:e441.