产品名称：2-Pyrazinecarboxamide, 3-amino-6-[4-[(4-methyl-1-piperazinyl)sulfonyl]phenyl]-N-3-pyridinyl-
产品别名：AZD-2461

生物活性：

Description

AZD-2461 is a potent PARP inhibitor, with IC_{50}s of 5 nM, 2 nM and 200 nM for PARP1, PARP2 and PARP3, respectively.

IC_{50} & Target

PARP2	PARP1	PARP3
2 nM (IC_{50})	5 nM (IC_{50})	200 nM (IC_{50})

In Vitro

AZD-2461 is a potent PARP inhibitor, with IC50s of 5 nM, 2 nM and 200 nM for PARP1, PARP2 and PARP3, respectively. AZD-2461 (500 nM) shows inhibitory activity against DNA single-strand break repair in human A459 cells. AZD-2461 cuases resistance and high P-gp expression levels in BRCA2-deficient mouse breast cancer line KB2P3.4[1]. AZD-2461 is cytotoxic to BT-20 cells (5-50 μM), increases the proportions of S- and G2-phase BT-20 cells (5-20 μM), and weakly affects the progression of cell cycle in SKBr-3 cells (5-20 μM)[2].

In Vivo

AZD-2461 (10 mg/kg, p.o.) enhances the antitumor activity of temozolomide in a mouse colorectal xenograft and exhibits low effect on mouse bone marrow cells. However, the increased bone marrow tolerability of AZD-2461 is not seen in rat models[1]. AZD-2461 (0.5% v/w HPMC, p.o.) increases the survival of mice bearing KB1P tumors after short-term treatment, and long-term treatment is well tolerated, but can not lead to tumor eradication[3].

Solvent&Solubility

In Vitro:

DMSO : ≥ 100 mg/mL (252.89 mM)

* "≥" means soluble, but saturation unknown.

	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
Preparing Stock Solutions	1 mM	2.5289 mL	12.6445 mL	25.2889 mL
	5 mM	.5058 mL	2.5289 mL	5.0578 mL
	10 mM	0.2529 mL	1.2644 mL	2.5289 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 (6.32 mM); Clear solution

此方案可获得 ≥ 2.5 mg/mL (6.32 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 (6.32 mM); Clear solution 此方案可获得 ≥ 2.5 mg/mL (6.32 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。 3.请依序添加每种溶剂： 10% DMSO →90% corn oil Solubility: ≥ 2.5 mg/mL (6.32 mM); Clear solution 此方案可获得 ≥ 2.5 mg/mL (6.32 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 25.0 mg/mL 的澄清 DMSO 储备液加到 900 μL 玉米油中，混合均匀。
References	[1]. Oplustil O'Connor L, et al. The PARP Inhibitor AZD2461 Provides Insights into the Role of PARP3 Inhibition for Both Synthetic Lethality and Tolerability with Chemotherapy in Preclinical Models. Cancer Res. 2016 Oct 15;76(20):6084-6094. Epub 2016 Aug 22. [2]. Węsierska-Gądek J, et al. Differential Potential of Pharmacological PARP Inhibitors for Inhibiting Cell Proliferation and Inducing Apoptosis in Human Breast Cancer Cells. J Cell Biochem. 2015 Dec;116(12):2824-39. [3]. Jaspers JE, et al. Loss of 53BP1 causes PARP inhibitor resistance in Brca1-mutated mouse mammary tumors. Cancer Discov. 2013 Jan;3(1):68-81.

实验参考：

Cell Assay	BT-20 and SKBr-3 human primary breast cancer cell lines are used in the assay. SKBr-3 cells are cultivated in DMEM medium with 10% FCS and BT-20 in RPMI medium under an atmosphere containing 5% CO2. Twenty four hours after plating (at 60-70% confluence), the cells are treated with the PARP-1 inhibitors NU1025, AZD-2461, iniparib, olaparib, and rucaparib at concentrations ranging from 50 to 200 μM, 5 to 50 μM, 5 to 50 μM, 1 to 10 μM, and 0.3 to 10 μM, respectively, for durations indicated in figures 1-7[2].
Animal Administration	Starting from 2 weeks after transplantation into mice, tumor size is monitored at least 3 times a week. All treatments are started when tumors reach a size of approximately 200 mm^3. Olaparib (50 mg/kg intraperitoneally) and AZD-2461 (100 mg/kg per os) are given for 28 consecutive days, unless otherwise indicated. If tumors do not shrink below 50% of the initial volume, treatment is continued for another 28 days; otherwise, a new treatment cycle of 28 days is started when the relapsing tumor reaches a size of 100% of the original volume. AZD-2461 is diluted in 0.5% w/v hydroxypropyl methylcellulose in deionized water to a concentration of 10 mg/mL[3].
References	[1]. Oplustil O'Connor L, et al. The PARP Inhibitor AZD2461 Provides Insights into the Role of PARP3 Inhibition for Both Synthetic Lethality and Tolerability with Chemotherapy in Preclinical Models. Cancer Res. 2016 Oct 15;76(20):6084-6094. Epub 2016 Aug 22. [2]. Węsierska-Gądek J, et al. Differential Potential of Pharmacological PARP Inhibitors for Inhibiting Cell Proliferation and Inducing Apoptosis in Human Breast Cancer Cells. J Cell Biochem. 2015 Dec;116(12):2824-39. [3]. Jaspers JE, et al. Loss of 53BP1 causes PARP inhibitor resistance in Brca1-mutated mouse mammary tumors. Cancer Discov. 2013 Jan;3(1):68-81.

源叶生物