产品名称：Rucaparib (AG-014699,PF-01367338)
产品别名：瑞卡帕布磷酸盐 ；Rucaparib phosphate

生物活性：

Description	Rucaparib phosphate (AG-014699 phosphate) is a potent and oral PARP inhibitor, with a K_i of 1.4 nM for PARP1 in cell-free assay, also showing binding affinity to eight other PARP domains.
IC_{50} & Target [1]	PARP-1
	1.4 nM (Ki)
In Vitro	Rucaparib is the most potent PARP inhibitor in enzyme assays (Ki, 1.4 nM), and a possible N-demethylation metabolite of AG14644[1]. The radio-sensitization by Rucaparib is due to downstream inhibition of activation of NF-κB, and is independent of SSB repair inhibition. Rucaparib could target NF-κB activated by DNA damage and overcome toxicity observed with classical NF-κB inhibitors without compromising other vital inflammatory functions[2]. Rucaparib inhibits PARP-1 activity by 97.1% at a concentration of 1 μM in permeabilised D283Med cells[3].
In Vivo	Rucaparib and AG14584 significantly ($P < 0.05$) increases temozolomide toxicity. Rucaparib (1 mg/kg) significantly increases temozolomide-induced body weight loss. Rucaparib (0.1 mg/kg) results in a 50% increase in the temozolomide-induced tumor growth delay[1]. Rucaparib is not toxic but significantly enhances temozolomide-induced TGD in the DNA repair protein-competent D384Med xenografts. Pharmacokinetics studies also show that Rucaparib is detected in the brain tissue, which indicates that Rucaparib has potential in intra-cranial malignancy therapy[3]. Rucaparib significantly potentiates the cytotoxicity of topotecan and temozolomide in NB-1691, SH-SY-5Y, and SKNBE (2c) cells. Rucaparib enhances the antitumor activity of temozolomide and indicates complete and sustained tumor regression in NB1691 and SHSY5Y xenografts[4].
Solvent&Solubility	***In Vitro:*** **DMSO : ≥ 33 mg/mL (78.32 mM)** * "≥" means soluble, but saturation unknown.

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	2.3733 mL	11.8663 mL	23.7327 mL
5 mM	0.4747 mL	2.3733 mL	4.7465 mL
10 mM	0.2373 mL	1.1866 mL	2.3733 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: ≥ 2.17 mg/mL (5.15 mM); Clear solution

此方案可获得 ≥ 2.17 mg/mL (5.15 mM，饱和度未知) 的澄清溶液。

	以 1 mL 工作液为例，取 100 μL 21.7 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: ≥ 2.17 mg/mL (5.15 mM); Clear solution 此方案可获得 ≥ 2.17 mg/mL (5.15 mM，饱和度未知) 的澄清溶液。 以 1 mL 工作液为例，取 100 μL 21.7 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: ≥ 2.17 mg/mL (5.15 mM); Clear solution 此方案可获得 ≥ 2.17 mg/mL (5.15 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 21.7 mg/mL 的澄清 DMSO 储备液加到 900 μL 玉米油中，混合均匀。
References	[1]. Thomas HD, et al. Preclinical selection of a novel poly(ADP-ribose) polymerase inhibitor for clinical trial. Mol Cancer Ther, 2007, 6(3), 945-956. [2]. Hunter JE, et al. NF-κB mediates radio-sensitization by the PARP-1 inhibitor, AG-014699. Oncogene, 2012, 31(2), 251-264. [3]. Daniel RA, et al. Central nervous system penetration and enhancement of temozolomide activity in childhood medulloblastoma models by poly(ADP-ribose) polymerase inhibitor AG-014699. Br J Cancer, 2010, 103(10), 1588-1596. [4]. Daniel RA, et al. Inhibition of poly(ADP-ribose) polymerase-1 enhances temozolomide and topotecan activity against childhood neuroblastoma. Clin Cancer Res, 2009, 15(4), 1241-1249.

实验参考：

Cell Assay	Medulloblastoma cell lines are seeded in 96-well plates at a density of 1×10^3, 3×10^3 and 3×10^3, respectively. At 24 hours (D384Med) or 48 hours (D283Med and D425Med) after seeding, the cells are exposed to various concentrations of temozolomide in the presence or absence of 0.4 μM Rucaparib. After 3 days (D425Med and D384Med) or 5 days (D283Med) of culture, cell viability is evaluated by a XTT cell proliferation kit assay. Cell growth is expressed as a percentage in relation to DMSO or 0.4 μM Rucaparib-alone controls. The concentration of temozolomide, alone or in combination with Rucaparib that inhibited growth by 50% (GI_{50}) is calculated. The potentiation factor 50 (PF50) is defined as the ratio of the GI_{50} of temozolomide in the presence of Rucaparib to the GI_{50} of temozolomide alone. [1]
Animal Administration	A single dose of temozolomide is administrated p.o. as a suspension in saline at 200 mg/kg either alone or in combination with a single i.p. administration of PARP inhibitor administered at 0.1 [Rucaparib and MS-AG14644 (equivalent to 0.078 mg/kg free AG14644 only)], 1.0, and 10 mg/kg (for the mesylate salts equivalent to 0.79 and 7.9 mg/kg free AG14451 and AG14452 and 0.78 and 7.8 free AG14531 and AG14644). Control animals are treated with either normal saline p.o. and i.p or normal saline p.o and PARP inhibitor 10 mg/kg i.p. [1]
Kinase Assay	Inhibition of PARP activity in 5×10^3 D283Med cells is measured using various concentrations of Rucaparib (0-1 μM), compared with DMSO-only. Maximally stimulated PARP activity is measured in samples of permeabilised cells by immunologica. [1]

References	[1]. Thomas HD, et al. Preclinical selection of a novel poly(ADP-ribose) polymerase inhibitor for clinical trial. Mol Cancer Ther, 2007, 6(3), 945-956. [2]. Hunter JE, et al. NF-κB mediates radio-sensitization by the PARP-1 inhibitor, AG-014699. Oncogene, 2012, 31(2), 251-264. [3]. Daniel RA, et al. Central nervous system penetration and enhancement of temozolomide activity in childhood medulloblastoma models by poly(ADP-ribose) polymerase inhibitor AG-014699. Br J Cancer, 2010, 103(10), 1588-1596. [4]. Daniel RA, et al. Inhibition of poly(ADP-ribose) polymerase-1 enhances temozolomide and topotecan activity against childhood neuroblastoma. Clin Cancer Res, 2009, 15(4), 1241-1249.