产品名称：Pimasertib (AS-703026)
产品别名：Pimasertib

生物活性：

Description	Pimasertib (AS703026) is a highly selective, potent, ATP non-competitive allosteric inhibitor of **MEK1/2**, used for cancer treatment.
IC_{50} & Target	MEK1 | MEK2
In Vitro	Pimasertib (5, 0.5, and 0.1 μM) specifically blocks ERK1/2 activation in MM cells, cultured alone or with BMSCs. Pimasertib inhibits the growth of MM cell lines in a dose-dependent manner, with IC50s ranging from 0.005 to 2 μM. The IC50s of Pimasertib against INA-6, U266, H929 cells are 10 nM, 5 nM, 200 nM respectively. Pimasertib induces apoptosis and modulates the cell cycle profile. Pimasertib targets MM cells in the BM microenvironment[1]. Pimasertib (10 μmol/L) inhibits ERK pathway, proliferation, and transformation in cetuximab-resistant D-MUT cells[2]. Pimasertib in combination with PLX4032 significantly induces apoptosis of RPMI-7951 cells, whereas each drug used alone does not. Pimasertib synergizes with small interfering RNA-mediated downregulation of BRAF to produce results similar to those of combined treatment with PLX4032 and Pimasertib[3].
In Vivo	Pimasertib (15, 30 mg/kg) significantly inhibits the growth of tumor in the human H929 MM xenograft model in CB17 SCID mice[1]. Pimasertib (10 mg/kg, p.o.) inhibits tumor growth of cetuximab-resistant tumor attributed by K-ras mutation[2].
Solvent&Solubility	***In Vitro:*** **DMSO : ≥ 100 mg/mL (231.91 mM)** * "≥" means soluble, but saturation unknown.

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	2.3191 mL	11.5955 mL	23.1911 mL
5 mM	0.4638 mL	2.3191 mL	4.6382 mL
10 mM	0.2319 mL	1.1596 mL	2.3191 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 (5.80 mM); Clear solution

此方案可获得 ≥ 2.5 mg/mL (5.80 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 (5.80 mM); Clear solution 此方案可获得 ≥ 2.5 mg/mL (5.80 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 (5.80 mM); Clear solution 此方案可获得 ≥ 2.5 mg/mL (5.80 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]. Kim K, et al. Blockade of the MEK/ERK signalling cascade by AS703026, a novel selective MEK1/2 inhibitor, induces pleiotropic anti-myeloma activity in vitro and in vivo. Br J Haematol, 2010, 149(4), 537-549. [2]. Park SJ, et al. The MEK1/2 inhibitor AS703026 circumvents resistance to the BRAF inhibitor PLX4032 in human malignant melanoma cells. Am J Med Sci. 2013 Dec;346(6):494-8. [3]. Yoon J, et al. MEK1/2 inhibitors AS703026 and AZD6244 may be potential therapies for KRAS mutated colorectal cancer that is resistant to EGFR monoclonal antibody therapy. Cancer Res, 2011, 71(2), 445-453.

实验参考：

Cell Assay	The inhibitory effects of study compounds on MM cell growth and survival are assessed by both [^{3}H]thymidine incorporation and by measuring MTT dye absorbance. Cells (10^4/well for MM cell line, in triplicates and 2-5×10^5/well for patient MM cells) are cultured in 96-well plates for 3 days (MM cell lines) or 5-days (patient MM cells). For the [^{3}H]thymidine incorporation assay, cells are pulsed with 0.5 μCi (0.0185 MBq)/well [^{3}H]thymidine for 6 h (cell lines), harvested onto glass fiber filters, and counted in a β-scintillation counter. Due to low DNA synthesis of patient MM cells, they are pulsed with 2 μCi/well [^{3}H]thymidine and measured during the last 36 h of culture. [1]
Animal Administration	CB17 severe combined immunodeficiency (SCID) mice are subcutaneously inoculated with H929 (4×10^6) cells in 100 μL RPMI-1640 medium. Mice developed palpable tumors (appr 130 mm^3) approximately 3 weeks after cell injection and are randomized to receive orally twice daily either Pimasertib (15 or 30 mg/kg) or control vehicle alone. Tumor size is measured every other day in 2 dimensions using calipers, and tumor volume is calculated. Animals are euthanized when their tumors reach 2 cm^3 in volume, when they are moribund or show paralysis or major compromise in their quality of life occurs. Tumor formation changes in mice treated with control vehicle vs. Pimasertib are plotted using the GraphPad Prism version 4.03 for Windows. Tumors are subjected to immunoblotting and immunochemistry analyses using specific monoclonal (m)Abs. Images are examined with a Leica DM LB research microscope, captured using Leica IM50 Image Manager, and processed using Adobe Photoshop Software version 7.0. [1]
References	[1]. Kim K, et al. Blockade of the MEK/ERK signalling cascade by AS703026, a novel selective MEK1/2 inhibitor, induces pleiotropic anti-myeloma activity in vitro and in vivo. Br J Haematol, 2010, 149(4), 537-549. [2]. Park SJ, et al. The MEK1/2 inhibitor AS703026 circumvents resistance to the BRAF inhibitor

	PLX4032 in human malignant melanoma cells. Am J Med Sci. 2013 Dec;346(6):494-8. [3]. Yoon J, et al. MEK1/2 inhibitors AS703026 and AZD6244 may be potential therapies for KRAS mutated colorectal cancer that is resistant to EGFR monoclonal antibody therapy. Cancer Res, 2011, 71(2), 445-453.