上海源叶生物科技有限公司
Shanghai yuanye Bio-Technology Co., Ltd
电话：021-61312973　　传真：021-55068248
网址：www.shyuanye.com
邮箱：shyysw@sina.com

产品名称：MI-773
产品别名：MI-773

生物活性：

Description	MI-773 is a new small molecule inhibitor of the MDM2-p53 interaction, binds to MDM2 with high affinity (K_i=0.88 nM) and blocks the p53-MDM2 interaction.
IC_{50} & Target	Ki: 0.88 nM (MDM2)[1]
In Vitro	MI-773 potently induces expression of p53 and its downstream targets p21, MDM2, and induces phosphorylation of p53 (serine 392) in low passage primary human ACC cells. Notably, MI-773 induces a dose-dependent increase in the fraction of apoptotic ACC cells and in the fraction of cells in the G1 phase of cell cycle (P<0.05). Consequently, MI-773 causes apoptotic cell death[1]. MI-773 is an advanced synthetic small molecule inhibitor, displays high binding affinity against MDM2 (Kd=8.2 nM)[2].
In Vivo	MI-773 at 10 mg/kg modestly reduces the rate of tumor growth, whereas 100 mg/kg causes significant tumor regression. Control tumors reach an average of 1,000 mm^3 at 20 days of treatment, compare to an average volume of 600 mm^3 for the 10 mg/kg group and 30 mm^3 for the 100 mg/kg group. Kaplan-Meier analysis shows an increase in tumor failure, define as two times increase in tumor volume as compared to pretreatment volume (P=0.044), for vehicle-treated mice when compare to mice treated with 100 mg/kg MI-773[1].
Solvent&Solubility	***In Vitro:*** **DMSO : ≥ 53 mg/mL (94.22 mM)** * "≥" means soluble, but saturation unknown.

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	1.7778 mL	8.8889 mL	17.7778 mL
	5 mM	0.3556 mL	1.7778 mL	3.5556 mL
	10 mM	0.1778 mL	0.8889 mL	1.7778 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 (4.44 mM); Clear solution

此方案可获得 ≥ 2.5 mg/mL (4.44 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 (4.44 mM); Clear solution 此方案可获得 ≥ 2.5 mg/mL (4.44 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 (4.44 mM); Clear solution 此方案可获得 ≥ 2.5 mg/mL (4.44 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]. Warner KA, et al. Targeting MDM2 for Treatment of Adenoid Cystic Carcinoma. Clin Cancer Res. 2016 Jul 15;22(14):3550-9. [2]. Zhang Q, et al. Targeting p53-MDM2-MDMX loop for cancer therapy. Subcell Biochem. 2014;85:281-319.

实验参考：

Cell Assay	Sulforhodamine B or the WST-1 cytotoxicity assay are performed to determine the effect of MI-773 on ACC cell viability. Briefly, 1 to 3×10^3 UM-HACC cells are plated per well, and treated with 0 to 40 μM MI-773 for 24 to 96 hours. To assess apoptosis, 2×10^5 cells are plated in 60 mm^3 dishes, attached overnight, and treated with 0 to 20 μM MI-773 for 72 hours. Cells are lysed with a hypotonic buffer and stained with propidium iodide. Primary low passage ACC cells (UM-HACC-5) are stably transduced with lentiviral vectors expressing shRNA-p53 or scrambled sequence control shRNA-C and selected with 1.0 μg/mL puromycin[1].
Animal Administration	Mice[1] To establish a patient-derived xenograft (PDX) model of ACC, human tumor fragments from the UM-HACC-5 patient are transplanted subcutaneously into the dorsal region of male severe combined immunodeficient (SCID) mice (CB.17.SCID). Two of six initial patient tumor fragments transplant, grow, and are retransplanted in vivo into new male or female mice for up to 12 passages. When tumors reach an average of 250 mm^3, mice are randomized into groups and received either vehicle (polyethylene glycol-200 + D-α-tocopherol polyethylene glycol 1000 succinate), or treatment with 10, 50, or 100 mg/kg MI-773 daily by oral gavage. The ACCx6 and ACCx9 models are treated with vehicle or 100 mg/kg MI-773.
References	[1]. Warner KA, et al. Targeting MDM2 for Treatment of Adenoid Cystic Carcinoma. Clin Cancer Res. 2016 Jul 15;22(14):3550-9. [2]. Zhang Q, et al. Targeting p53-MDM2-MDMX loop for cancer therapy. Subcell Biochem. 2014;85:281-319.