产品名称：Nutlin-3a
产品别名：Nutlin (3a)

生物活性：

Description	Nutlin 3a is an active enantiomer of Nutlin-3, acts as a murine double minute (MDM2) inhibitor that inhibits MDM2-p53 interactions and stabilizes the p53 protein, and thereby induces cell cycle arrest and apoptosis.
IC_{50} & Target	MDM2-p53[1]
In Vitro	Nutlin 3a (Nutlin-3a) is a therapeutic which inhibits MDM2, activates wild-type p53, and induces apoptosis-as a therapeutic compound for TP53 wild-type ovarian carcinomas. Three cell lines (HOC-7, OVCA429 and A2780) with wild-type TP53 are highly sensitive to Nutlin 3a (IC50=4 to 6 μM). SKOV3 cells have an IC50 of 38 μM to Nutlin 3a. The two remaining ovarian clear cell lines (TOV21G and OVAS), both with TP53 wild-type, are relatively more sensitive to growth inhibition with Nutlin 3a (IC50=14 and 25 μm respectively) than the TP53 mutant cell lines[1]. Nutlin 3a (Nutlin-3a) is the active enantiomer of Nutlin-3. Nutlin 3a is a highly selective MDM2 antagonist and p53 inducer. Seven days of incubation with 10 μM Nutlin 3a leads to >90% inhibition of NIH/3T3 cells'growth but does not affect the proliferation of MEF in which both targets of the drug are eliminated. Nutlin 3a effectively arrestes cell-cycle progression in all cell lines, depleting the S-phase compartment to 0.2-2% and increasing the G1- and G2/M-phase compartments, indicating G1 and G2 arrest. The p53 targets p21 and MDM2 are elevated significantly 3 h after Nutlin 3a addition and reach maximal levels at 8 h. Nutlin 3a induces apoptosis in ≈60% of SJSA-1 and MHM cells after 40 h, which increase further after 60 h (85% and 65%, respectively)[2].
In Vivo	Nutlin 3a (Nutlin-3a) is efficacious in all models with average tumor growth inhibition ≥98%. Nutlin 3a suppresses xenograft growth in a dose-dependent fashion with the highest dose (200 mg/kg) showing a substantial tumor shrinkage (eight partial and one full regressions). The established SJSA-1 and MHM osteosarcoma xenografts with Nutlin 3a causes extensive tumor regression[2].
Solvent&Solubility	***In Vitro:*** **DMSO : ≥ 100 mg/mL (171.97 mM)** **H_2O : < 0.1 mg/mL** (insoluble) * "≥" means soluble, but saturation unknown.

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	1.7197 mL	8.5986 mL	17.1972 mL
5 mM	0.3439 mL	1.7197 mL	3.4394 mL
10 mM	0.1720 mL	0.8599 mL	1.7197 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 (4.30 mM); Clear solution 此方案可获得 ≥ 2.5 mg/mL (4.30 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 (4.30 mM); Suspended solution; Need ultrasonic 此方案可获得 2.5 mg/mL (4.30 mM)的均匀悬浊液，悬浊液可用于口服和腹腔注射。 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 (4.30 mM); Clear solution 此方案可获得 ≥ 2.5 mg/mL (4.30 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]. Crane EK, et al. Nutlin-3a: A Potential Therapeutic Opportunity for TP53 Wild-Type Ovarian Carcinomas. PLoS One. 2015 Aug 6;10(8):e0135101. [2]. Tovar C, et al. Small-molecule MDM2 antagonists reveal aberrant p53 signaling in cancer: implications for therapy. Proc Natl Acad Sci U S A. 2006 Feb 7;103(6):1888-93. [3]. M Ulrich, et al. Murine tumor models for the in vivo evaluation of natural compounds and their derivatives as new cancer therapeutics. München. 2016.

实验参考：

Cell Assay	All 15 cell lines are plated at a density of 1×10^3 cells per well in 96-well plates. After 24h, media is exchanged and cells are treated with incremental concentrations of Nutlin 3a (1 μM, 5 μM, 10 μM, 25 μM, 50 μM, and 70 μM). After 72 h of incubation, WST-1 is added to each well, and a microplate reader is used at an absorbance of 450 nm to measure the number of remaining viable cells. Experiments are repeated with smaller titrations of Nutlin 3a as needed to determine the exact IC50 of cell lines. The IC50 is defined. Cell lines are again plated in a manner identical to above and treated with Nutlin 3a at their respective IC50, and WST-1 is added with cell viability measurement at 24, 48, and 72h[1].
Animal Administration	Mice[2] Nude mice bearing s.c. tumor xenografts (10 mice per group in the SJSA-1, LnCaP, and 22Rv1 study and 15 mice per group in the MHM study) are dosed orally twice daily with Nutlin 3a (50-200 mg/kg) or vehicle (1% Klucel, 0.1% Tween 80) for 2 weeks (22Rv1 and LnCap) or 3 weeks (SJSA-1 and MHM). Tumor volume is measured with a caliper and calculated. For Western blot analysis, nude mice with established SJSA-1 tumors (200-400 mm^3, three animals per group are treated with three doses of Nutlin 3a at 150 mg/kg (at 0, 8, and 24 h), and tumors are harvested 3 h after the last dose. Tumor samples are flash-frozen and processed[2].
	[1]. Crane EK, et al. Nutlin-3a: A Potential Therapeutic Opportunity for TP53 Wild-Type Ovarian

References	Carcinomas. PLoS One. 2015 Aug 6;10(8):e0135101. [2]. Tovar C, et al. Small-molecule MDM2 antagonists reveal aberrant p53 signaling in cancer: implications for therapy. Proc Natl Acad Sci U S A. 2006 Feb 7;103(6):1888-93. [3]. M Ulrich, et al. Murine tumor models for the in vivo evaluation of natural compounds and their derivatives as new cancer therapeutics. München. 2016.