产品名称：**Tasquinimod**
产品别名：他喹莫德

生物活性：	
Description	Tasquinimod is an oral antiangiogenic agent in clinical trials for the treatment of castration-resistant prostate cancer. Tasquinimod binds to the regulatory Zn2+ binding domain of HDAC4 with Kd of 10-30 nM. Tasquinimod also is a S100A9 inhibitor.
IC_{50} & Target	HDAC4 [1]
	10-30 nM (Kd)
In Vitro	Tasquinimod suppresses hypoxia induced decrease in histone acetylation without lowering HDAC expression or directly inhibiting HDAC activity. Tasquinimod binds allosterically within the regulatory Zinc domain of HDAC4 with a Kd of 10-30 nM, which results in inhibition of co-localization of N-CoR/HDAC3, thereby inhibiting deacetylation of histones and HDAC4 client transcription factors, such as HIF-1α. TAMs secrete angiogenic factors like VEGF, FGF, TNF- α, and TGF-β when myeloid-derived suppressor cells differentiate. Tasquinimod can suppress tumor angiogenesis due to inhibition of S100A9/TLR4 dependent MDSCs tumor infiltration and/or to inhibition of HDAC4/N-CoR/HDAC3 dependent deacetylation of HIF-1α by MDSCs suppressing their differentiation into TAMs.[1]. Tasquinimod, an orally active quinoline-3-carboxamide, binds with high affinity to HDAC4 and S100A9 in cancer and infiltrating host cells within compromised tumor microenvironment inhibiting adaptive survival pathways needed for an angiogenic response[2]. At 10 μM Tasquinimod, the TSP1 mRNA expression is elevated at 6 h and peaked after 72 h. Moreover, after 72 h exposure the TSP1 mRNA levels is already elevated at a dose of 1 μM Tasquinimod, indicating that Tasquinimod-induced changes in TSP1 mRNA expression occurrs in a dose range. At higher dose levels (i.e. 50-100 μM) the mRNA levels decline at 72 h, indicating additional drug effects at these concentrations. The up-regulation of TSP1 mRNA in LNCaP cells by Tasquinimod is manifested by an increased expression of TSP1 protein, as shown by western blot analysis of cell lysates prepared from cells cultured for 24 h and 72 h. Accompanied by increased intracellular TSP1 protein levels are also a statistically significant ($p<0.05$) accumulation of extracellular TSP1 in the cell culture medium detected. The extracellular secretion of TSP1 is time dependent and could clearly be detected after 24 h exposure to Tasquinimod at 10 μM. Also, TSP1 mRNA levels are induced by Tasquinimod at 10 μM in the hormone insensitive cell line LNCaP19 but not in DU145 cells[3].
In Vivo	The bioavailability and oral absorption of Tasquinimod is excellent when adult male mice (i.e., C57Bl/6J, or athymic nude mice) are given 0.1-30 mg/kg (i.e., 0.2-74 μmoles/kg) via gavage or the drinking water. The potency of Tasquinimod expressed as the daily oral dose of Tasquinimod which inhibits cancer growth by 50% ranges from 0.1-1.0 mg/kg/d (i.e., 0.24-2.40 μmoles/kg/day) against a series (n>5) of human prostate cancer xenografts in immune-deficient mice. Tasquinimod at a chronic dose of 5 mg/kg/day via the drinking water produces > 80% inhibition ($p<0.05$) of TRAMP-C2 mouse prostate cancer growth in immune-competent syngeneic mice[2]. Nude mice carrying subcutaneous LNCaP tumors are treated with Tasquinimod for 3 weeks. Exposure to Tasquinimod at 1 mg/kg/day and 10 mg/kg/day started on day 7 after inoculation. There is a statistically significant dose dependent reduction in tumor weight both at 1 mg/kg/day and 10 mg/kg/day compare to the untreated control group 28 days after inoculation ($p<0.001$), illustrating the anti-tumor effect of Tasquinimod[3].
	In Vitro: **DMSO : ≥ 42 mg/mL (103.36 mM)** * "≥" means soluble, but saturation unknown.

<table>
<tr><td rowspan="5">Solvent&Solubility</td><td rowspan="4">Preparing Stock Solutions</td><td>Solvent / Mass / Concentration</td><td>1 mg</td><td>5 mg</td><td>10 mg</td></tr>
<tr><td>1 mM</td><td>2.4609 mL</td><td>12.3044 mL</td><td>24.6087 mL</td></tr>
<tr><td>5 mM</td><td>0.4922 mL</td><td>2.4609 mL</td><td>4.9217 mL</td></tr>
<tr><td>10 mM</td><td>0.2461 mL</td><td>1.2304 mL</td><td>2.4609 mL</td></tr>
<tr><td colspan="5">*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 (6.15 mM); Clear solution
此方案可获得 ≥ 2.5 mg/mL (6.15 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 (6.15 mM); Clear solution
此方案可获得 ≥ 2.5 mg/mL (6.15 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 (6.15 mM); Clear solution
此方案可获得 ≥ 2.5 mg/mL (6.15 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 25.0 mg/mL 的澄清 DMSO 储备液加到 900 μL 玉米油中，混合均匀</td></tr>
<tr><td>References</td><td colspan="4">[1]. Isaacs JT, et al. Tasquinimod Is an Allosteric Modulator of HDAC4 survival signaling within the compromised cancer microenvironment. Cancer Res. 2013 Feb 15;73(4):1386-99.
[2]. Isaacs JT, et al. Anti-cancer potency of tasquinimod is enhanced via albumin-binding facilitating increased uptake in the tumor microenvironment. Oncotarget. 2014 Sep 30;5(18):8093-106.
[3]. Olsson A, et al. Tasquinimod (ABR-215050), a quinoline-3-carboxamide anti-angiogenic agent, modulates the expression of thrombospondin-1 in human prostate tumors. Mol Cancer. 2010 May 17;9:107.</td></tr>
<tr><td colspan="5">实验参考：</td></tr>
<tr><td></td><td colspan="4">Two human prostate cancer cell lines, CWR-22RH and LNCaP (ATCC) are both androgen independent, but remain sensitive to androgen stimulation of growth, express PSA and a mutated</td></tr>
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Cell Assay	androgen receptor. The hormone independent cell lines LNCaP19 and DU145 are also tested for TSP1 induction after in vitro exposure to Tasquinimod (0.1-100 μM). CWR-22RH, LNCaP and DU145 are grown in RPMI Medium 1640 containing 10% FCS and L-Glutamine mixture, while LNCAP19 is cultured in RPMI-medium with 10% hormone free (RDCC) FCS[3].
Animal Administration	Mice[3] Nude BALB/c mice are used for subcutaneous implantation of human prostate tumor cells LNCaP and CWR-22RH. Tumor growth is measured with a microcaliper twice a week throughout the experiment, and the final tumor burden is measured by weight on the day of termination of the experiment. Distribution of Tasquinimod at 1 mg/kg/day and 10 mg/kg/day (administered orally via the drinking water) started on day 7 after inoculation.
References	[1]. Isaacs JT, et al. Tasquinimod Is an Allosteric Modulator of HDAC4 survival signaling within the compromised cancer microenvironment. Cancer Res. 2013 Feb 15;73(4):1386-99. [2]. Isaacs JT, et al. Anti-cancer potency of tasquinimod is enhanced via albumin-binding facilitating increased uptake in the tumor microenvironment. Oncotarget. 2014 Sep 30;5(18):8093-106. [3]. Olsson A, et al. Tasquinimod (ABR-215050), a quinoline-3-carboxamide anti-angiogenic agent, modulates the expression of thrombospondin-1 in human prostate tumors. Mol Cancer. 2010 May 17;9:107.