产品名称：GSK 2830371
产品别名：GSK 2830371

生物活性：

Description	GSK 2830371 is a highly selective Wip1 phosphatase inhibitor with IC50 of 6 nM.
IC_{50} & Target	IC50: 6 nM (Wip1 phosphatase)[1]
In Vitro	GSK 2830371 potently inhibits Wip1 (2-420) dephosphorylation of FDP and the endogenous substrates phospho-p38 MAPK (T180) with IC_{50} values of 6 nM and 13 nM, respectively. In the *PPM1D*-amplified MCF7 breast carcinoma cells, treatment with GSK 2830371 (0.04, 0.11, 0.33, 1, 3, and 9 μM) increased phosphorylation of substrates in a concentration-dependent manner. Treatment of MX-1 and MCF7 cells (Wip1amplified, p53 wild type) with GSK 2830371 (0.001, 0.01, 0.1, 1, and 10 μM) causes concentration-dependent effects in cell growth assays[1]. GSK2830371 has a 50% growth inhibitory concentration (GI_{50}) of 2.65 μM±0.54 (SEM) in MCF-7 cells. Treatment of MCF-7 cells with 2.5μM GSK2830371 results in marked time-dependent degradation of both isoforms of WIP1 over 8 hours which correlated with p53 stabilisation and phospho-$p53^{Ser15}$ ($pp53^{Ser15}$)[2].
In Vivo	In a pharmacodynamic assay, orally administered GSK 2830371 increases phosphorylation of Chk2 (T68) and p53 (S15) and decreased Wip1protein concentrations in DOHH2 tumors. Following 14 d of oral dosing at 150 mg per kg body weight, BID (twice daily) and TID (thrice daily), GSK 2830371 inhibits the growth of DOHH2 tumor xenografts by 41% and 68%, respectively. Comparable tumor growth inhibition is observed in mice treated BID with either 75 or 150 mg per kg body weight. Greater tumor growth inhibition with the TID schedule is consistent with a short half-life of GSK 2830371 in mice and suggests that sustained inhibition of Wip1 may be required for maximal antitumor effect[1].
Solvent&Solubility	***In Vitro:*** **DMSO : ≥ 51 mg/mL (110.62 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	2.1691 mL	10.8455 mL	21.6910 mL
	5 mM	0.4338 mL	2.1691 mL	4.3382 mL
	10 mM	0.2169 mL	1.0846 mL	2.1691 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 (5.42 mM); Clear solution

此方案可获得 ≥ 2.5 mg/mL (5.42 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 (5.42 mM); Suspended solution; Need ultrasonic 此方案可获得 2.5 mg/mL (5.42 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 (5.42 mM); Clear solution 此方案可获得 ≥ 2.5 mg/mL (5.42 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]. Gilmartin AG, et al. Allosteric Wip1 phosphatase inhibition through flap-subdomain interaction. Nat Chem Biol. 2014 Mar;10(3):181-7. [2]. Esfandiari A, et al. Chemical Inhibition of Wild-Type p53-Induced Phosphatase 1 (WIP1/PPM1D) by GSK2830371 Potentiates the Sensitivity to MDM2 Inhibitors in a p53-Dependent Manner. Mol Cancer Ther. 2016 Mar;15(3):379-91.

实验参考：

Cell Assay	Cells are seeded into 96 well plates at 200-400 cells per well and treated with GSK 2830371 dilution series on day 1. After 7 d, we used the CellTiter-Glo cell viability assay to determine effects on cell growth. Luminescent signal is detected on an EnVision 2104. For clonogenic assays, cells are seeded in 12-well tissue culture plates at 2,000 cells per well. Cells are treated with a compound dilution series on day 1 and again on day 7. After 14 d, cells are washed with 1× PBS, stained with 1 mL of Coomassie Brilliant Blue R-250, and colonies are quantitated with the Optomax Sorcerer colony counter[1].
Kinase Assay	The primary in vitro Wip1 enzymatic assay measured fluorescence generated by Wip-1 (2-420) hydrolysis of fluorescein diphosphate (FDP). 50 μM FDP substrate is added with GSK 2830371 or DMSO at room temperature before addition of 10 nM Wip1 in assay buffer (50 mM TRIS, pH 7.5, 30 mM $MgCl_2$, 0.8 mM CHAPS, 0.05 mg/mL BSA). Fluorescent signal is detected on a Spectramax microplate reader (485/530 nm)[1].
References	[1]. Gilmartin AG, et al. Allosteric Wip1 phosphatase inhibition through flap-subdomain interaction. Nat Chem Biol. 2014 Mar;10(3):181-7. [2]. Esfandiari A, et al. Chemical Inhibition of Wild-Type p53-Induced Phosphatase 1 (WIP1/PPM1D) by GSK2830371 Potentiates the Sensitivity to MDM2 Inhibitors in a p53-Dependent Manner. Mol Cancer Ther. 2016 Mar;15(3):379-91.