产品名称：GSK461364
产品别名：GSK461364A

生物活性：

Description	GSK461364 is a selective, reversible and ATP-competitive Polo-like kinase 1 (PLK1) inhibitor with a K_i value of 2.2 nM.
IC_{50} & Target	PLK1 [3]
	2.2 nM (Ki)
In Vitro	GSK461364 is a potent, selective, and reversible ATP-competitive Plk1 inhibitor (Ki, 2.2 nM) with at least 390-fold greater selectivity for Plk1 than for Plk2 and Plk3 and 1,000-fold greater selectivity than for a panel of 48 other kinases[1]. GSK461364 (GSK461364A, 250 nM) inhibiting plk1 causes prolonged mitotic delay, aberrant mitotic exit, and p53 activation in A549 and PL45 cells. Knockdown of p53 significantly enhances the sensitivity of the cells to GSK461364A (30 or 300 nM) in preventing outgrowth in A549 and NCI-H460 cells, compared with cells with nonsilencing control siRNA[2]. GSK461364 can inhibits cell growth of most proliferating cancer cell lines, and suppresses 89% of cancer cell line (66 of 74 lines) proliferation, with a GI50 (concentration required to inhibit 50% cell growth) of ≤100 nM. GSK461364 (GSK461364A, >20 nM) blocks cells in G2-M phase with reduction of cells in G1 phase of A549 lung carcinoma line. GSK461364 (10-250 nM) blocks cells in G2 and M phases of the cell cycle and causes M-phase caspase-3/caspase-7 activation in cancer cells[3]. GSK461364 (0.5-2 μM) decreases level of PLK1 and pCDC25C, and cuases a dose- and time-dependent increase in pHisH3, an indicator of mitotic arrest in OS cell lines[4].
In Vivo	GSK461364 (50 mg/kg) exhibits various degrees of tumor growth delay (TGD) in multiple xenograft tumor models by i.p. one dose every 2 days repeated twelve times (q2d×12) [1]
Solvent&Solubility	***In Vitro:***

DMSO : 50 mg/mL (91.98 mM; Need ultrasonic)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	1.8396 mL	9.1979 mL	18.3959 mL
	5 mM	0.3679 mL	1.8396 mL	3.6792 mL
	10 mM	0.1840 mL	0.9198 mL	1.8396 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 (4.60 mM); Clear solution

此方案可获得 ≥ 2.5 mg/mL (4.60 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 (4.60 mM); Clear solution 此方案可获得 ≥ 2.5 mg/mL (4.60 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 (4.60 mM); Clear solution 此方案可获得 ≥ 2.5 mg/mL (4.60 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]. Olmos D, et al. Phase I study of GSK461364, a specific and competitive Polo-like kinase 1 inhibitor, in patients with advanced solid malignancies. Clin Cancer Res. 2011 May 15;17(10):3420-30. [2]. Degenhardt Y, et al. Sensitivity of cancer cells to Plk1 inhibitor GSK461364A is associated with loss of p53 function and chromosome instability. Mol Cancer Ther. 2010 Jul;9(7):2079-89 [3]. Gilmartin AG, et al. Distinct concentration-dependent effects of the polo-like kinase 1-specific inhibitor GSK461364A, including differential effect on apoptosis. Cancer Res. 2009 Sep 1;69(17):6969-77. [4]. Chou YS, et al. Cytotoxic mechanism of PLK1 inhibitor GSK461364 against osteosarcoma: Mitotic arrest, apoptosis, cellular senescence, and synergistic effect with paclitaxel. Int J Oncol. 2016 Mar;48(3):1187-94.

实验参考：

Cell Assay	Cell lines grow in the recommended media at 37°C, 5% CO_2 in a humidified incubator. Cells are plated in triplicate 96-well microtiter plates at 1,000 cells per well in culture media. GSK461364 (GSK461364A) dissolved in DMSO or negative control (0.1% DMSO) are added the following day, and one plate is harvested with 50 μL of CellTiter-Glo for a time 0 (T=0) measurement. [3]
Animal Administration	Cells are implanted in Nude mice and grown as tumor xenografts. Dosing began when tumors achieve appr 100 mm^3. GSK461364 (GSK461364A) or the vehicle [4% DMA/Cremaphore (50:50), pH 5.6] is given i.p. to mice every 2 d (q2d×6, q2d×12) or every 4 d (q4d×3) at nominal dose levels of 25, 50, and 100 mg/kg/dose. Results are reported as median tumor volume for n=7 to 8 mice. Paclitaxel (30 mg/kg i.v.; q4d×3) is used as a positive control for comparison. Tumors are measured thrice a week with Vernier calipers, and tumor volume is calculated from two-dimensional measurements using an equation approximating the volume of a prolate ellipsoid [tumor volume mm^3=(length × $width^2$) × 0.5]. The maximum tolerated dose is defined as the highest dose that produces >20% mortality or >20% weight loss (appr 4 g). Antitumor activity is defined as tumor growth delay (TGD), partial regression (PR), or complete regression (CR). TGD represents the time differential between the treated and control tumors to reach a predetermined tumor volume of 1,000 mm^3. PR is defined as a decrease in an individual tumor volume to one-half the initial starting volume for at least 1 wk (three consecutive measurements). CR is defined as a decrease in an individual tumor volume to <13 mm^3 for at least 1 wk. [3]
	Kinase reactions are performed in a final assay volume of 10 μL using the Z'-Lyte Assay kit (Ser/Thr peptide 16). Briefly, reactions contained 50 mM HEPES (pH 7.5), 10 mM $MgCl_2$, 1 mM EGTA, 1 mM

Kinase Assay	DTT, 0.01% Brij 35, 0.01 mg/mL casein, 200 μM ATP, 200 μM Polo Box peptide (NH2-MAGPMQS[pT]PLNGAKK-OH), and 6 nM recombinant Plk1 (H6-tev-PLK 1-603). Plk1 is preincubated for 60 min in the presence or absence of 0 to 1,000 nM GSK461364. Reactions are then initiated by the addition of 2 μM peptide. After 15 min at 23°C, reactions are quenched and processed according the Z'-Lyte protocol and read on an plate reader. Raw fluorescence values are converted to concentration of product formed using substrate and product standards. IC_{50} values are determined using a two-parameter fit (Hill coefficient and IC_{50}) using GraFit software. Because the potency of inhibition for GSK461364 is observed to vary as a function of the ATP concentration in a manner consistent with an ATP-competitive mode of inhibition, an upper limit for the K_i^{*app} for GSK461364 is determined by applying the Cheng-Prusoff relationship for a competitive inhibitor (ATP K_m^{*app}=16 μM) to the IC_{50} value obtained with 60 min preincubation of GSK461364. [3]
References	[1]. Olmos D, et al. Phase I study of GSK461364, a specific and competitive Polo-like kinase 1 inhibitor, in patients with advanced solid malignancies. Clin Cancer Res. 2011 May 15;17(10):3420-30. [2]. Degenhardt Y, et al. Sensitivity of cancer cells to Plk1 inhibitor GSK461364A is associated with loss of p53 function and chromosome instability. Mol Cancer Ther. 2010 Jul;9(7):2079-89 [3]. Gilmartin AG, et al. Distinct concentration-dependent effects of the polo-like kinase 1-specific inhibitor GSK461364A, including differential effect on apoptosis. Cancer Res. 2009 Sep 1;69(17):6969-77. [4]. Chou YS, et al. Cytotoxic mechanism of PLK1 inhibitor GSK461364 against osteosarcoma: Mitotic arrest, apoptosis, cellular senescence, and synergistic effect with paclitaxel. Int J Oncol. 2016 Mar;48(3):1187-94.