产品名称：**GSK690693**
产品别名：**GSK690693**

生物活性：

Description	GSK-690693 is an ATP-competitive pan-Akt inhibitor with IC50s of 2, 13, 9 nM for Akt1, Akt2 and Akt3, respectively. GSK-690693, an AMP-activated protein kinase (AMPK) inhibitor, affects Unc-51-like autophagy activating kinase 1 (ULK1) activity and robustly inhibits STING-dependent IRF3 activation[1][2][3].

IC_{50} & Target					
Akt1	Akt3	Akt2	PKCη	PKCθ	PrkX
2 nM (IC_{50})	9 nM (IC_{50})	13 nM (IC_{50})	2 nM (IC_{50})	2 nM (IC_{50})	5 nM (IC_{50})
PAK6	PAK4	PKCδ	PKCβ1	PKCε	PKA
6 nM (IC_{50})	10 nM (IC_{50})	14 nM (IC_{50})	19 nM (IC_{50})	21 nM (IC_{50})	24 nM (IC_{50})
PKG1β	AMPK	PAK5	DAPK3	Autophagy	
33 nM (IC_{50})	50 nM (IC_{50})	52 nM (IC_{50})	81 nM (IC_{50})		

In Vitro	GSK690693 is very selective for the Akt isoforms versus the majority of kinases in other families. However, GSK690693 is less selective for members of the AGC kinase family including PKA, PrkX, and PKC isozymes with IC50 of 24 nM, 5 nM, and 2-21 nM, respectively. GSK690693 also potently inhibits AMPK and DAPK3 from the CAMK family with IC50 of 50 nM and 81 nM, respectively, and PAK4, 5, and 6 from the STE family with IC50 of 10 nM, 52 nM, and 6 nM, respectively. GSK690693 inhibits the phosphorylation of GSK3β in tumor cells with IC50 ranging from 43 nM to 150 nM. GSK690693 treatment leads to a dose-dependent increase in the nuclear accumulation of the transcription factor FOXO3A. GSK690693 potently inhibits the proliferation of T47D, ZR-75-1, BT474, HCC1954, MDA-MB-453, and LNCaP cells with IC50 of 72 nM, 79 nM, 86 nM, 119 nM, 975 nM, and 147 nM, respectively. GSK690693 treatment induces apoptosis at concentrations > 100 nM in both LNCaP and BT474 cells[1]. Consistent with the role of AKT in cell survival, GSK690693 induces apoptosis in sensitive ALL cell lines[2].
In Vivo	A single administration of GSK690693 inhibits GSK3β phosphorylation in human breast carcinoma (BT474) xenografts in a dose- and time-dependent manner. Similarly, GSK690693 induces a reduction in phosphorylation of the Akt substrates, PRAS40, and FKHR/FKHRL1. GSK690693 also results in an acute increase in blood glucose, returning to baseline 8 to 10 hours after drug administration. Administration of GSK690693 induces reductions in phosphorylated Akt substrates in vivo, and potently inhibits the growth of human SKOV-3 ovarian, LNCaP prostate, and BT474 and HCC-1954 breast carcinoma xenografts, with maximal inhibition of 58% to 75% at the dose of 30 mg/kg/day[1]. GSK690693 exhibits efficacy irrespective of the mechanism of Akt activation involved. GSK690693 is most effective in delaying tumor progression in Lck-MyrAkt2 mice expressing a membrane-bound, constitutively active form of Akt[3].

In Vitro:

DMSO : 25 mg/mL (**58.76 mM;** Need ultrasonic)

Preparing Stock Solutions	Solvent / Mass / Concentration	**1 mg**	**5 mg**	**10 mg**
	1 mM	2.3503 mL	11.7514 mL	23.5029 mL
	5 mM	0.4701 mL	2.3503 mL	4.7006 mL
	10 mM	0.2350 mL	1.1751 mL	2.3503 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

Solvent&Solubility	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 (5.88 mM); Clear solution 此方案可获得 ≥ 2.5 mg/mL (5.88 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 (5.88 mM); Clear solution 此方案可获得 ≥ 2.5 mg/mL (5.88 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 (5.88 mM); Clear solution 此方案可获得 ≥ 2.5 mg/mL (5.88 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]. Rhodes N, et al. Characterization of an Akt kinase inhibitor with potent pharmacodynamic and antitumor activity. Cancer Res, 2008, 68(7), 2366-2374. [2]. Levy DS, et al. AKT inhibitor, GSK690693, induces growth inhibition and apoptosis in acute lymphoblastic leukemia cell lines. Blood, 2009, 113(8), 1723-1729. [3]. Altomare DA, et al. GSK690693 delays tumor onset and progression in genetically defined mouse models expressing activated Akt. Clin Cancer Res, 2010, 16(2), 486-496. [4]. Konno H, et al. Pro-inflammation Associated with a Gain-of-Function Mutation (R284S) in the Innate Immune Sensor STING. Cell Rep. 2018 Apr 24;23(4):1112-1123.

实验参考：

Cell Assay	Cells are plated at densities that allow untreated cells to grow logarithmically during the course of a 3-day assay. Briefly, cells are plated in 96- or 384-well plates and incubated overnight. Cells are then treated with GSK690693 (ranging from 30 μM-1.5 nM) and incubated for 72 hours. Cell proliferation is measured using the CellTiter Glo reagent. Data are analyzed using the XLFit curve-fitting tool for Microsoft Excel. IC_{50} values are obtained by fitting data to Eq, 2.［1］
	Tumors are initiated by injection of tumor cell suspension (HCC1954, MDA-MB-453, and LNCaP) or tumor fragments (BT474, SKOV-3, and PANC1) s.c. in 8- to 12-wk-old CD1 Swiss Nude mice

Animal Administration	(LNCaP, SKOV-3, and PANC1) or SCID mice (HCC1954, MDA-MB-453, and BT474). When tumors reach a volume of 100 to 200 mm^3, mice are randomized and divided into groups of 8 to 12 mice per group. GSK690693 is administered once daily at 10, 20, and 30 mg/kg by i.p. administration. Animals are euthanized by inhalation of CO_2 at the completion of the study. Tumor volume is measured twice weekly by calipers, using the equation: tumor volume (mm^3)=(length × $width^2$)/2. Results are reported as % inhibition on day 21 of treatment=100× [1-(average growth of the drug-treated population/average growth of vehicle-treated control population)]. Statistical analysis is done using two-tailed t test. [1]
Kinase Assay	His-tagged full-length Akt1, 2, or 3 are expressed and purified from baculovirus. Activation is carried out with purified PDK1 to phosphorylate Thr308 and purified MK2 to phosphorylate Ser473. To more accurately measure time-dependent inhibition of Akt, activated Akt enzymes are incubated with GSK690693 at various concentrations at room temperature for 30 minutes before the reaction is initiated with the addition of substrate. Final reaction contains 5 nM to 15 nM Akt1, 2, and 3 enzymes; 2 μM ATP; 0.15 μCi/μL[γ-^{33}P]ATP; 1 μM Peptide (Biotin-aminohexanoicacid-ARKR-ERAYSFGHHA-amide); 10 mM $MgCl_2$; 25 mM MOPS (pH 7.5); 1 mM DTT; 1 mM CHAPS; and 50 mM KCl. The reactions are incubated at room temperature for 45 minutes, followed by termination with Leadseeker beads in PBS containing EDTA (final concentration, 2 mg/mL beads and 75 mM EDTA). The plates are then sealed, the beads are allowed to settle for at least 5 hours, and product formation is quantitated using a Viewlux Imager. [1]
References	[1]. Rhodes N, et al. Characterization of an Akt kinase inhibitor with potent pharmacodynamic and antitumor activity. Cancer Res, 2008, 68(7), 2366-2374. [2]. Levy DS, et al. AKT inhibitor, GSK690693, induces growth inhibition and apoptosis in acute lymphoblastic leukemia cell lines. Blood, 2009, 113(8), 1723-1729. [3]. Altomare DA, et al. GSK690693 delays tumor onset and progression in genetically defined mouse models expressing activated Akt. Clin Cancer Res, 2010, 16(2), 486-496. [4]. Konno H, et al. Pro-inflammation Associated with a Gain-of-Function Mutation (R284S) in the Innate Immune Sensor STING. Cell Rep. 2018 Apr 24;23(4):1112-1123.

源叶生物