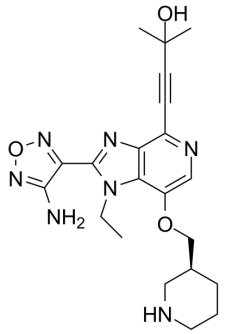
GSK-690693

Cat. No.:	HY-10249
CAS No.:	937174-76-0
Molecular Formula:	$C_{21}H_{27}N_7O_3$
Molecular Weight:	425.48
Target:	Akt; Autophagy; AMPK
Pathway:	PI3K/Akt/mTOR; Autophagy; Epigenetics
Storage:	Powder -20°C 3 years 4°C 2 years In solvent -80°C 1 year -20°C 6 months



SOLVENT & SOLUBILITY

In Vitro

DMSO : 20 mg/mL (47.01 mM; ultrasonic and warming and heat to 60°C)

H_2O : 5 mg/mL (11.75 mM; ultrasonic and adjust pH to 5 with HCl)

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

Please refer to the solubility information to select the appropriate solvent.

In Vivo

1. Add each solvent one by one: 20% HP-β-CD/10 mM citrate pH 2.0
   Solubility: 10 mg/mL (23.50 mM); Clear solution; Need ultrasonic
2. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (5.88 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
   Solubility: 2 mg/mL (4.70 mM); Clear solution; Need ultrasonic
4. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: 2 mg/mL (4.70 mM); Suspended solution; Need ultrasonic

BIOLOGICAL ACTIVITY

Description

GSK-690693 is an ATP-competitive pan-Akt inhibitor with IC_{50}s of 2 nM, 13 nM, 9 nM for Akt1, Akt2 and Akt3, respectively. GSK-690693 is also an 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 2 nM (IC_{50})	Akt3 9 nM (IC_{50})	Akt2 13 nM (IC_{50})	PKCη 2 nM (IC_{50})
	PKCθ 2 nM (IC_{50})	PrkX 5 nM (IC_{50})	PAK6 6 nM (IC_{50})	PAK4 10 nM (IC_{50})
	PKCδ 14 nM (IC_{50})	PKCβ1 19 nM (IC_{50})	PKCε 21 nM (IC_{50})	PKA 24 nM (IC_{50})
	PKG1β 33 nM (IC_{50})	AMPK 50 nM (IC_{50})	PAK5 52 nM (IC_{50})	DAPK3 81 nM (IC_{50})
	Autophagy			

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 IC_{50} of 24 nM, 5 nM, and 2-21 nM, respectively. GSK690693 also potently inhibits AMPK and DAPK3 from the CAMK family with IC_{50} of 50 nM and 81 nM, respectively, and PAK4, 5, and 6 from the STE family with IC_{50} of 10 nM, 52 nM, and 6 nM, respectively. GSK690693 inhibits the phosphorylation of GSK3β in tumor cells with IC_{50} 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 IC_{50} 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].

MCE has not independently confirmed the accuracy of these methods. They are for reference only.

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].

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PROTOCOL

Kinase Assay [1]

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.

MCE has not independently confirmed the accuracy of these methods. They are for reference only.

Cell Assay [1]

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 μ M-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.

	MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [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 (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. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Sci Transl Med. 2018 Jul 18;10(450):eaaq1093.
- Nat Commun. 2023 Mar 28;14(1):1726.
- Cell Rep Med. 2023 Sep 12;101200.
- J Exp Clin Cancer Res. 2021 Oct 27;40(1):340.
- EBioMedicine. 2019 Sep;47:114-127.

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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.

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