产品名称：GSK2126458 (GSK458)
产品别名：Omipalisib

生物活性：

Description	Omipalisib (GSK2126458) is a highly selective and potent inhibitor of PI3K with Kis of 0.019 nM/0.13 nM/0.024 nM/0.06 nM and 0.18 nM/0.3 nM for p110α/β/δ/γ, mTORC1/2, respectively.

IC_{50} & Target					
	p110α	p110α-E545K	p110α-E542K	p110α-H1047R	p110δ
	0.019 nM (Ki)	0.008 nM (Ki)	0.008 nM (Ki)	0.009 nM (Ki)	0.024 nM (Ki)
	p110γ	p110β	mTORC1	mTORC2	
	0.06 nM (Ki)	0.13 nM (Ki)	0.18 nM (Ki)	0.3 nM (Ki)	

In Vitro	Omipalisib (GSK2126458) potently inhibits the activity of common activating mutants of p110α (E542K, E545K, and H1047R) found in human cancer with Ki of 8 pM, 8 pM and 9 pM, respectively. Omipalisib causes a significant reduction in the levels of pAkt-S473 with remarkable potency in T47D and BT474 cells with IC50 of 0.41 nM and 0.18 nM, respectively. Furthermore, Omipalisib (GSK2126458) leads to a G1 cell cycle arrest and produces the inhibitory effect on cell proliferation in a large panel of cell lines, including T47D and BT474 breast cancer lines with IC50 of 3 nM and 2.4 nM, respectively[1]. The combination of Omipalisib or GSK1120212 with Omipalisib enhances cell growth inhibition and decreases S6 ribosomal protein phosphorylation in drug-resistant clones from the A375 BRAF(V600E) and the YUSIT1 BRAF(V600K) melanoma cell lines[2]. Omipalisib (GSK2126458) potentiates the antiproliferative activity of DDR1-IN-1 in colorectal cancer cell lines[3].
In Vivo	In a BT474 human tumor xenograft model, Omipalisib (GSK2126458) treatment results in a dose-dependent reduction in pAkt-S473 levels, and exhibits dose-dependent tumor growth inhibition at a low dose of 300 μg/kg. Besides, Omipalisib (GSK2126458) shows low blood clearance and good oral bioavailability in four preclinical species (mouse, rat, dog, and monkey)[1].

Solvent&Solubility

In Vitro:

DMSO : 50 mg/mL (98.91 mM; Need ultrasonic)

H_2O : < 0.1 mg/mL (insoluble)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	1.9782 mL	9.8912 mL	19.7824 mL
	5 mM	0.3956 mL	1.9782 mL	3.9565 mL
	10 mM	0.1978 mL	0.9891 mL	1.9782 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 (4.95 mM); Clear solution 此方案可获得 ≥ 2.5 mg/mL (4.95 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。
References	[1]. Knight SD, et al. Discovery of GSK2126458, a Highly Potent Inhibitor of PI3K and the Mammalian Target of Rapamycin. ACS Med. Chem. Lett. 2010, 1 (1), 39-43. [2]. Greger JG, et al. Combinations of BRAF, MEK, and PI3K/mTOR inhibitors overcome acquired resistance to the BRAF inhibitor GSK2118436 dabrafenib, mediated by NRAS or MEK mutations. Mol Cancer Ther. 2012 Apr;11(4):909-20. [3]. Kim HG, et al. Discovery of a potent and selective DDR1 receptor tyrosine kinase inhibitor. ACS Chem Biol. 2013 Oct 18;8(10):2145-50.

实验参考：

Cell Assay	BT474, HCC1954 and T-47D (human breast) are cultured in RPMI-1640 containing 10% fetal bovine serum at 37°C in 5% CO_2 incubator. Cells are split into T75 flask two to three days prior to assay set up at density which yields approximately 70-80% confluence at time of harvest for assay. Cells are harvested using 0.25% trypsin-EDTA. Cell counts are performed on cell suspension using Trypan Blue exclusion staining. Cells are then plated in 384 well black flat bottom polystyrene in 48 μL of culture media per well at 1,000 cells/well. All plates are placed at 5% CO_2, 37°C overnight and Omipalisib (GSK2126458) is added the following day. One plate is treated with CellTiter-Glo for a day 0 (t=0) measurement and read as described below. Omipalisib (GSK2126458) is prepared in clear bottom polypropylene 384 well plates with consecutive two fold dilutions. 4 μL of these dilutions are added to 105 μL culture media, after mixing the solution, 2 μL of these dilutions are added into each well of the cell plates. The final concentration of DMSO in all wells is 0.15%. Cells are incubated at 37°C, 5% CO_2 for 72 hours. Following 72 hours of incubation with Omipalisib each plate is developed and read. CellTiter-Glo reagent is added to assay plates using a volume equivalent to the cell culture volume in the wells. Plates are shaken for approximately two minutes and incubated at room temperature for approximately 30 minutes and chemiluminescent signal is read on the Analyst GT reader. Results are expressed as a percent of the t=0 and plotted against the Omipalisib (GSK2126458) concentration. Cell growth inhibition is determined for Omipalisib (GSK2126458) by fitting the dose response with a 4 or 6 parameter curve fit using XLfit software and determining the concentration that inhibits 50% of the cell growth (gIC_{50}) with the Y min as the t=0 and Y max as the DMSO control. Value from wells with no cells is subtracted from all samples for background correction.. [1]
References	[1]. Knight SD, et al. Discovery of GSK2126458, a Highly Potent Inhibitor of PI3K and the Mammalian Target of Rapamycin. ACS Med. Chem. Lett. 2010, 1 (1), 39-43. [2]. Greger JG, et al. Combinations of BRAF, MEK, and PI3K/mTOR inhibitors overcome acquired resistance to the BRAF inhibitor GSK2118436 dabrafenib, mediated by NRAS or MEK mutations. Mol Cancer Ther. 2012 Apr;11(4):909-20. [3]. Kim HG, et al. Discovery of a potent and selective DDR1 receptor tyrosine kinase inhibitor. ACS Chem Biol. 2013 Oct 18;8(10):2145-50.