产品名称：VS-5584 (SB2343)
产品别名：VS-5584

生物活性：

Description

S-5584 is a **pan-PI3K/mTOR** kinase inhibitor with **IC_{50}**s of 16 nM, 68 nM, 42 nM, 25 nM, and 37 nM for PI3Kα, PI3Kβ, PI3Kδ, PI3Kγ and mTOR, respectively. VS-5584 simultaneously blocks **mTORC2** as well as **mTORC1**.

IC_{50} & Target

PI3Kα	PI3Kγ	PI3Kδ	PI3Kβ	Vps34	mTOR
16 nM (IC_{50})	25 nM (IC_{50})	42 nM (IC_{50})	68 nM (IC_{50})	7470 nM (IC_{50})	37 nM (IC_{50})
mTORC1	mTORC2	DNA-PK			
		1270 nM (IC_{50})			

In Vitro

VS-5584 is an ATP-competitive inhibitor which selectively inhibits PI3K/mTOR signaling with equivalent low nanomolar potency against all human Class I PI3K isoforms and mTOR kinase. VS-5584 (0.001, 0.01, 0.1,1,10 and 100 μM) preferentially inhibits cancer stem cells in HMLE breast cancer cells while Paclitaxel increases the percentage of cancer stem cells. VS-5584 (0.1, 1, 10, 100 and 1000 nM) reduces the number of Aldefluor-positive cancer stem cells while Paclitaxel increases the percentage of cancer stem cells. VS-5584 (10, 30, 100, 300 nM) reduces the percentage of cancer stem cells (side population) in a Hoechst dye exclusion assay[1]. VS-5584 is a potent inhibitor of mTOR (IC50=37 nM) as well as class I PI3K isoforms (IC50: PI3Kα=16 nM; PI3Kβ=68 nM; PI3Kγ=25 nM; PI3Kδ=42 nM). All other evaluated kinases show negligible binding when tested up to 10 μM VS-5584[1].

In Vivo

Nude mice bearing MDA-MB-231 human breast cancer tumors are treated for 5 days with once daily oral VS-5584 (25 mg/kg). Oral treatment of tumor bearing mice with VS-5584 reduces cancer atem cells analyzed from extracted tumors. Mice are implanted with tumor fragments from a docetaxel-resistant patient-derived triple negative breast cancer. Mice are treated with VS-5584 (20 mg/kg, po, qd) or Docetaxel (20 mg/kg, i.v.). Oral VS-5584 induces tumor regression in a Docetaxel-resistant patient-derived breast cancer model[1]. A single oral dose of VS-5584 is rapidly absorbed with a t_{max} of 0.9 hours and an elimination half-life of 10 hours. To determine the pharmacokinetic and pharmacodynamic relationship in tumors, PC3-tumor–bearing mice are treated with a single dose of VS-5584 and plasma and tumors are harvested after 6 hours and analyzed for concentrations of VS-5584 and effects on target efficacy biomarkers. Plasma levels of VS-5584 increase dose-dependently. For evaluation of efficacy in a Rapamycin-sensitive PC3 engraftment model, tumor-bearing mice are treated with VS-5584 for 28 days in comparison with the rapalog Everolimus. VS-5584 is well tolerated at both doses tested (11 and 25 mg/kg) with minimal weight loss (mean 4.7% on day 27). Treatment with VS-5584 leads to significant tumor growth inhibition (TGI) of 79% and 113% for 11 and 25 mg/kg, respectively[1].

In Vitro:

DMSO : 33.33 mg/mL (94.04 mM; Need ultrasonic)

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	2.8216 mL	14.1080 mL	28.2159 mL
5 mM	0.5643 mL	2.8216 mL	5.6432 mL
10 mM	0.2822 mL	1.4108 mL	2.8216 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。

Solvent&Solubility	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 (7.05 mM); Clear solution 此方案可获得 ≥ 2.5 mg/mL (7.05 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 (7.05 mM); Clear solution 此方案可获得 ≥ 2.5 mg/mL (7.05 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 (7.05 mM); Clear solution 此方案可获得 ≥ 2.5 mg/mL (7.05 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]. Hart S, et al. VS-5584, a novel and highly selective PI3K/mTOR kinase inhibitor for the treatment of cancer. Mol Cancer Ther, 2013, 12(2), 151-161.

实验参考：

Cell Assay	For proliferation assays in 96-well plates, SET-2, SNU-478, SNU-1196, SNU-245, SNU-1079, SNU-308, SNU-869, and MKN7 cells are used. The multiple myeloma cells (H929, MM1.S, MM1.R, R8226, U266) and nasopharyngeal cells (CNE-1, CNE-2, HONE1, HK1) are used. Cells are seeded at 30% to 50% confluency for adherent cells, or 2,000 to 6,000 cells for suspension cells and treated the following day with VS-5584 (in triplicates) at concentrations up to 10 μM for 48 hours. Cell viability is monitored using the CellTiter-Glo assay. Dose-response curves were plotted to determine IC50 values for the compounds using the XL-fit software[1].
Animal Administration	Mice[1] Athymic BALB/c nude mice (BALB/cOlaHsd-Foxn1nu) are used. Fox-Chase severe combined immunodeficient (SCID) mice (CB17/Icr-Prkdc ^{scid}/CrlBltw) are used. Male (PC3 and COLO 205) or female (MV4-11 and HuH7) BALB/c nude mice or female SCID mice (NCI-N87) are implanted intradermally in the right flank with 5×10^6 (PC3, COLO205, HuH7, NCI-N87) or 1×10^7 (MV4-11) cells. Cells are resuspended in 70% (v/v; COLO205 and HuH7 only) or 50% (v/v) serum-free growth medium/Matrigel and injected in a total volume of 100 μL, using a 27.5-gauge needle. Dosing started 7 to 14 days after tumor implantation. VS-5584 (11 and 25 mg/kg) is dosed daily orally[1].

References	[1]. Hart S, et al. VS-5584, a novel and highly selective PI3K/mTOR kinase inhibitor for the treatment of cancer. Mol Cancer Ther, 2013, 12(2), 151-161.