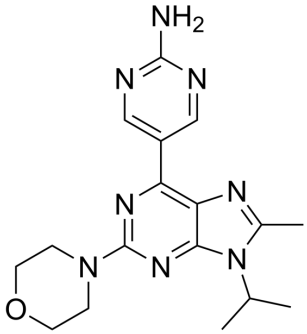
VS-5584

Cat. No.:	HY-16585
CAS No.:	1246560-33-7
Molecular Formula:	$C_{17}H_{22}N_8O$
Molecular Weight:	354.41
Target:	PI3K; mTOR
Pathway:	PI3K/Akt/mTOR
Storage:	Powder -20°C 3 years 4°C 2 years In solvent -80°C 2 years -20°C 1 year



SOLVENT & SOLUBILITY

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

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

In Vivo

1. Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
   Solubility: ≥ 2.5 mg/mL (7.05 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.5 mg/mL (7.05 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (7.05 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

VS-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 16 nM (IC_{50})	PI3Kγ 25 nM (IC_{50})	PI3Kδ 42 nM (IC_{50})	PI3Kβ 68 nM (IC_{50})
Vps34 7470 nM (IC_{50})	mTOR 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 (IC_{50}=37 nM) as well as class I PI3K isoforms (IC_{50}: 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]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
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]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Cell Assay [1]	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 IC_{50} values for the compounds using the XL-fit software[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [1]	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]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Br J Cancer. 2022 Jul 27.

- Front Pharmacol. 2020 Nov 11;11:580407.
- Sci Rep. 2022 Apr 12;12(1):6090.
- Research Square Print. 2023 Mar 9.
- Research Square Preprint. 2020 Sep.

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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.

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