产品名称：**OSI-027**
产品别名：**OSI-027**

生物活性：

Description	OSI-027 is an ATP-competitive mTOR kinase activity inhibitor with an IC_{50} of 4 nM. OSI-027 targets both mTORC1and mTORC2 with IC_{50}s of 22 nM and 65 nM, respectively.

IC_{50} & Target						
	mTORC1	mTORC2	mTOR	PI3K-γ	PI3K-α	DNA-PK
	22 nM (IC_{50})	65 nM (IC_{50})	4 nM (IC_{50})	0.42 μM (IC_{50})	1.3 μM (IC_{50})	1 μM (IC_{50})
	Autophagy					

In Vitro	OSI-027 is an ATP-competitive inhibitor, which targets both mTORC1 and mTORC2 with IC_{50}s of 22 nM and 65 nM. OSI-027 also inhibits PI3K-α, PI3K-γ and DNA-PK with IC_{50}s of 1.3 μM, 0.42 μM and 1.0 μM. OSI-027 inhibits mTOR signaling of phospho-4E-BP1 with an IC_{50} of 1 μM[1].
In Vivo	Effects on GEO colorectal xenograft growth treated with Rapamycin or OSI-027 for 12 days are consistent with our in vitro experiments. Treatment with Rapamycin (20 mg/kg) inhibits phospho-S6 and phospho-4E-BP1, while Akt phosphorylation is increased by 29%. In contrast, OSI-027 (65 mg/kg) inhibits both mTORC1 and mTORC2 effectors. After 2 hours, decreased 4E-BP1, Akt, and S6 phosphorylation is observed and inhibition of S6 and Akt is sustained for 24 hours. The plasma drug concentration of OSI-027 inversely correlated with these effects on mTORC1 and mTORC2 signaling. The median plasma drug concentration with OSI-027 is 21.3 μM at 2 hours and 14.9 μM at 8 hours. The in vivo efficacy of OSI-027 plus Sunitinib is tested in H292 human lung and Ovcar-5 human ovarian xenograft tumors. H292 tumors, treated with OSI-027 (50 mg/kg) for 21 days have 61% median tumor growth inhibition for the duration of treatment (TGI). Sunitinib (40 mg/kg) for 21 days had 47% median TGI. Combining OSI-027 with Sunitinib, however, has a median TGI of 100% with 59% maximal tumor regression, a statistically significant improvement over either agent alone. Ovcar-5 xenograft tumors treated with OSI-027 or Sunitinib have a 55% and 68% median TGI, respectively. OSI-027 administered with Sunitinib has a significantly better median TGI of 100% with 38% maximal tumor regression[1].In the Rapamycin (RAPA) group, three rats exhibit symptoms typical of LTx-aGVHD and die 27 to 35 days after liver transplantation (LT); the remaining five rats do not develop LTx-aGVHD symptoms and survive for more than 100 days. In contrast, seven rats in the OSI-027 group survive for more than 100 days without symptoms of LTx-aGVHD, and only one rat exhibits LTx-aGVHD symptoms and dies on day 33 after LT[2].

In Vitro:

DMSO : 83.33 mg/mL (205.02 mM; Need ultrasonic)

H_2O : < 0.1 mg/mL (insoluble)

Preparing Stock Solutions	Solvent / Mass / Concentration	**1 mg**	**5 mg**	**10 mg**
	1 mM	2.4604 mL	12.3019 mL	24.6039 mL
	5 mM	0.4921 mL	2.4604 mL	4.9208 mL
	10 mM	0.2460 mL	1.2302 mL	2.4604 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:

Solvent&Solubility	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: ≥ 2.08 mg/mL (5.12 mM); Clear solution 此方案可获得 ≥ 2.08 mg/mL (5.12 mM，饱和度未知) 的澄清溶液。 以 1 mL 工作液为例，取 100 μL 20.8 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: ≥ 2.08 mg/mL (5.12 mM); Clear solution 此方案可获得 ≥ 2.08 mg/mL (5.12 mM，饱和度未知) 的澄清溶液。 以 1 mL 工作液为例，取 100 μL 20.8 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。
References	[1]. Falcon BL, et al. Reduced VEGF production, angiogenesis, and vascular regrowth contribute to the antitumor properties of dual mTORC1/mTORC2 inhibitors. Cancer Res. 2011 Mar 1;71(5):1573-83. [2]. Zhang Y, et al. PP2AC Level Determines Differential Programming of p38-TSC-mTOR Signaling and Therapeutic Response to p38-Targeted Therapy in Colorectal Cancer. EBioMedicine. 2015 Nov 19;2(12):1944-56. [3]. Zhi X, et al. OSI-027 modulates acute graft-versus-host disease after liver transplantation in a rat model. Liver Transpl. 2017 Sep;23(9):1186-1198.

实验参考：

Cell Assay	To study the effect of drug treatment on cellular signaling, Ovcar-3 cells are plated in normal growth medium. After 24 hours, serum is removed and cells are serum-starved overnight. Rapamycin, OSI-027 and OXA-01 are solubilized in DMSO and added to cells at varying concentrations. After a two-hour incubation cells are growth factor stimulated with 10 ng/mL Insulin for 3 to 5 minutes, then rinsed with cold PBS and lysed[1].
Animal Administration	Mice[1] For xenograft models, cells are harvested, implanted s.c. in the right flank of nu/nu CD-1 mice and tumor growth is analyzed. Mice bearing GEO xenografts are treated for 12 days with OSI-027 (65mg/kg) or vehicle and tumors collected at 2, 8, and 24 hours. Tumor growth inhibition and regression calculations are included. Rats[2] Specific pathogen-free female Lewis rats, male BN rats, male Lew-Tg(CAG-EGFP)YsRrrc rats and male Lew-TgYsRrrc rats are used. Orthotopic LT is undertaken. No antibiotics were used. Freshly prepared splenocytes (4×108, suspended in 500 μL PBS) of Lew-Tg YsRrrc rats are infused into each recipient via the dorsal penile vein immediately after LT (within 30 min). LTx-aGVHD model rats are divided into three experimental groups: RAPA (1 mg/kg), OSI-027 (1 mg/kg) or control (equal quantity of vehicle) groups; treatments are administered via the vena caudalis from day 7 to day 15.

Kinase Assay	Assays of a panel of 40 other recombinant kinases including both protein and lipid kinases are performed at 100 mM ATP concentration by SelectScreen profiling service. A broad panel of kinases is tested at a single concentration of OSI-027 or OXA-01 (3 μM) to evaluate percent inhibition of each kinase or mutant variant, using the Ambit KinomeScan platform[1].
References	[1]. Falcon BL, et al. Reduced VEGF production, angiogenesis, and vascular regrowth contribute to the antitumor properties of dual mTORC1/mTORC2 inhibitors. Cancer Res. 2011 Mar 1;71(5):1573-83. [2]. Zhang Y, et al. PP2AC Level Determines Differential Programming of p38-TSC-mTOR Signaling and Therapeutic Response to p38-Targeted Therapy in Colorectal Cancer. EBioMedicine. 2015 Nov 19;2(12):1944-56. [3]. Zhi X, et al. OSI-027 modulates acute graft-versus-host disease after liver transplantation in a rat model. Liver Transpl. 2017 Sep;23(9):1186-1198.