OSI-027

Cat. No.: HY-10423

CAS No.: 936890-98-1

Molecular Formula: $C_{21}H_{22}N_6O_3$

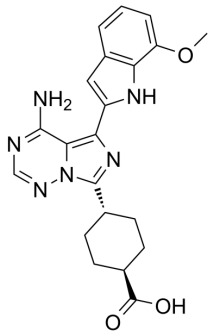
Molecular Weight: 406.44

Target: mTOR; Autophagy

Pathway: PI3K/Akt/mTOR; Autophagy

Storage:

Powder	-20°C	3 years
In solvent	-80°C	6 months
	-20°C	1 month



SOLVENT & SOLUBILITY

In Vitro

DMSO : 100 mg/mL (246.04 mM; Need ultrasonic)

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

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 (6.15 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: 2.5 mg/mL (6.15 mM); Suspended solution; Need ultrasonic

BIOLOGICAL ACTIVITY

Description

OSI-027 (ASP7486) is a potent, selective, orally active and ATP-competitive mTOR kinase activity inhibitor with an IC_{50} of 4 nM. OSI-027 targets both mTORC1 and mTORC2 with IC_{50}s of 22 nM and 65 nM, respectively[1][2].

IC_{50} & Target

mTOR 4 nM (IC_{50})	mTORC1 22 nM (IC_{50})	mTORC2 65 nM (IC_{50})	PI3K-γ 0.42 μM (IC_{50})
PI3K-α 1.3 μM (IC_{50})	DNA-PK 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]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
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[3]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Kinase Assay [1]	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]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Cell Assay [1]	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]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [1]	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 (4×10^8, 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. 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.

- EBioMedicine. 2015 Nov 19;2(12):1944-56.
- Cell Syst. 2018 Apr 25;6(4):424-443.e7.
- Int J Mol Sci. 2023 Apr 10, 24(8), 6987.
- Cancers (Basel). 2022, 14(23), 5854

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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]. 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.

[3]. 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.

[4]. Mateo J, et al. A first in man, dose-finding study of the mTORC1/mTORC2 inhibitor OSI-027 in patients with advanced solid malignancies. Br J Cancer. 2016;114(8):889-896.

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