Palomid 529

Cat. No.: HY-14581

CAS No.: 914913-88-5

Molecular Formula: $C_{24}H_{22}O_6$

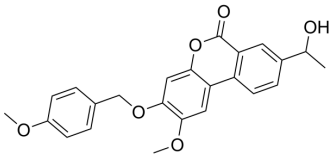
Molecular Weight: 406.43

Target: mTOR; Apoptosis

Pathway: PI3K/Akt/mTOR; Apoptosis

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 : 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	12.3022 mL	24.6045 mL
	5 mM	0.4921 mL	2.4604 mL	4.9209 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 >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (6.15 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Palomid 529 is a potent inhibitor of mTORC1 and mTORC2 complexes.

IC_{50} & Target

TORC1 | TORC2

In Vitro

Palomid 529 (P529) inhibits both VEGF-driven (IC_{50}, 20 nM) and bFGF-driven (IC_{50}, 30 nM) endothelial cell proliferation and retained the ability to induce endothelial cell apoptosis[1]. Palomid 529 (RES-529) is a PI3K/AKT/mTOR pathway inhibitor that interferes with the pathway through both mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2) dissociation. Palomid 529 inhibits mTORC1/mTORC2 activity in various cancer cell lines, as noted by decreased phosphorylation of substrates including ribosomal protein S6, 4E-BP1, and AKT, leading to cell growth inhibition and death, with activity generally in the range of 5-15 μM. At 10 μM concentrations, Palomid 529 reduces the binding of 0.5 nM [^{3}H]estradiol to estrogen receptor (ER)α and ERβ by 3% or less. Palomid 529 inhibits both VEGF-stimulated and β fibroblast growth factor-stimulated HUVEC cell proliferation with IC_{50} of ~10 and 30 nM, respectively. Treatment of HUVEC cells with Palomid 529

	also results in a four-fold induction of apoptosis on the basis of DNA fragmentation. Growth inhibition is observed with Palomid 529 treatment in various cancer cell lines from the National Cancer Institute-60 (NCI-60) tumor panel, with IC_{50} ranges of 5-15 μM for central nervous system cancer cells and 5-30 μM for prostate cancer cells[2]. Palomid 529 (P529) results in a dose- and time-dependent decrease in Akt activity in PC3, LnCaP, and 22rv1 cells as evidenced by a reduced phosphorylation of Akt (Ser^{473}). Similar results are observed in all PCa cells with similar enzymatic IC_{50}s of about 0.2 μM. Palomid 529 inhibits the cell proliferation of neoplastic cells at different extent (IC_{50}s ranged from 5 to 28 μM), whereas very few effects are observed in non-neoplastic BPH1 and EPN cells. Treatment with Palomid 529 results in a concentration-dependent reduction in viable/proliferating tumor cells compared with non-neoplastic BPH1 and EPN cells. IC_{50}s range from 5 to 28 μM[3]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	Palomid 529 (200 mg/kg/2d) inhibits C6V10 glioma tumor growth in nude mice following i.p. dosing. Analysis of signaling within the tumor lysates reveals that Palomid 529 (P529) also reduces AktS473 but not AktT308 signaling[1]. Palomid 529 (RES-529) has shown antitumor activity in a variety of mouse models, including those for glioblastoma, and prostate and breast cancer. In a C6V10 glioblastoma subcutaneous xenograft model, mice pretreated with Palomid 529 (200 mg/kg/2 days, intraperitoneal) 1 week before and for 3 weeks after a tumor cell injection showed an ~70% decrease in tumor volume compared with the control. In another glioblastoma tumor model using human U87 cells, mice treated with micronized Palomid 529 3 days after a tumor cell injection showed a reduction in tumor growth by ~78 and 29% with 50 and 25 mg/kg/2 days, intraperitoneal, Palomid 529, respectively, after 24 days compared with the control[2]. Palomid 529 (P529) is able to reduce tumor growth in a dose-dependent manner both in PC3 and 22rv1 xenografts. A 10, 47.6, and 59.3% reduction of tumor mass is demonstrated in mice bearing PC3 xenografts receiving 50, 100, and 200 mg/kg Palomid 529 respectively and a 9, 38.7, and 51.5% reduction of tumor mass in mice bearing 22rv1 xenografts receiving 50, 100, and 200 mg/kg Palomid 529 respectively[3]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Kinase Assay [1]	The proteins are produced with rabbit reticulocyte lysates that couples transcription and translation in a single reaction. The amount of template used in each reaction is determined empirically and expression is monitored in parallel reactions where [^{35}S]methionine is incorporated into the receptor followed by gel electrophoresis and exposure to film. Binding reactions of the estrogen receptors (ER) and Palomid 529 (P529) are carried out in 100 mL final volumes in TEG buffer [10 mM Tris (pH 7.5), 1.5 mM EDTA, 10% glycerol]. In vitro transcribed-translated receptor (5 AL) is used in each binding reaction in the presence of 0.5 nM [^{3}H]estradiol (E_2). All compounds are routinely tested from 10−11 to 10−6 M and diluted in ethanol. The reactions are incubated at 4°C overnight and bound E_2 is quantified by adding 200 mL dextran-coated charcoal. After a 15-min rotation at 4°C, the tubes are centrifuged for 10 min and 150 mL of the supernatant are added to 5 mL scintillation mixture for determination of cpm by liquid scintillation counting. The maximum binding is determined by competing bound E_2 with only the ethanol vehicle. Controls for background are included in each experiment using 5 mL unprogrammed rabbit reticulocyte lysate. This value, typically 10% to 15% of the maximal counts, is subtracted from all values. The data are plotted and K_is are calculated using the Prism software. Experiments are conducted at least thrice in duplicate[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Cell Assay [1]	The proliferation assay is carried out by seeding the HUVECs in 96-well plates at a density of 1,000 per well in complete medium. Following a 24-h plating period, the cells are starved for 24 h in 0.5% serum before being treated with Palomid 529 in the presence of 10 ng/mL basic fibroblast growth factor (bFGF) or VEGF in complete medium. After 48 h, cell number is determined using a colorimetric method as described by the supplier. The results are expressed as the percentage of the maximal bFGF or VEGF response in the absence of P529. Nonproliferating endothelial cells are assayed by growing HUVECs to quiescence in 96-well plates and treating with Palomid 529 (0, 100, 200, 300 and 400 nM) for 48 h. Initially, 5,000 cells per well are seeded and confluence is achieved the next day. The plates are incubated for another 24 h to ensure growth arrest before treatment with P529. Cell number is determined as outlined above[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal	Mice[1]

Administration [1]	Four- to 6-wk-old female nude mice are pretreated with Palomid 529 (200 mg/kg/2d, i.p.) for 1 wk, and then 1×10^5 C6V10 rat glioma cells are injected s.c.. Treatment continued while tumors are allowed to grow for 21 d. U87 cells (3×10^6/100 AL) are injected s.c. into nude mice. From day 3 after injection of tumor cells, mice are treated by micronized Palomid 529 (P529) at doses of 50 mg and 25 mg/kg/2 d i.p., respectively. Mice without drug treatment served as controls. U87 tumors are allowed to grow for 24 d. During drug treatment, tumor volumes are measured with a caliper and estimated as length×width×width×0.53. Animals are euthanized and the tumors are taken for immunohistologic and immunoblotting studies. 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.
- Front Pharmacol. 2020 Nov 11;11:580407.
- Molecules. 2020 Apr 23;25(8):1980.
- Biochem Biophys Res Commun. 2018 Mar 4;497(2):499-505.
- Harvard Medical School LINCS LIBRARY

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REFERENCES

[1]. Xue Q, et al. Palomid 529, a novel small-molecule drug, is a TORC1/TORC2 inhibitor that reduces tumor growth, tumor angiogenesis, and vascular permeability. Cancer Res, 2008, 68(22), 9551-9557.

[2]. Weinberg MA, et al. RES-529: a PI3K/AKT/mTOR pathway inhibitor that dissociates the mTORC1 and mTORC2 complexes. Anticancer Drugs. 2016 Jul;27(6):475-87.

[3]. Gravina GL, et al. The TORC1/TORC2 inhibitor, Palomid 529, reduces tumor growth and sensitizes to docetaxel andcisplatin in aggressive and hormone-refractory prostate cancer cells. Endocr Relat Cancer. 2011 Jul 1;18(4):385-400.

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