Pictilisib dimethanesulfonate

Cat. No.: HY-20180

CAS No.: 957054-33-0

Molecular Formula: $C_{25}H_{35}N_7O_9S_4$

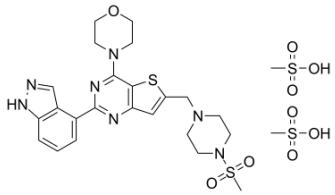
Molecular Weight: 705.85

Target: PI3K; Autophagy; Apoptosis

Pathway: PI3K/Akt/mTOR; Autophagy; Apoptosis

Storage:

Powder	-20°C	3 years
	4°C	2 years
In solvent	-80°C	6 months
	-20°C	1 month



SOLVENT & SOLUBILITY

In Vitro

DMSO : 50 mg/mL (70.84 mM; Need ultrasonic)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	1.4167 mL	7.0837 mL	14.1673 mL
	5 mM	0.2833 mL	1.4167 mL	2.8335 mL
	10 mM	0.1417 mL	0.7084 mL	1.4167 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 (3.54 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: 2.5 mg/mL (3.54 mM); Suspended solution; Need ultrasonic
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (3.54 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Pictilisib dimethanesulfonate (GDC-0941 dimethanesulfonate) is a potent inhibitor of PI3Kα/δ with IC_{50} of 3 nM, with modest selectivity against p110β (11-fold) and p110γ (25-fold).

IC_{50} & Target

p110α 3 nM (IC_{50})	p110α-H1047R 3 nM (IC_{50})	p110α-E545K 3 nM (IC_{50})	p110δ 3 nM (IC_{50})
p110β 33 nM (IC_{50})	p110γ 75 nM (IC_{50})	mTOR 0.58 μM (Ki)	DNA-PK 1.23 μM (IC_{50})

	Autophagy
In Vitro	Pictilisib (GDC-0941) and RP-56976 reduce tumor cell viability by 80% or greater in the breast cancer cell lines than single-agent treatment. GDC-0941 inhibits Akt phosphorylation and downstream targets of Akt signaling such as pPRAS40 and pS6 in Hs578T1.2 (PI3Kα wild-type), MCF7-neo/HER2 (PI3Kα-mutant), and MX-1 (PTEN-null) tumor models. Pictilisib (GDC-0941) decreases the time of RP-56976-induced mitotic arrest prior to apoptosis[1]. Pictilisib (GDC-0941) shows a high efficacy of antitumor activity in two ZD1839-resistant non-small cell lung cancer (NSCLC) cell lines, A549 and H460. Pictilisib (GDC-0941) is highly efficacious in combination with U0126 in inducing cell growth inhibition, G0-G1 arrest and cell apoptosis. H460 cells with activating mutations of PIK3CA are relatively more sensitive to Pictilisib (GDC-0941) than A549 cells with wild-type PIK3CA[3]. Pictilisib (GDC-0941) reduces PI3K pathway activity in both cell lines, illustrated by decreased pAK. Pictilisib (GDC-0941) significantly reduces secreted VEGF detected in the medium after hypoxic/anoxic exposure in all cells[4]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	Pictilisib (GDC-0941) (150 mg/kg, p.o.) leads to tumor stasis in MCF7-neo/HER2-bearing animals model. Pictilisib (GDC-0941) and RP-56976 result in tumor regressions during the treatment period leading to enhanced antitumor responses[1]. Tumours in the Pictilisib (GDC-0941)-treated mice show a marked non-linear shrinkage, and when the Pictilisib (GDC-0941) treatment ceased, the tumours in the test cohort mice grow again[2]. GDC-0941Pictilisib (GDC-0941) (25 or 50 mg/kg) reduces tumor growth and PI3K and HIF-1 pathway activity in eGFP-FTC133 tumor-bearing mice[4]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Cell Assay [1]	Cells are treated at EC_{50} concentrations of Pictilisib (GDC-0941), RP-56976, or both for 4 or 24 hours and lysed in 1×Cell Extraction Buffer supplemented with protease inhibitors and Phosphatase Inhibitor Cocktails 1 and 2. Protein concentrations are determined using the Pierce BCA Protein Assay Kit. For immunoblots, equal amounts of protein are separated by electrophoresis through NuPAGE Bis-Tris 10% gradient gels, transferred onto polyvinylidene difluoride membranes using the Criterion system, and probed with monospecific primary antibodies. Specific antigen-antibody interactions are detected with IRDye 680 or IRDye 800 infrared secondary antibodies using a LI-COR imaging system[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [1]	Mice[1] Female nu/nu mice are inoculated subcutaneously with MCF7-neo/HER2 or MX-1 breast cancer cells. When tumors reach a mean volume of 200 to 250 mm^3, animals are size-matched and distributed into groups consisting of 10 animals per group. RP-56976 formulated in 3% EtOH, 97% saline is administered intravenously once weekly. Pictilisib (GDC-0941), formulated in MCT (0.5% methylcellulose, 0.2% Tween-80) is dosed orally and daily. MAXF1162 is an HER2+/ER+/PR+ patient-derived breast cancer tumor xenograft model established by directly implanting tumors subcutaneously from patient to NMRI nu/nu mice. Tumor volume is calculated. Tumor sizes are recorded twice weekly over the course of a study. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Nature. 2018 Aug;560(7719):499-503.
- Cancer Discov. 2012 May;2(5):425-33.
- Cell Metab. 2012 Mar 7;15(3):382-94.
- Nat Biomed Eng. 2018 Aug;2(8):578-588.
- Sci Transl Med. 2018 Jul 18;10(450):eaaq1093.

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REFERENCES

[1]. Wallin JJ, et al. GDC-0941, a novel class I selective PI3K inhibitor, enhances the efficacy of RP-56976 in human breast cancer models by increasing cell death in vitro and in vivo.Clin Cancer Res. 2012 Jul 15;18(14):3901-11. Epub 2012 May 14.

[2]. Wullschleger S, et al. Quantitative MRI establishes the efficacy of PI3K inhibitor (GDC-0941) multi-treatments in PTEN-deficient mice lymphoma.Anticancer Res. 2012 Feb;32(2):415-20.

[3]. Zou ZQ, et al. The novel dual PI3K/mTOR inhibitor GDC-0941 synergizes with the MEK inhibitor U0126 in non-small cell lung cancer cells.Mol Med Report. 2012 Feb;5(2):503-8.

[4]. Burrows N, et al. GDC-0941 inhibits metastatic characteristics of thyroid carcinomas by targeting both the phosphoinositide-3 kinase (PI3K) and hypoxia-inducible factor-1α (HIF-1α) pathways.J Clin Endocrinol Metab. 2011 Dec;96(12):E1934-43. Epub 2011 Oct

[5]. Folkes AJ, et al. The identification of 2-(1H-indazol-4-yl)-6-(4-methanesulfonyl-piperazin-1-ylmethyl)-4-morpholin-4-yl-thieno[3,2-d]pyrimidine (GDC-0941) as a potent, selective, orally bioavailable inhibitor of class I PI3 kinase for the treatment of cancer . J Med Chem. 2008 Sep 25;51(18):5522-32.

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