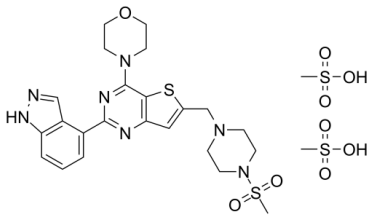
Data Sheet

Product Name:	Pictilisib (dimethanesulfonate)
Cat. No.:	CS-0082
CAS No.:	957054-33-0
Molecular Formula:	C25H35N7O9S4
Molecular Weight:	705.85
Target:	Autophagy; PI3K
Pathway:	Autophagy; PI3K/Akt/mTOR
Solubility:	DMSO : 50 mg/mL (70.84 mM; Need ultrasonic); H2O : < 0.1 mg/mL (insoluble)



BIOLOGICAL ACTIVITY:

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). IC50 & Target: IC50: 3 nM (PI3Kα), 3 nM (PI3Kδ)[5] **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]. **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].

PROTOCOL (Extracted from published papers and Only for reference)

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].

Animal Administration: GDC-0941 is formulated in MCT (0.5% methylcellulose, 0.2% Tween-80) (Mice)[1].[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.

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.

CAIndexNames:

Thieno[3,2-d]pyrimidine, 2-(1H-indazol-4-yl)-6-[[4-(methylsulfonyl)-1-piperazinyl]methyl]-4-(4-morpholinyl)-, methanesulfonate (1:2)

SMILES:

O=S(N1CCN(CC1)CC2=CC3=C(S2)C(N4CCOCC4)=NC(C5=CC=CC6=C5C=NN6)=N3)(C)=O.O=S(O)(C)=O.O=S(O)(C)=O

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