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产品名称: **GDC-0941 Bimesylate**

产品别名: **Pictilisib dimethanesulfonate; GDC-0941 dimethanesulfonate; GDC-0941 2 MeSO₃H salt**

生物活性:

Description	Pictilisib dimethanesulfonate (GDC-0941 dimethanesulfonate) is a potent inhibitor of PI3Kα/δ with IC50 of 3 nM, with modest selectivity against p110β (11-fold) and p110γ (25-fold).				
IC50 & Target	p110α	p110β	p110δ	p110γ	p110α-H1047R
	3 nM (IC50)	33 nM (IC50)	3 nM (IC50)	75 nM (IC50)	3 nM (IC50)
	p110α-E545K	DNA-PK	mTOR	Autophagy	
	3 nM (IC50)	1.23 μM (IC50)	0.58 μM (Ki)		
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].				
	In Vitro:				
	DMSO : 50 mg/mL (70.84 mM; Need ultrasonic)				
	H2O : < 0.1 mg/mL (insoluble)				
	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	
*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。					



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Solvent&Solubility	In Vivo: 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: ≥ 2.5 mg/mL (3.54 mM); Clear solution 此方案可获得 ≥ 2.5 mg/mL (3.54 mM, 饱和度未知) 的澄清溶液。 以 1 mL 工作液为例, 取 100 μL 25.0 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: 2.5 mg/mL (3.54 mM); Suspended solution; Need ultrasonic 此方案可获得 2.5 mg/mL (3.54 mM) 的均匀悬浊液, 悬浊液可用于口服和腹腔注射。 以 1 mL 工作液为例, 取 100 μL 25.0 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。 3.请依序添加每种溶剂: 10% DMSO →90% corn oil Solubility: ≥ 2.5 mg/mL (3.54 mM); Clear solution 此方案可获得 ≥ 2.5 mg/mL (3.54 mM, 饱和度未知) 的澄清溶液, 此方案不适用于实验周期在半个月以上的实验。 以 1 mL 工作液为例, 取 100 μL 25.0 mg/mL 的澄清 DMSO 储备液加到 900 μL 玉米油中, 混合均匀。
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]. 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. [3]. Wulschleger 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. [4]. 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. [5]. 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
实验参考:	
	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



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Cell Assay	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	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]. 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. [3]. Wullschlegel 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. [4]. 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. [5]. 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