

产品名称：**GDC-0941**
产品别名：**Pictilisib**

生物活性:						
Description	Pictilisib (GDC-0941) is a potent inhibitor of PI3K α/δ with an IC ₅₀ of 3 nM, with modest selectivity against p110 β (11-fold) and p110 γ (25-fold).					
IC ₅₀ & Target	p110 α	p110 β	p110 δ	p110 γ	p110 α -H1047R	p110 α -E545K
	3 nM (IC ₅₀)	33 nM (IC ₅₀)	3 nM (IC ₅₀)	75 nM (IC ₅₀)	3 nM (IC ₅₀)	3 nM (IC ₅₀)
	DNA-PK	mTOR	Autophagy			
	1.23 μ M (IC ₅₀)	0.58 μ M (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 (PI3K α wild-type), MCF7-neo/HER2 (PI3K α -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]. Pictilisib (GDC-0941) (25 or 50 mg/kg) reduces tumor growth and PI3K and HIF-1 pathway activity in eGFP-FTC133 tumor-bearing mice[4].					
Solvent&Solubility	In Vitro: DMSO : $\geq$ 100 mg/mL (194.69 mM) * " $\geq$ " means soluble, but saturation unknown.					
	Preparing Stock Solutions	Solvent Concentration Mass	1 mg	5 mg	10 mg	
		1 mM	1.9469 mL	9.7344 mL	19.4689 mL	
		5 mM	0.3894 mL	1.9469 mL	3.8938 mL	
		10 mM	0.1947 mL	0.9734 mL	1.9469 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。 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 (4.87 mM); Clear solution 此方案可获得 ≥ 2.5 mg/mL (4.87 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。
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]. 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. [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. [6]. Ni J, et al. Functional characterization of an isoform-selective inhibitor of PI3K-p110β as a potential anticancer agent. Cancer Discov. 2012 May;2(5):425-33. [7]. Cheng H, et al. A genetic mouse model of invasive endometrial cancer driven by concurrent loss of Pten and Lkb1 Is highly responsive to mTOR inhibition. Cancer Res. 2014 Jan 1;74(1):15-23.
实验参考：	
Cell Assay	Cells are treated at EC₅₀ 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	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 mm³, 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. [1]

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.
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源叶生物