

产品名称: **GDC-0084**

产品别名: **GDC-0084**

生物活性:					
Description	GDC-0084 is a brain penetrant inhibitor of PI3K and mTOR , with K_s of 2 nM, 46 nM, 3 nM, 10 nM and 70 nM for PI3K α PI3K β , PI3K δ , PI3K γ and mTOR, respectively.				
IC ₅₀ & Target	PI3K α	PI3K δ	PI3K γ	PI3K β	mTOR
	2 nM (Ki)	3 nM (Ki)	10 nM (Ki)	46 nM (Ki)	70 nM (Ki)
In Vitro	GDC-0084 (Compound 16) maintains inhibition of each of the Class I PI3K isoforms but with more potent inhibition of mTOR. GDC-0084 is also tested in five different GBM cell lines and is found to have antiproliferative EC ₅₀ s ranging from 0.3 to 1.1 μ M[1].				
In Vivo	After a 25 mg/kg dose of GDC-0084 (Compound 16) administered orally, pAKT in normal mouse brain tissue is significantly inhibited at 1 and 6 h postdose. The potent inhibition of pAKT at both time points in this study demonstrates that GDC-0084 inhibits its target behind a fully intact BBB. In addition to the pharmacodynamic effect in normal brain tissue, GDC-0084 is studied in a subcutaneous U87 tumor xenograft model of glioblastoma in mice. In this study, GDC-0084 achieves significant and dose-dependent tumor growth inhibition. Tumor growth inhibition is first observed at a 2.2 mg/kg dose level. Higher doses led to greater tumor growth inhibition, including tumor regressions at the 17.9 mg/kg dose level. Each of these doses is well tolerated for the duration of the study[1].				
Solvent&Solubility	In Vitro: DMSO : 6 mg/mL (15.69 mM; Need ultrasonic)				
	Preparing Stock Solutions	Solvent Concentration	Mass	1 mg	5 mg
		1 mM		2.6149 mL	13.0746 mL
		5 mM		0.5230 mL	2.6149 mL
		10 mM		0.2615 mL	1.3075 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。				
References	[1]. Heffron TP, et al. Discovery of Clinical Development Candidate GDC-0084, a Brain Penetrant Inhibitor of PI3K and mTOR. ACS Med Chem Lett. 2016 Feb 16;7(4):351-6.				

实验参考:

Animal Administration	Mice[1] PTEN-null U-87 MG/M human glioblastoma cancer cells are cultured in RPMI 1640 media plus 1% L-glutamine with 10% fetal bovine serum. Cells in log-phase growth are harvested and resuspended in HBSS:Matrigel (1:1, v:v) for injection into female NCr nude mice aged 20 weeks. Animals receive five million cells subcutaneously in the right lateral thorax in 0.1 mL. Mice bearing established tumors in the range of 200-500 mm ³ are separated into groups of equally sized tumors (n=6-7/group) to receive escalating doses of GDC-0084 (Compound 16). GDC-0084 is formulated once weekly in 0.5% methylcellulose and 0.2% Tween-80 at concentrations needed for target doses in a volume of 0.2 mL. All formulations are stored in a refrigerator and brought to room temperature
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	and mixed well by vortex before oral administration by gavage once daily for 23 days. Tumor volumes are calculated. Changes in body weights are reported as a percentage change from the starting weight.
Kinase Assay	<p>Enzymatic activity of PI3Kα is measured using a fluorescence polarization assay that monitors formation of the product 3,4,5-inositoltriphosphate molecule (PIP3) as it competes with fluorescently labeled PIP3 for binding to the GRP-1 pleckstrin homology domain protein. An increase in phosphatidyl inositide-3-phosphate product results in a decrease in fluorescence polarization signal as the labeled fluorophore is displaced from the GRP-1 protein binding site. PI3Kα is expressed and purified as heterodimeric recombinant protein. PI3Kα is assayed under initial rate conditions in the presence of 10 mM Tris (pH 7.5), 25 μM ATP, 9.75 μM PIP2, 5% glycerol, 4 mM MgCl₂, 50 mM NaCl, 0.05% (v/v) Chaps, 1 mM dithiothreitol, 2% (v/v) DMSO at a 60 ng/mL concentration of PI3Kα. After assay for 30 min at 25°C, reactions are terminated with a final concentration of 9 mM EDTA, 4.5 nM TAMRA-PIP3, and 4.2 μg/mL GRP-1 detector protein before reading fluorescence polarization on an Envision plate reader. IC₅₀s are calculated from the fit of the dose-response curves to a 4-parameter equation. Apparent K_is, where measured, are determined at a fixed concentration of ATP near the measured K_m for ATP for PI3Kα, and are calculated by fitting of the dose-response curves to an equation for tightbinding competitive inhibition[1].</p>
References	[1]. Heffron TP, et al. Discovery of Clinical Development Candidate GDC-0084, a Brain Penetrant Inhibitor of PI3K and mTOR. ACS Med Chem Lett. 2016 Feb 16;7(4):351-6.

源叶生物