

产品名称: **XL-147**
 产品别名: **Pilaralisib; SAR245408**

生物活性:

Description	Pilaralisib (XL147; SAR245408) is a potent and highly selective class I PI3Ks inhibitor with IC ₅₀ s of 39 nM, 383 nM, 23 nM and 36 nM for PI3Kα, PI3Kβ, PI3Kγ, and PI3Kδ.					
IC ₅₀ & Target	PI3Kα	PI3Kβ	PI3Kδ	PI3Kγ	Vps34	DNA-PK
	39 nM (IC ₅₀)	383 nM (IC ₅₀)	36 nM (IC ₅₀)	23 nM (IC ₅₀)	6974 nM (IC ₅₀)	4750 nM (IC ₅₀)
In Vitro	Pilaralisib (XL147) displays potent inhibitory activity against Class I PI3K isoforms p110α, p110δ, and p110γ, with IC₅₀s of 39, 36, and 23 nM, respectively. Pilaralisib (XL147) is less potent against the remaining Class I isoform, p110β, with an IC₅₀ value of 383 nM. The IC₅₀ value for inhibition of PI3Kα by Pilaralisib (XL147) is determined at various concentrations of ATP, revealing XL147 to be an ATP-competitive inhibitor with an equilibrium inhibition constant (K_i) value of 42 nM. Pilaralisib (XL147) has relatively weak inhibitory activity toward the class III PI3K vacuolar sorting protein 34 (VPS34; IC₅₀ value of ~7.0 M) and the PI3K-related DNA-dependent protein kinase (DNA-PK; IC₅₀ value of 4.75 μM). In an mTOR kinase immunoprecipitation assay using cell lysates, Pilaralisib (XL147) does not inhibit mTOR activity toward the physiologic substrate protein eukaryotic translation initiation factor 4E-binding protein 1 (4EBP1; IC₅₀>15 μM). Consistent with its inhibitory activity against purified PI3K proteins, Pilaralisib (XL147) inhibits EGF-induced PIP₃ production in PC-3 and MCF7 cells in serum-free medium with IC₅₀s of 220 and 347 nM, respectively. The ability of Pilaralisib (XL147) to inhibit phosphorylation of key signaling proteins downstream of PI3K is examined by assessing its effects on EGF-stimulated phosphorylation of AKT and on nonstimulated phosphorylation of S6 in PC-3 cells in serum-free media by cell-based ELISA. Pilaralisib (XL147) inhibits these activities with IC₅₀s of 477 and 776 nM, respectively [1].					
In Vivo	The ability of Pilaralisib (XL147) to inhibit this endogenous phosphorylation of AKT, p70S6K, and S6 is examined following a single oral dose of 10, 30, 100, or 300 mg/kg. The tumors are harvested 4, 24, or 48 hours postdose and homogenized in lysis buffer. Tumor lysates from each animal (n=4) are then pooled for each group and analyzed for levels of total and phosphorylated AKT, p70S6K, and S6 by Western immunoblotting. Administration of Pilaralisib (XL147) causes a dose-dependent decrease in phosphorylation of AKT, p70S6K, and S6 in the tumors, reaching a maximum of 81% inhibition of AKT phosphorylation at 300 mg/kg at 4 hours. The dose-response relationships derived from the 4-hour time point predict 50% inhibition of AKT, p70S6K, and S6 phosphorylation at doses of approximately 100 mg/kg (pAKT^{T308}), 54 mg/kg (pAKT^{S473}), 71 mg/kg (p-p70S6K), and 103 mg/kg (pS6). The inhibition of AKT, p70S6K, and S6 phosphorylation in MCF7 tumors following a 100 mg/kg dose of Pilaralisib (XL147) is maximal at 4 hours, reaching 55% to 75%; however, the level of inhibition decreased to 8% to 45% by 24 hours, and only minimal or no inhibition was evident by 48 hours. Following a 300 mg/kg dose of Pilaralisib (XL147), inhibition is also maximal at 4 hours (65%-81%). However, in contrast with the 100 mg/kg dose, inhibition at 24 hours (51%-78%) is almost comparable with that seen at 4 hours, and partial inhibition (25%-51%) persisted through 48 hours[1].					
	In Vitro:					
	DMSO : 6 mg/mL (11.09 mM; Need ultrasonic and warming)					
Preparing	Solvent Mass Concentration	1 mg	5 mg	10 mg		
	1 mM	1.8484 mL	9.2418 mL	18.4836 mL		

Solvent&Solubility	Stock Solutions	5 mM	0.3697 mL	1.8484 mL	3.6967 mL
		10 mM	0.1848 mL	0.9242 mL	1.8484 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℃，6 months；-20℃，1 month。-80℃ 储存时，请在 6 个月内使用，-20℃ 储存时，请在 1 个月内使用。				
References	[1]. Foster P, et al. The Selective PI3K Inhibitor XL147 (SAR245408) Inhibits Tumor Growth and Survival and Potentiates the Activity of Chemotherapeutic Agents in Preclinical Tumor Models. Mol Cancer Ther. 2015 Apr;14(4):931-40.				
实验参考：					
Cell Assay	MCF7 human mammary carcinoma cells and PC-3 human prostate adenocarcinoma cells are maintained in culture conditions at 37°C under 5% CO₂. For PI3K pathway status assessment following EGF treatment, the culture medium is replaced with test compounds dissolved in serum-free DMEM containing 0.3% DMSO. After incubation for 3 hours, cells are stimulated with 100 ng/mL of EGF for 10 minutes and Western immunoblot analysis of cell lysates is performed. Assessment of mTOR pathway status in Ramos cells is performed. Cellular proliferation is assessed using the Cell Proliferation ELISA, bromodeoxyuridine (BrdUrd) chemiluminescence kit. Cytotoxicity, apoptosis (caspases-3/7), anchorage-independent growth, and PC-3 cell migration assays are performed. Hepatocyte growth factor (HGF)-induced chemotaxis is assessed. The endothelial cell tube formation assay is performed, with minor modifications. Total tube length is quantified with Image Pro Plus software[1].				
Animal Administration	Mice[1]. Female athymic nude mice and male nude mice are used. Tumor cells are cultured and established as xenografts in mice, and body and tumor weights assessed. Statistical significance is determined using the two-tailed Student ttest (significance defined as P<0.05). Pilaralisib (XL147) is formulated in sterile water/10 mmol/L HCl or water and administered at the indicated doses and regimens by oral gavage at a dose volume of 10 mL/kg.				
References	[1]. Foster P, et al. The Selective PI3K Inhibitor XL147 (SAR245408) Inhibits Tumor Growth and Survival and Potentiates the Activity of Chemotherapeutic Agents in Preclinical Tumor Models. Mol Cancer Ther. 2015 Apr;14(4):931-40.				