产品名称：**PKI-402**
产品别名：**PKI-402**

生物活性：					
Description	PKI-402 is a selective, reversible, ATP-competitive inhibitor of PI3K, including PI3K-α mutants, and mTOR (IC_{50}=2, 3, 7,14 and 16 nM for PI3Kα, mTOR, PI3Kβ, PI3Kδ and PI3Kγ).				
IC_{50} & Target	PI3Kα	PI3Kα-H1047R	PI3Kα-E545K	PI3Kβ	PI3Kδ
	2 nM (IC_{50})	3 nM (IC_{50})	3 nM (IC_{50})	7 nM (IC_{50})	14 nM (IC_{50})
	PI3Kγ	mTOR			
	16 nM (IC_{50})	3 nM (IC_{50})			
In Vitro	PKI-402 is an equipotent inhibitor of class I PI3K, including the E545K and H1047R PI3K-α mutants (IC50=2, 3 and 3 nM for PI3Kα, PI3Kα-H1047R and PI3Kα-E545K, respectively). PKI-402 causes in vitro growth inhibition of human tumor cell lines derived from a diverse set of human tumor tissues, including breast, brain (glioma), pancreas, and non-small cell lung cancer (NSCLC) tissues. PKI-402 inhibits MDA-MB-361 [breast: Her2+ and PIK3CA mutant (E545K)], with an IC50 of 6 nM. PKI-402 inhibits HCT116 (K-Ras and PIK3CA mutant) with an IC50 of 33 nM[1].				
In Vivo	PKI-402 displays antitumor activity (i.v. route) in breast [MDA-MB-361: Her2+ and PIK3CA (E545K)], glioma (U87MG and PTEN), and NSCLC (A549; K-Ras and STK11) xenograft models. PKI-402 causes regression in the MDA-MB-361 xenograft model. PKI-402 effect is most pronounced at 100 mg/kg (daily for 5 days, one round), which reduces initial tumor volume and prevents tumor re-growth for 70 days. In MDA-MB-361 tumor tissue, PKI-402 at 100 mg/kg (single dose) fully suppresses p-Akt at both the T308 and the S473 sites at 8 hours and induces cleaved PARP. At 24 hours, p-Akt suppression is still evident, as is cleaved PARP[1].				
Solvent&Solubility	***In Vitro:*** **DMSO : < 1 mg/mL** (insoluble or slightly soluble)				
References	[1]. Mallon R et al. Antitumor efficacy profile of PKI-402, a dual phosphatidylinositol 3-kinase/mammalian target of rapamycin inhibitor. Mol Cancer Ther. 2010 Apr;9(4):976-84.				

实验参考：	
Cell Assay	MDA-MB-361, MDA-MB-468, T47D, MCF7, BT474, HT29, HCT116, DLD1, U87MG, H157, NCI-H460, A549, NCI-H1975, NCI-H1650, NCI-H2170, KB, 786-0, A498, MIA-PaCa-2, and PC3 cell lines are propagated at 37°C in 5% CO2 incubators in supplier-recommended growth medium. Cell growth inhibition is determined using the CellTiter 96 AQueous proliferation assay. Data are collected after 72 h using a Wallac Victor2 V 1420 multilabel HTS counter. FOXO-GFP translocation in U2OS cells is quantified after 60-min PKI-402 exposure using a Cellomics ArrayScan VTI Reader[1].
Animal Administration	Mice[1] PKI-402 or vehicle is administered by i.v. route. Nude mice bearing MDA-MB-361 tumors are used. Tumor weight is calculated. Pharmacodynamic (biomarker) measurements are done on tumor-bearing female nude mice administered PKI-402. Tumor or normal tissue samples are collected from euthanized animals, homogenized, washed twice with cold (4°C) PBS, and then treated with cell lysis buffer[1].
	Enzyme assays are done in fluorescent polarization (FP) format. Human class I PI3Ks and PI3K-α mutants (E545K and H1047R) are produced in Sf9. GST-GRP1 (murine) is produced in Escherichia

Kinase Assay	coli and isolated by GST-Sepharose. Assay buffers are reaction buffer [20 mM HEPES (pH 7.1), 2 mM MgCl2, 0.05% CHAPS, and 0.01% β-mercaptoethanol] and stop/detection buffer [100 mM HEPES (pH 7.5), 4 mM EDTA, 0.05% CHAPS]. FP reaction is run for 30 min at room temperature in 20 μL of reaction buffer containing 20 μM phosphatidylinositol 4,5-bisphosphate (PIP2), 25 μM ATP, and <4% DMSO (compound solvent). FP reaction is stopped with 20 μL of stop/detection buffer (10 nM probe and 40 nM GST-GRP), and after 2 h, data are collected. Selectivity of PKI-402 is evaluated in the 236 human kinase panel at [ATP]=Km for each enzyme[1].
References	[1]. Mallon R et al. Antitumor efficacy profile of PKI-402, a dual phosphatidylinositol 3-kinase/mammalian target of rapamycin inhibitor. Mol Cancer Ther. 2010 Apr;9(4):976-84.