产品名称：**LY3023414**
产品别名：**LY3023414**

生物活性：

Description	LY3023414 potently and selectively inhibits class I PI3K isoforms, DNA-PK, and mTORC1/2 with IC_{50}s of 6.07 nM, 77.6 nM, 38 nM, 23.8 nM, 4.24 nM and 165 nM for PI3Kα, PI3Kβ, PI3Kδ, PI3Kγ, DNA-PK and mTOR, respectively. LY3023414 potently inhibits mTORC1/2 at low nanomolar concentrations.

IC_{50} & Target						
	PI3Kα	PI3Kβ	PI3Kδ	PI3Kγ	mTOR	mTORC1
	6.07 nM (IC_{50})	77.6 nM (IC_{50})	38 nM (IC_{50})	23.8 nM (IC_{50})	165 nM (IC_{50})	
	mTORC2	DNA-PK				
		4.24 nM (IC_{50})				

In Vitro	In cell-based assays, LY3023414 inhibition of PI3K and mTOR is assessed in the PTEN-deficient U87 MG glioblastoma cell line. LY3023414 inhibits the phosphorylation of Akt at position T308 downstream of PI3K at an IC50 of 106 nM. Similarly, LY3023414 inhibits phosphorylation of Akt at position S473 (IC50=94.2 nM) by mTORC2 as well as phosphorylation of mTORC1 kinase targets p70S6K (position T389; IC50=10.6 nM) and 4E-BP1 (positions T37/46; IC50=187 nM). The downstream phosphorylation of S6RP at positions pS240/244 (IC50=19.1 nM) by p70S6K is inhibited as well, indicating target inhibition along the entire PI3K/Akt/mTOR pathway by LY3023414. Similar IC50 concentrations for PI3K and mTOR phosphorylation targets are observed in other cell lines with activated PI3K/Akt/mTOR pathways. The ability of LY3023414 to inhibit cancer cell proliferation is evaluated in 32 human cancer cell lines from different tumor types in culture after LY3023414 treatment for 2 to 3 cell doublings in dose–response studies. LY3023414 demonstrates potent single-agent activity and IC50 values below 122 nM in half of the cell lines tested[1].
In Vivo	The ability of LY3023414 to inhibit tumor growth is studied in several xenograft models exhibiting mutations or deletions that activate the PI3K/Akt/mTOR pathway. Treatment with LY3023414 at 3, 6, or 10 mg/kg twice daily orally for 28 days results in dose-responsive inhibition of tumor growth in the PTEN-deleted U87 MG xenograft model. This treatment produces similar TGI in models exhibiting PTEN truncation (786-O), activating PI3Kα mutation (NCI-H1975), and transgenic Eμ-myc mutant PI3Kα-driven leukemia models. Of note, the total daily dose of LY3023414 appears to result in equipotent antitumor activity: 12 mg/kg once daily and 6 mg/kg twice daily produces similar delta T/C values (42% and 38%, respectively) in U87 MG[1].

In Vitro:

DMSO : 50 mg/mL (123.01 mM; Need ultrasonic)

Preparing Stock Solutions	Solvent / Mass / Concentration	**1 mg**	**5 mg**	**10 mg**
	1 mM	2.4601 mL	12.3007 mL	24.6015 mL
	5 mM	0.4920 mL	2.4601 mL	4.9203 mL
	10 mM	0.2460 mL	1.2301 mL	2.4601 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：

Solvent&Solubility	——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 (6.15 mM); Clear solution 此方案可获得 ≥ 2.5 mg/mL (6.15 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 (6.15 mM); Clear solution 此方案可获得 ≥ 2.5 mg/mL (6.15 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 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 (6.15 mM); Clear solution 此方案可获得 ≥ 2.5 mg/mL (6.15 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]. Wei L, et al. Genomic profiling is predictive of response to CDDP treatment but not to PI3K inhibition in bladder cancer patient-derived xenografts. Oncotarget. 2016 Nov 22;7(47):76374-76389. [2]. Smith MC, et al. Characterization of LY3023414, a Novel PI3K/mTOR Dual Inhibitor Eliciting Transient Target Modulation to Impede Tumor Growth. Mol Cancer Ther. 2016 Oct;15(10):2344-2356

实验参考：

Cell Assay	The CellTiter-Glo luminescent cell viability assay system is used to measure the antiproliferative effects of LY3023414 after 2 cell doublings on cells plated on plastic or incubated for 2 weeks in soft agar with a collection of standard cell lines and human patient–derived tumor xenografts passaged in nude mice. For the soft-agar assay, RKO and SK-OV-3 cells; MOLT-4 and L-363 cells; DLD-1, HCT-116, HCT-15, and NCI-H460 cells are used. These standard cell lines are genotyped by STR and matched to existing STR reference genotypes. Oncotest PDX models (including model MX1 originally derived at NCI) are characterized using the Affymetrix genome-wide human SNP Array 6.0 as well as whole-exome sequencing. Genetic identity analysis confirm that all PDX models are derived from independent patient samples. Combination studies are conducted in which LY3023414 is mixed with other therapeutic agents in fixed ratios of concentrations corresponding to the IC50 equivalents of each single agent. The combination index at 50% inhibition (CI50) is calculated[1].
Animal Administration	Mice[1] Xenograft tumors are implanted subcutaneously in athymic nude, CD-1 nude mice, and NMRI athymic nude mice. B6.Cg-Tg(IghMyc)22Bri/J mice and C57BL/6NTac mice are used in the Eμ-myc transgenic orthotopic mutant PI3Kα E545K-driven leukemia model similar to the Akt1 E17K cancer model. LY3023414 is formulated in 1% HEC in distilled water containing 0.25% polysorbate 80 and 0.05% Dow-Corning Antifoam 1510-US and administered by oral gavage (final volume 0.2 mL) at the indicated doses and schedules. Efficacy and in vivo target inhibition studies are carried out after

	tumor volumes reach 150 to 200 mm^3. Target inhibition studies are conducted at various time points after administration of a single dose of LY3023414 to mice harboring tumors. Tumors are harvested, flash frozen, lysed in MSD buffer, and then analyzed using the MSD-ELISA multiplex method.
Kinase Assay	The selectivity and inhibitory potential of LY3023414 are assessed against a panel of 192 kinases in PC-3 cell lysates using the KiNativ platform and a panel of 102 kinases as purified enzymes from Cerep. Together, the 2 kinase panels covered approximately 266 unique kinases. These kinases are tested with three concentrations of LY3023414 to measure inhibition and calculate approximate IC50 values. The IC50 of LY3023414 for PI3Kα is measured using 5 nM recombinant human PI3Kα, 0.01 mM ATP with a 1.76 mM Triton X 100/0.04 mM PIP2/0.2 mM PS mixed micelle as the lipid substrate in a scintillation proximity assay (SPA) with neomycin-linked beads. The IC50 of LY3023414 for PI3Kβ is measured using a mixed micelle SPA format with 0.04 mM ATP with a 0.27 mM Triton X 100/0.05 mM PIP2/0.04 mM PA mixed micelle as the lipid substrate. The IC50s of PI3Kδ and PI3Kγand of DNA-PK are measured. The IC50 for mTOR is measured[1].
References	[1]. Wei L, et al. Genomic profiling is predictive of response to CDDP treatment but not to PI3K inhibition in bladder cancer patient-derived xenografts. Oncotarget. 2016 Nov 22;7(47):76374-76389. [2]. Smith MC, et al. Characterization of LY3023414, a Novel PI3K/mTOR Dual Inhibitor Eliciting Transient Target Modulation to Impede Tumor Growth. Mol Cancer Ther. 2016 Oct;15(10):2344-2356