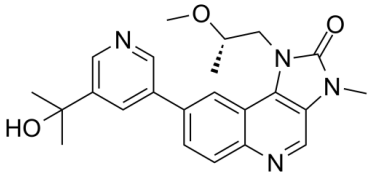
Data Sheet

Product Name:	LY3023414
Cat. No.:	CS-5361
CAS No.:	1386874-06-1
Molecular Formula:	C23H26N4O3
Molecular Weight:	406.48
Target:	Autophagy; DNA-PK; mTOR; PI3K
Pathway:	Autophagy; Cell Cycle/DNA Damage; PI3K/Akt/mTOR
Solubility:	DMSO : 50 mg/mL (123.01 mM; Need ultrasonic)



BIOLOGICAL ACTIVITY:

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. IC50 & Target: IC50: 6.07±3.38 nM (PI3Kα), 77.6±40.1 nM (PI3Kβ), 38 nM (PI3Kδ), 23.8 nM (PI3Kγ), 165±92.5 nM (mTOR), 4.24 nM (DNA-PK)[2]

mTORC1/2[2] **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 IC_{50} of 106 nM. Similarly, LY3023414 inhibits phosphorylation of Akt at position S473 (IC_{50}=94.2 nM) by mTORC2 as well as phosphorylation of mTORC1 kinase targets p70S6K (position T389; IC_{50}=10.6 nM) and 4E-BP1 (positions T37/46; IC_{50}=187 nM). The downstream phosphorylation of S6RP at positions pS240/244 (IC_{50}=19.1 nM) by p70S6K is inhibited as well, indicating target inhibition along the entire PI3K/Akt/mTOR pathway by LY3023414. Similar IC_{50} 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 IC_{50} 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].

PROTOCOL (Extracted from published papers and Only for reference)

Kinase Assay: [1]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 IC_{50} values. The IC_{50} 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 IC_{50} 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 IC_{50}s of PI3Kδ and PI3Kγand of DNA-PK are measured. The IC_{50} for mTOR is measured[1].

Cell Assay: [1]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 IC_{50} equivalents of each single agent. The combination index at 50% inhibition (CI_{50}) is calculated[1].

Animal Administration: LY3023414 is formulated in 1% HEC in distilled water containing 0.25% polysorbate 80 and 0.05% Dow-Corning Antifoam 1510-US[1].[1]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.

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

CAIndexNames:

2H-Imidazo[4,5-c]quinolin-2-one, 1,3-dihydro-8-[5-(1-hydroxy-1-methylethyl)-3-pyridinyl]-1-[(2S)-2-methoxypropyl]-3-methyl-

SMILES:

O=C(N1C[C@@H](OC)C)N(C)C2=C1C3=CC(C4=CC(C(C)(O)C)=CN=C4)=CC=C3N=C2

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