Samotolisib

Cat. No.: HY-12513

CAS No.: 1386874-06-1

Molecular Formula: $C_{23}H_{26}N_4O_3$

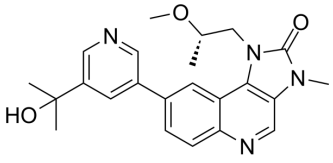
Molecular Weight: 406.48

Target: PI3K; DNA-PK; mTOR; Autophagy

Pathway: PI3K/Akt/mTOR; Cell Cycle/DNA Damage; Autophagy

Storage:

Powder	-20°C	3 years
	4°C	2 years
In solvent	-80°C	2 years
	-20°C	1 year



SOLVENT & SOLUBILITY

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

Please refer to the solubility information to select the appropriate solvent.

In Vivo

1. Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
   Solubility: ≥ 2.5 mg/mL (6.15 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.5 mg/mL (6.15 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (6.15 mM); Clear solution
4. Add each solvent one by one: 5% DMSO >> 40% PEG300 >> 5% Tween-80 >> 50% saline
   Solubility: ≥ 2.5 mg/mL (6.15 mM); Clear solution
5. Add each solvent one by one: 5% DMSO >> 95% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.5 mg/mL (6.15 mM); Clear solution
6. Add each solvent one by one: 1% DMSO >> 99% saline
   Solubility: ≥ 0.5 mg/mL (1.23 mM); Clear solution

BIOLOGICAL ACTIVITY

Description Samotolisib (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. Samotolisib potently inhibits mTORC1/2 at low nanomolar concentrations[1][2].

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

In Vitro

In cell-based assays, Samotolisib (LY3023414) inhibition of PI3K and mTOR is assessed in the PTEN-deficient U87 MG glioblastoma cell line. Samotolisib inhibits the phosphorylation of Akt at position T308 downstream of PI3K at an IC_{50} of 106 nM. Similarly, Samotolisib 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 Samotolisib. 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 Samotolisib to inhibit cancer cell proliferation is evaluated in 32 human cancer cell lines from different tumor types in culture after Samotolisib treatment for 2 to 3 cell doublings in dose–response studies. Samotolisib demonstrates potent single-agent activity and IC_{50} values below 122 nM in half of the cell lines tested[1].

MCE has not independently confirmed the accuracy of these methods. They are for reference only.

In Vivo

The ability of Samotolisib (LY3023414) to inhibit tumor growth is studied in several xenograft models exhibiting mutations or deletions that activate the PI3K/Akt/mTOR pathway. Treatment with Samotolisib 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 Samotolisib 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].

MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Cell Assay [1]

The CellTiter-Glo luminescent cell viability assay system is used to measure the antiproliferative effects of Samotolisib 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 Samotolisib 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].

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Animal Administration [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. Samotolisib 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 Samotolisib to mice harboring tumors. Tumors are harvested, flash frozen, lysed in MSD buffer, and then analyzed using the MSD-ELISA multiplex method.

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CUSTOMER VALIDATION

- Front Pharmacol. 2020 Nov 11;11:580407.
- Arch Pharm (Weinheim). 2024 Sep;357(9):e2400066.
- Gynecol Oncol. 2021 Jun 25;S0090-8258(21)00495-9.
- Toxicol Appl Pharmacol. 2024 Apr 28:486:116945.
- J Surg Res. 2022 Oct 20;282:137-146.

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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

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