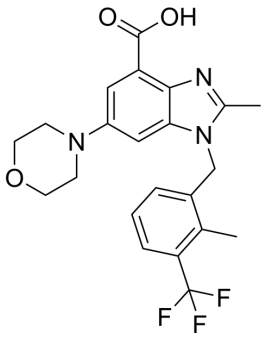
GSK2636771



Cat. No.:	HY-15245
CAS No.:	1372540-25-4
Molecular Formula:	$C_{22}H_{22}F_3N_3O_3$
Molecular Weight:	433.42
Target:	PI3K
Pathway:	PI3K/Akt/mTOR
Storage:	Powder -20°C 3 years 4°C 2 years In solvent -80°C 1 year -20°C 6 months

SOLVENT & SOLUBILITY

In Vitro

DMSO : 16.67 mg/mL (38.46 mM; ultrasonic and warming and heat to 60°C)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	2.3072 mL	11.5362 mL	23.0723 mL
	5 mM	0.4614 mL	2.3072 mL	4.6145 mL
	10 mM	0.2307 mL	1.1536 mL	2.3072 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 (5.77 mM); Suspended solution; Need ultrasonic
2. Add each solvent one by one: 50% PEG300 >> 50% saline
   Solubility: 1.67 mg/mL (3.85 mM); Suspended solution; Need ultrasonic

BIOLOGICAL ACTIVITY

Description

GSK2636771 is a potent, selective and orally bioavailable inhibitor of PI3Kβ with a K_i of 0.89 nM and an IC_{50} of 5.2 nM, showing 900-fold selectivity over p110α and p110γ, and 10-fold selectivity over p110δ isoforms.

IC_{50} & Target		
	PI3Kβ 0.89 nM (Ki)	PI3Kβ 5.2 nM (IC_{50})

In Vitro

GSK2636771 treatment causes cell viability significantly more decreased in the control cells (p110β-reliant PTEN-deficient PC3 prostate and BT549 and HCC70 breast cancer cell lines) than in PTEN-mutant and PTEN wild-type EEC cells. Inhibition of p110β by GSK2636771 or AZD6482 leads to a marked decrease of AKT phosphorylation only in the control prostate and breast cancer cell lines, whereas only marginal effects on AKT activation are observed in EEC cells[1].

	MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	GSK2636771 is a p110β inhibitor, and the p110β primes cells for response to growth factor stimulation. While p110β inhibition suppresses cell and tumor growth, dual targeting of p110α/β enhances apoptosis and provides sustained tumor response in mice model[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Cell Assay [1]	Cells are plated in 96-well microtiter plates at densities ranging from 1,500 to 15,000 cells/well, optimized for untreated control cells to be 80-90% confluent at the endpoint of the experiment. After 24 h, cells are treated with serial dilutions (100 pM to 10 μM) of the PI3K pathway inhibitors GDC-0941, A66, TGX-221, GSK2636771, AZD6482, CCI-779, AZD8055, PF-04691502, and of the MAPK pathway inhibitors AZD6244, PD0325901, AZD628, and PLX4032. Cell viability is assessed after 72 h of treatment by incubation with CellTiter Blue for 1.5 h. The drug concentration required for survival of 50% of cells relative to untreated cells is determined using GraphPad Prism version 5.0 d. Cell lines that fail to achieve the SF50 to a given drug are nominally assigned as the highest concentration screened (10 μM). At least three independent experiments in triplicate per cell line/targeted drug are performed. Association between a mutation and response to a targeted agent is determined using a Fisher's exact test, and a two-tailed P value. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Sci Transl Med. 2018 Jul 18;10(450):eaaq1093.
- Sci Signal. 2021 Dec 21;14(714):eabj0057.
- Mol Pharmacol. 2016 Dec;90(6):726-737.
- Mol Cell Neurosci. 2021 Dec 3;103691.
- Biochem Biophys Res Commun. 2022.

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REFERENCES

[1]. Weigelt B, et al. PI3K pathway dependencies in endometrioid endometrial cancer cell lines. Clin Cancer Res. 2013, 19(13), 3533-3544.

[2]. Hosford SR, et al. Combined inhibition of both p110α and p110β isoforms of phosphatidylinositol 3-kinase is required for sustained therapeutic effect in PTEN-deficient, ER+ breast cancer. Clin Cancer Res. 2016 Nov 30

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