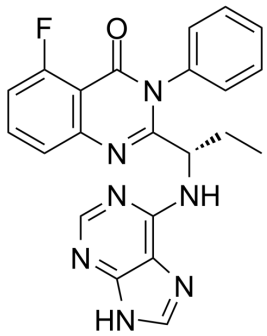
Idelalisib



Cat. No.:	HY-13026
CAS No.:	870281-82-6
Molecular Formula:	$C_{22}H_{18}FN_7O$
Molecular Weight:	415
Target:	PI3K; Autophagy
Pathway:	PI3K/Akt/mTOR; Autophagy
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 : ≥ 59.7 mg/mL (143.86 mM)

* "≥" means soluble, but saturation unknown.

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	2.4096 mL	12.0482 mL	24.0964 mL
5 mM	0.4819 mL	2.4096 mL	4.8193 mL
10 mM	0.2410 mL	1.2048 mL	2.4096 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 (6.02 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.5 mg/mL (6.02 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (6.02 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Idelalisib (CAL-101; GS-1101) is a highly selective and orally bioavailable p110δ inhibitor with an IC_{50} of 2.5 nM, showing 40- to 300-fold selectivity for p110δ over other PI3K class I enzymes.

IC_{50} & Target

p110δ 2.5 nM (IC_{50})	p110γ 89 nM (IC_{50})	p110β 565 nM (IC_{50})	p110α 820 nM (IC_{50})
hVps34	DNA-PK		

	978 nM (IC_{50})	6729 nM (IC_{50})

In Vitro

Idelalisib (CAL-101; GS-1101) is a highly selective and potent p110δ inhibitor (EC_{50}=8 nM). Greater selectivity (400- to 4000-fold) is seen against related kinases C2β, hVPS34, DNA-PK, and mTOR, whereas no activity is observed against a panel of 402 diverse kinases at 10 μM. CAL-101 reduces PDGF-induced pAkt by only 25% at 10 μM. Idelalisib (CAL-101) inhibits LPA-induced pAkt with an EC_{50} of 1.9 μM. Idelalisib (CAL-101) blocks FcεRI p110δ-mediated CD63 expression with an EC_{50} of 8 nM, whereas formyl-methionyl-leucyl-phenylalanine activation of p110γ is inhibited with an EC_{50} of 3 μM. Thus, in cell-based assays, CAL-101 has 240- to 2500-fold selectivity for p110δ over the other class I PI3K isoforms[1]. CAL-101Idelalisib (CAL-101)-induced apoptosis of chronic lymphocytic leukemia (CLL) cells is significant compare with vehicle treatment alone (P<0.001). Idelalisib (CAL-101) induces selective cytotoxicity in CLL cells independent of IgVH mutational status or interphase cytogenetics[2].

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

In Vivo

A significant reduction is observed in the $CD11b^{+}Ly6G^{+}$ neutrophils from brain homogenates of both$p110\delta^{D910A/D910A}$ mice and Idelalisib (CAL-101) (40 mg/kg, i.v.) post-treated mice[3].

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PROTOCOL

Cell Assay [2]

MTT assays are performed to determine cytotoxicity. Briefly, 1×10^5 cells (CLL B cells or healthy volunteer T cells or NK cells) are incubated for 48 hours with different concentrations of Idelalisib (CAL-101) (0.1 μM, 1 μM, 5 μM, 10 μM), 25 μM LY294002, or vehicle control. MTT reagent is then added. DMSO is added, and absorbance is measured by spectrophotometry at 540 nm in a Labsystems plate reader. Cell viability is also measured at various time points with the use of annexin/PI flow cytometry. Data are analyzed with Expo-ADC32 software package. At least 10,000 cells are counted for each sample. Results are expressed as the percentage of total positive cells over untreated control. Experiments examining caspase-dependent apoptosis included the addition of 100 μM Z-VAD. Experiments examining survival signals include the addition of 1 μg/mL CD40L, 800 U/mL IL-4, 50 ng/mL BAFF, 20 ng/mL TNF-α, or coculturing on fibronectin or stromal (HS-5 cell line) coated plates. Stromal coculture is done by plating a 75-cm2 flask (80%-100% confluent) per 6-well plate 24 hours before the addition of CLL cells[2].

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Animal Administration [3]

Mice[3]

For Idelalisib (CAL-101) treatment, wild-type C57BL/6 mice are administered either 40 mg/kg Idelalisib (CAL-101) or vehicle DMSO, by 25 μL infusion into the femoral vein, 15 min before I/R (pre-treatment), or 3 and 6 h after initiation of reperfusion (post-treatment). Controls and animals treated with Idelalisib (CAL-101) underwent cerebral blood flow (CBF) measurements using a laser Doppler perfusion monitor. The CBF measurements obtained immediately before and after MCAO and again at 3 h after reperfusion showed an ~90-95% reduction in the blood flow to the MCAO infarct region, which does not differ between groups.

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

CUSTOMER VALIDATION

- Cancer Cell. 2023 Jun 12;41(6):1103-1117.e12.
- Mol Cancer. 2022 Feb 4;21(1):35.
- Sci Transl Med. 2018 Jul 18;10(450):eaaq1093.
- Clin Cancer Res. 2018 Mar 1;24(5):1103-1113.
- Exp Hematol Oncol. 2016 Jul 29;5:22.

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REFERENCES

[1]. Lannutti BJ, et al. CAL-101, a p110delta selective phosphatidylinositol-3-kinase inhibitor for the treatment of B-cell malignancies, inhibits PI3K signaling and cellular viability. Blood, 2011, 117(2), 591-594.

[2]. Herman SE, et al. Phosphatidylinositol 3-kinase-δ inhibitor CAL-101 shows promising preclinical activity in chronic lymphocytic leukemia by antagonizing intrinsic and extrinsic cellular survival signals. Blood, 2010, 116(12), 2078-2088.

[3]. Low PC, et al. PI3Kδ inhibition reduces TNF secretion and neuroinflammation in a mouse cerebral stroke model. Nat Commun. 2014 Mar 14;5:3450.

[4]. Cooney J, et al. Synergistic targeting of the regulatory and catalytic subunits of PI3Kδ in mature B cell malignancies. Clin Cancer Res. 2018 Mar 1;24(5):1103-1113.

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