CAL-130 Hydrochloride

Cat. No.: HY-16122B

CAS No.: 1431697-78-7

Molecular Formula: $C_{23}H_{23}ClN_8O$

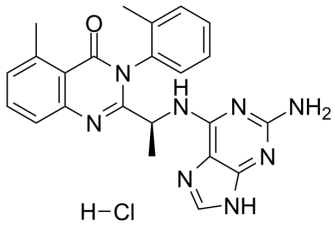
Molecular Weight: 462.93

Target: PI3K

Pathway: PI3K/Akt/mTOR

Storage: 4°C, sealed storage, away from moisture

* In solvent : -80°C, 6 months; -20°C, 1 month (sealed storage, away from moisture)



SOLVENT & SOLUBILITY

In Vitro

DMSO : 50 mg/mL (108.01 mM; Need ultrasonic)

H_2O : < 0.1 mg/mL (ultrasonic;warming;heat to 60°C) (insoluble)

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	2.1602 mL	10.8008 mL	21.6015 mL
5 mM	0.4320 mL	2.1602 mL	4.3203 mL
10 mM	0.2160 mL	1.0801 mL	2.1602 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: ≥ 3 mg/mL (6.48 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 3 mg/mL (6.48 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 3 mg/mL (6.48 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

CAL-130 is a PI3Kδ and PI3Kγ inhibitor with IC_{50}s of 1.3 and 6.1 nM, respectively.

IC_{50} & Target

p110δ	p110γ	p110β	p110α
1.3 nM (IC_{50})	6.1 nM (IC_{50})	56 nM (IC_{50})	115 nM (IC_{50})

In Vitro

CAL-130 preferentially inhibits the function of both p110γ and p110δ catalytic domains. IC_{50} values of CAL-130 are 1.3 and 6.1 nM for p110δ and p110γ, respectively, as compared to 115 and 56 nM for p110α and p110β. CAL-130 does not inhibit additional intracellular signaling pathways (i.e., p38 MAPK or insulin receptor tyrosine kinase) that are critical for general cell

	function and survival[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	The clinical significance of interfering with the combined activities of PI3Kγ and PI3Kδ is determined by administering CAL-130 to Lck/Pten$^{fl/fl}$ mice with established T cell acute lymphoblastic leukemia (T-ALL). Candidate animals for survival studies are ill appearing, have a white blood cell (WBC) count above 45,000 μL^{-1}, evidence of blasts on peripheral smear, and a majority of circulation cells (>75%) staining double positive for Thy1.2 and Ki-67. Mice receive an oral dose (10 mg/kg) of CAL-130 every 8 hr for a period of 7 days and are then followed until moribund. Despite the limited duration of therapy, CAL-130 is highly effective in extending the median survival for treated animals to 45 days as compared 7.5 days for the control group[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Kinase Assay [1]	IC_{50} values for CAL-130 inhibition of PI3K isoforms are determined in ex vivo PI3 kinase assays using recombinant PI3K. A ten-point kinase inhibitory profile is determined with ATP at a concentration consistent with the K_M for each enzyme[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Cell Assay [1]	Cell proliferation of CCRF-CEM cells or shRNA-transfected CCRF-CEM cells, in presence or absence of CAL-130 (1, 2.5 and 5 μM), is followed by cell counting of samples in triplicate using a hemocytometer and trypan blue. For apoptosis determinations of untransfected or shRNA-transfected CCRF-CEMs, cells are stained with APC-conjugated Annexin-V in Annexin Binding Buffer and analyzed by flow cytometry. For primary T-ALL samples, cell viability is assessed using the BD Cell Viability kit coupled with the use of fluorescentcounting beads. For this, cells are plated with MS5-DL1 stroma cells, and after 72 hr following CAL-130 treatment, cells are harvested and stained with an APC-conjugated antihuman CD45 followed by a staining with the aforementioned kit[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [1]	Mice[1] For subcutaneous xenograft experiments, luminescent CCRF-CEM (CEMluc) cells are generated by lentiviral infection with FUW-luc and selection with Neomycin. Luciferase expression is verified with the Dual-Luciferase Reporter Assay kit. 2.5×10^6 CEM-luc cells embedded in Matrigel are injected in the flank of NOD.Cg-***Prkdc^{scid} Il2rg^{tm1Wjl}***/Sz mice. After 1 week, mice are treated by oral gavage with vehicle (0.5% methyl cellulose, 0.1% Tween 80), or CAL-130 (10 mg/kg) every 8 hr daily for 4 days , and then tumors are imaged as follows: mice anesthetized by isoflurane inhalation are injected intraperitoneally with D-luciferin (50 mg/kg). Photonic emission is imaged with the in vivo imaging system. Tumor bioluminescence is quantified by integrating the photonic flux (photons per second) through a region encircling each tumor using the Living Image software package. Administration of D-luciferin and detection of tumor bioluminescence in Lck/Pten$^{fl/fl}$/Gt(ROSA)26Sor$^{tm1(Luc)Kael}$/J mice are performed in a similar manner. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

REFERENCES

[1]. Subramaniam Prem S, et al. Targeting nonclassical oncogenes for therapy in T-ALL. Cancer cell (2012), 21(4), 459-72.

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