Product Data Sheet

Product Name: CAL-130
Cat. No.: GC35579

Chemical Properties

Cas. No.	1431697-74-3		
SMILES	O=C1N(C2=CC=CC=C2C)C([C@H](C)NC3=C4N=CNC4=NC(N)=N3)=NC5=C1C(C)=CC=C5		
Formula	$C_{23}H_{22}N_8O$	M.Wt	426.47
Solubility	Soluble in DMSO	Storage	Store at -20°C
General tips	For obtaining a higher solubility , please warm the tube at 37 ℃ and shake it in the ultrasonic bath for a while.Stock solution can be stored below -20℃ for several months.		
Shipping Condition	Evaluation sample solution : ship with blue ice All other available size: ship with RT , or blue ice upon request.		
Structure	CAL-130		

Protocol

Kinase experiment: IC50 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 KM for each enzyme[1].

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Cell experiment: 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].

Animal experiment: 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. 2.5×106 CEM-luc cells embedded in Matrigel are injected in the flank of NOD.Cg-Prkdcscid Il2rgtm1Wjl/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/Ptenfl/fl/Gt(ROSA)26Sortm1(Luc)Kael/J mice are performed in a similar manner.

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References:

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

Background

CAL-130 is a PI3Kδ and PI3Kγ inhibitor with IC50s of 1.3 and 6.1 nM, respectively. p110δ|1.3 nM (IC50)|p110γ|6.1 nM (IC50)|p110β|56 nM (IC50)|p110α|115 nM (IC50)

CAL-130 preferentially inhibits the function of both p110γ and p110δ catalytic domains. IC50 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].

The clinical significance of interfering with the combined activities of PI3Kγ and PI3Kδ is determined by administering CAL-130 to Lck/Ptenfl/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].

[1]. Subramaniam Prem S, et al. Targeting nonclassical oncogenes for therapy in T-ALL.

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