Product Data Sheet

Product Name: CAY10594
Cat. No.: GC18691

Chemical Properties

Cas. No.	1130067-34-3		
Chemical Name	N-[2-(4-oxo-1-phenyl-1,3,8-triazaspiro[4,5]dec-8-yl)ethyl]-2-naphthalenecarboxamide		
SMILES	O=C(NCCN1CCC2(C(NCN2C3=CC=CC=C3)=O)CC1)C4=CC(C=CC=C5)=C5C=C4		
Formula	$C_{26}H_{28}N_4O_2$	M.Wt	428.5
Solubility	DMF: 20 mg/ml,DMSO: 20 mg/ml,DMSO:PBS(pH7.2) (1:1): 0.5 mg/ml	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	CAY10594		

Protocol

Cell experiment [1]:

Cell lines	Human RPMI 8226 multiple myeloma B cells and human A431 skin epithelial carcinoma cells
Preparation Method	Human RPMI 8226 multiple myeloma B cells and human A431 skin epithelial carcinoma cells were maintained in complete RPMI-1640 medium at 37 °C and 95 % air/5 % CO2. HEK-293 cells were maintained in complete DMEM/F12 medium. Cells in NaCl medium were pre-incubated at 37 °C for 15 min in the presence of DMSO, or 10 μM CAY10593, CAY10594 or halopemide.

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Reaction Conditions	10 μM for 500 seconds
Applications	The PLD1 antagonist CAY10593 and to a lesser extent the PLD2 antagonist CAY10594 (both at 10 μM) significantly impaired ATP-induced CD23 shedding. The non-selective PLD antagonist and structural analogue of CAY10593, halopemide (10 μM) however had no significant effect on ATP-induced CD23 shedding. In the absence of ATP, no antagonist significantly altered cell-surface expression of CD23 compared to control-treated cells.

Animal experiment [2]:

Animal models	C57BL/6 mice
Preparation Method	Mice were fasted for 16 hours before APAP injection. APAP (500 mg/kg) was administered with oral gavage in mice. CAY10594 was dissolved in 1% DMSO and intraperitoneally administered to mice 30 minutes prior to APAP injection for examining protective effects or after 3 hours from APAP challenge for investigating therapeutic effects of CAY10594.
Dosage form	4/8/mg/kg

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Applications	Injection of APAP (500 mg/kg) caused marked liver injury, which was measured by hematoxylin and eosin staining of the livers. APAP-induced liver injury was almost completely blocked by the administration of a CAY10594 in a dose-dependent manner. APAP-induced hepatocyte death was measured by the TUNEL assay. Hepatocyte apoptosis was induced by APAP, which was also markedly decreased in CAY10594-administered mice compared with vehicle-treated mice. The protective effects of the CAY10594 against hepatocyte apoptosis were strongly induced at 4 or 8 mg/kg.

References:

[1]. Pupovac A, Stokes L, Sluyter R. CAY10593 inhibits the human P2X7 receptor independently of phospholipase D1 stimulation[J]. Purinergic Signalling, 2013, 9(4): 609-619.
[2]. Lee S K, Bae G H, Kim Y S, et al. A phospholipase D2 inhibitor, CAY10594, ameliorates acetaminophen-induced acute liver injury by regulating the phosphorylated-GSK-3β/JNK axis[J]. Scientific Reports, 2019, 9(1): 1-10.

Background

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CAY10594 is an effective inhibitor of phospholipase D2 (PLD2) (IC50 140 nm in vitro and 110 nm in cells). Cay10594 highly inhibits the invasive migration of breast cancer cells in vitro and regulates the phosphorylation of GSK-3 β/ JNK axis ameliorates paracetamol induced acute liver injury.

CAY10594 significantly improved intestinal mucosal inflammation, which was characterized by higher survival rate, slight decrease in body weight, less or no bloody stool and lower pathological score level,compared with the control group. RNA was extracted from colon tissue to detect the expression of cytokines, as well as proinflammatory cytokines, such as TNF- α? IL-6, IL-23 and IL-1 β It was found that PLD2 was significantly decreased after blocking in DSS induced colitis, while anti-inflammatory cytokines were significantly increased after inhibiting PLD2. In addition, fresh colon samples were also obtained and cultured in vitro for 24 hours; The supernatant was collected to detect cytokines by ELISA. Proinflammatory cytokines (e.g., IL-17A, TNF- α and IL-1 β) [1] While anti-inflammatory cytokines (for example, IL-10 was found to increase after PLD2 blockade), indicating that PLD2 blockade can improve intestinal mucosal inflammation [2].

CAY10594 induced a strong therapeutic effect in APAP challenged mice. The results show that PLD2 plays an important role in mediating APAP induced liver injury [3]. Because PLD2 has basic activity, the administration of cay10594 will block the production of PLD2 enzyme active product PA in an experimental acute liver injury model. Therefore, it is reasonable to assume that the protective and therapeutic effects of cay10594 in the acute liver injury model will be mediated by blocking the production of PA. Cay10594 may regulate early liver pathology to prevent APAP induced liver injury by rapidly restoring GSH levels without affecting antioxidant gene expression [4].

References:

[1] Lee S K, Kim S D, Kook M, et al. Phospholipase D2 drives mortality in sepsis by inhibiting neutrophil extracellular trap formation and down-regulating CXCR2[J]. Journal of Experimental Medicine, 2015, 212(9): 1381-1390.
[2] Zhou G, Yu L, Yang W, et al. Blockade of PLD2 ameliorates intestinal mucosal inflammation of inflammatory bowel disease[J]. Mediators of inflammation, 2016, 2016.
[3] Mitchell J R, Jollow D J, Potter W Z, et al. Acetaminophen-induced hepatic necrosis. I. Role of drug metabolism[J]. Journal of Pharmacology and Experimental Therapeutics, 1973, 187(1): 185-194.
[4] Lee S K, Bae G H, Kim Y S, et al. A phospholipase D2 inhibitor, CAY10594, ameliorates

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