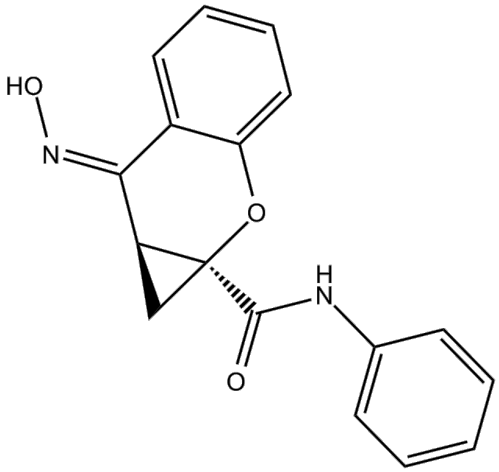
Product Data Sheet

Product Name: PHCCC
Cat. No.: GC17383

Chemical Properties

Cas. No.	179068-02-1		
Chemical Name	(1aS,7aS,Z)-7-(hydroxyimino)-N-phenyl-1,1a,7,7a-tetrahydrocyclopropa[b]chromene-1a-carboxamide		
SMILES	O=C([C@]1([C@H]/2C1)OC3=CC=CC=C3C2=N/O)NC4=CC=CC=C4		
Formula	$C_{17}H_{14}N_2O_3$	M.Wt	294.31
Solubility	Soluble in DMSO	Storage	Store at -20°C
General tips	For obtaining a higher solubility , please warm the tube at 37 °C and shake it in the ultrasonic bath for a while.Stock solution can be stored below -20°C 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



Protocol

Cell experiment [1]:

Cell lines D283med cells

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Preparation Method	D283med cells were cultured in Dulbecco's modified Eagle's medium/Nutrient Mix F12 supplemented with 10% fetal bovine serum, 100U/ml penicillin, and 100μg/ml streptomycin at 37°C with 5% CO_2 and 95% saturated atmospheric humidity. Cells were seeded into 96-well microplates at a density of 3×10^4 cells/well. After 24h, cells were serum starved for 16-18h and challenged with different concentrations of PHCCC (0, 0.3, 3, 10, and 30μM) for 24h. [^{3}H]Thymidine (1μCi/well) was added for the last 16-18h. The DNA synthesis in D283med cells was analyzed.
Reaction Conditions	0, 0.3, 3, 10, and 30μM; 24h
Applications	PHCCC treatment significantly reduced DNA synthesis in D283med cells in a dose-dependent manner.

Animal experiment [2]:

Animal models	C57B6/J mice
Preparation Method	C57B6/J mice, 7 weeks old, were maintained under a 12-h light and 12-h dark cycle at a temperature of 25°C and humidity of 50%±10%, free with water and diet. OS18 cells were mixed with 1:1 Matrigel: Minimum Essential medium, and a total volume of 100μl (10^6 cells) was injected subcutaneously in the flank. Mice were monitored for tumor growth relative to the adjacent non-tumor cell-injected leg. One week later, a 10mg/kg dose of PHCCC was intraperitoneally injected every other day for 20 days. The tumor growth and body weight of the mice were analyzed.
Dosage form	10mg/kg; every other day for 20 days; i.p.

Caution: Product has not been fully validated for medical applications. For research use only.
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Applications	PHCCC significantly inhibited tumor growth in the OS18 xenograft mouse model without affecting the body weight.

References:
[1] Iacovelli L, Arcella A, Battaglia G, et al. Pharmacological activation of mGlu4 metabotropic glutamate receptors inhibits the growth of medulloblastomas[J]. Journal of Neuroscience, 2006, 26(32): 8388-8397.
[2] Kansara M, Thomson K, Pang P, et al. Infiltrating myeloid cells drive osteosarcoma progression via GRM4 regulation of IL23[J]. Cancer discovery, 2019, 9(11): 1511-1519.

Background

PHCCC is a group I mGluR antagonist with an IC_{50} value of 3μM [1]. PHCCC acts as the small molecule glutamate receptor enhancer, altering the functions of dendritic cells to metabolize glutamate, skewing cytokine secretion to bias T cell function [2]. PHCCC has been widely used to activate the mGlu6 receptor and regulate the natural calcium current in the sympathetic neurons isolated from the superior cervical ganglia of rats[3].

In vitro, PHCCC treatment (30μM) for 5 minutes significantly reduced the activity of the PI-3-K pathway in D283med cells and DAOY cells, and inhibited cAMP production[4]. In the presence of 1μM retinoic acid (RA), treatment with PHCCC (30μM) for 4 days enhanced the differentiation of mouse embryonic stem cells into neuronal lineage cells, resulting in increased expression of early neural markers Dlx-2 and Nestin[5].

In vivo, PHCCC treatment via a single intracerebroventricular injection (75nmol/2.5μl) for 30 minutes significantly reversed the movement disorders induced by reserpine in rats [6]. Intraperitoneal injection of PHCCC at a dose of 10mg/kg every other day for 20 days significantly inhibited tumor growth in the OS18 xenograft mouse model without affecting the body weight of the mice[7]. Subcutaneous injection of PHCCC at a dose of 3mg/kg every three days for 18 days significantly delayed disease progression and alleviated disease severity in mice with experimental autoimmune encephalomyelitis[8].

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References:

[1] Recasens M, Guiramand J, Aimar R, et al. Metabotropic glutamate receptors as drug targets[J]. Current Drug Targets, 2007, 8(5): 651-681.
[2] Fallarino F, Volpi C, Fazio F, et al. Metabotropic glutamate receptor-4 modulates adaptive immunity and restrains neuroinflammation[J]. Nature medicine, 2010, 16(8): 897-902.
[3] Beqollari D, Kammermeier P J. The mGlu4 receptor allosteric modulator N-phenyl-7-(hydroxyimino) cyclopropa [b] chromen-1a-carboxamide acts as a direct agonist at mGlu6 receptors[J]. European journal of pharmacology, 2008, 589(1-3): 49-52.
[4] Iacovelli L, Arcella A, Battaglia G, et al. Pharmacological activation of mGlu4 metabotropic glutamate receptors inhibits the growth of medulloblastomas[J]. Journal of Neuroscience, 2006, 26(32): 8388-8397.
[5] Sarichelou I, Cappuccio I, Ferranti F, et al. Metabotropic glutamate receptors regulate differentiation of embryonic stem cells into GABAergic neurons[J]. Cell Death & Differentiation, 2008, 15(4): 700-707.
[6] Marino M J, Williams Jr D L, O'Brien J A, et al. Allosteric modulation of group III metabotropic glutamate receptor 4: a potential approach to Parkinson's disease treatment[J]. Proceedings of the National Academy of Sciences, 2003, 100(23): 13668-13673.
[7] Kansara M, Thomson K, Pang P, et al. Infiltrating myeloid cells drive osteosarcoma progression via GRM4 regulation of IL23[J]. Cancer discovery, 2019, 9(11): 1511-1519.
[8] Gammon J M, Tostanoski L H, Adapa A R, et al. Controlled delivery of a metabolic modulator promotes regulatory T cells and restrains autoimmunity[J]. Journal of Controlled Release, 2015, 210: 169-178.

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