CB-1158 dihydrochloride

Cat. No.: HY-101979A

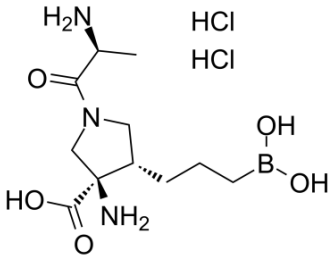
Molecular Formula: $C_{11}H_{24}BCl_2N_3O_5$

Molecular Weight: 360.04

Target: Arginase

Pathway: Immunology/Inflammation; Metabolic Enzyme/Protease

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

H_2O : 120 mg/mL (333.30 mM; Need ultrasonic)
DMSO : 55 mg/mL (152.76 mM; Need ultrasonic)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	2.7775 mL	13.8873 mL	27.7747 mL
	5 mM	0.5555 mL	2.7775 mL	5.5549 mL
	10 mM	0.2777 mL	1.3887 mL	2.7775 mL

Please refer to the solubility information to select the appropriate solvent.

In Vivo

1. Add each solvent one by one: 1% DMSO >> 99% saline
   Solubility: ≥ 0.27 mg/mL (0.75 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: 3.25 mg/mL (9.03 mM); Suspended solution; Need ultrasonic
3. Add each solvent one by one: 5% DMSO >> 40% PEG300 >> 5% Tween-80 >> 50% saline
   Solubility: ≥ 2.75 mg/mL (7.64 mM); Clear solution
4. Add each solvent one by one: 5% DMSO >> 95% (20% SBE-β-CD in saline)
   Solubility: ≥ 1.38 mg/mL (3.83 mM); Clear solution
5. Add each solvent one by one: PBS
   Solubility: 100 mg/mL (277.75 mM); Clear solution; Need ultrasonic

BIOLOGICAL ACTIVITY

Description

CB-1158 dihydrochloride (INCB01158 dihydrochloride) is a potent and orally active inhibitor of arginase, with IC_{50}s of 86 nM and 296 nM for recombinant human arginase 1 and recombinant human arginase 2, respectively. Immuno-oncology agent[1].

IC_{50} & Target	IC50: 86 nM (Arginase 1), 296 nM (Arginase 2)[1]
In Vitro	CB-1158 dihydrochloride is a potent and orally-bioavailable inhibitor of arginase, with IC_{50}s of 86 and 296 nM for recombinant human arginase 1 and 2, respectively. CB-1158 inhibits native rginase 1 (Arg1) in human granulocyte, erythrocyte, and hepatocyte lysate with IC_{50}s of 178 nM, 116 nM and 158 nM, respectively, and blocks Arg1 in cancer patient plasma (IC_{50}, 122 nM). CB-1158 also exhibits potent inhibitory activity against arginase in human HepG2, K562 cell lines and primary human hepatocytes with IC_{50}s of 32, 139, 210 μM, respectively. CB-1158 shows no effect on NOS. In addition, CB-1158 is not directly cytotoxic to murine cancer cell lines[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	CB-1158 (100 mg/kg, p.o., twice per day) increases the number of tumor-infiltrating cytotoxic cells and decreases myeloid cells in mice. CB-1158 in combination with PD-L1 blockade or LY 188011 inhibits tumor growth in mice bearing CT26 cancer cells[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Cell Assay [1]	Intracellular arginase activity is determined for the arginase-expressing HepG2 and K-562 cell lines as follows. HepG2 cells are seeded at 100,000 cells per well one day prior to treatment with CB-1158. K-562 cells are seeded at 200,000 cells per well on the day of CB-1158 treatment. Cells are treated with a dose-titration of CB-1158 in SILAC RPMI-1640 media containing 5% heat-inactivated and dialyzed FBS, antibiotics/anti-mycotic, 10 mM L-arginine, 0.27 mM L-lysine, and 2 mM L-glutamine. The medium is harvested after 24 h and urea generated is determined. Wells containing media without cells are used as background controls. For assessing the effect of CB-1158 on Arg1 in primary hepatocytes, frozen human hepatocytes are thawed, allowed to adhere onto collagen-coated wells for 4 h, and then incubated for 48 h in SILAC-RPMI containing 10 mM L-ornithine, no L-arginine, and a dose-titration of CB-1158, at which time the media are analyzed for urea[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [1]	Mice[1] For the 4T1 tumor model, 10^5 cells are injected orthotopically into the mammary fat pad; for all other tumor models, 10^6 cells are injected subcutaneously (s.c.) in the right flank. For all studies, CB-1158 is administered by oral gavage twice per day at 100 mg/kg starting on study day 1 (1 day after tumor implant). Control groups receive vehicle (water) twice daily by gavage. Tumor volume measured by digital caliper (length × width × width/2) and body weight are recorded three times per week. Mice are euthanized when tumors necrotize or volumes reach 2000 mm^3. For the CT26 model, anti-PD-L1 antibody (5 mg/kg) is injected intraperitoneally (i.p.) on days 5, 7, 9, 11, 13, and 15. For the 4T1 model, anti-CTLA-4 antibody (5 mg/kg) is injected i.p. on days 2, 5, and 8; anti-PD-1 antibody (5 mg/kg) is injected i.p. on days 3, 6, and 9. 4T1 tumors are harvested on study day 25 into Fekete's solution and tumor nodules are enumerated visually. LY 188011 is dosed 50 mg/kg i.p. on days 10 and 16 for the CT26 model, 60 mg/kg i.p. on days 6 and 10 for the LLC model, or 30 mg/kg i.p. on day 5 for the 4T1 model. With these regimens, LY 188011 modestly reduces tumor growth and spares most tumor-infiltrating immune cells, allowing for the evaluation of combination activity with CB-1158[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- J Physiol. 2020 Nov;598(21):4907-4925.

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REFERENCES

[1]. Steggerda SM, et al. Inhibition of arginase by CB-1158 blocks myeloid cell-mediated immune suppression in the tumor microenvironment. J Immunother Cancer. 2017 Dec 19;5(1):101.

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