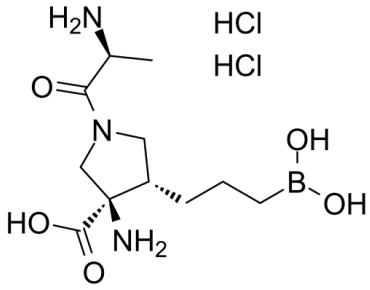
Data Sheet

Product Name:	CB-1158 (dihydrochloride)
Cat. No.:	CS-0047528
Molecular Formula:	C11H24BCl2N3O5
Molecular Weight:	360.04
Target:	Arginase
Pathway:	Immunology/Inflammation; Metabolic Enzyme/Protease
Solubility:	DMSO : < 1 mg/mL (insoluble or slightly soluble); H2O : ≥ 50 mg/mL (138.87 mM)



BIOLOGICAL ACTIVITY:

CB-1158 dihydrochloride (INCB01158 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. IC50 & 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]. **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 gemcitabine inhibits tumor growth in mice bearing CT26 cancer cells[1].

PROTOCOL (Extracted from published papers and Only for reference)

Cell Assay: CB-1158 is dissolved in ultrapure water[1].[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].

Animal Administration: CB-1158 is dissolved in ultrapure water[1].[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. Gemcitabine 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, gemcitabine modestly reduces tumor growth and spares most tumor-infiltrating immune cells, allowing for the evaluation of combination activity with CB-1158[1].

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.

CAIndexNames:

CB-1158 (dihydrochloride)

SMILES:

O=C([C@@H](N)C)N1C[C@H](CCCB(O)O)[C@](N)(C(O)=O)C1.Cl.Cl

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