Product Data Sheet

Product Name: CB-1158 Hydrochloride (INCB01158 Hydrochloride)
Cat. No.: GC34368

Chemical Properties

Cas. No.			
SMILES	O=C([C@@H](N)C)N1C[C@H](CCCB(O)O)[C@](N)(C(O)=O)C1.Cl.Cl		
Formula	$C_{11}H_{24}BCl_2N_3O_5$	M.Wt	360.04
Solubility	Water : ≥ 50 mg/mL (138.87 mM);DMSO : < 1 mg/mL (insoluble or slightly soluble)	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			

Protocol

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Cell experiment:

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].

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Animal experiment:

Mice[1]For the 4T1 tumor model, 105 cells are injected orthotopically into the mammary fat pad; for all other tumor models, 106 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 mm3. 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].

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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.

Background

CB-1158 is an inhibitor of arginase I and II (IC_{50}s = 0.086 and 0.296 ?M for the human enzymes, respectively).[1] It is selective for arginase I and II over neuronal nitric oxide synthase (nNOS), endothelial NOS (eNOS), and inducible NOS (iNOS; IC_{50}s = >50 ?M for all). CB-1158 reverses inhibition of T cell proliferation induced by granulocytes *in vitro* (IC_{50} = 0.204 ?M). It reduces tumor growth in a CT26 murine colon cancer model when administered at a dose of 100 mg/kg twice per day.

1.Steggerda, S.M., Bennett, M.K., Chen, J., et al.Inhibition of arginase by CB-1158 blocks myeloid cell-mediated immune suppression in the tumor microenvironmentJ. Immunother. Cancer5(1)101(2017)

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