Product Data Sheet

Product Name: Avacopan
Cat. No.: GC19043

Chemical Properties

Cas. No.	1346623-17-3		
SMILES	O=C([C@@H]1[C@H](C2=CC=C(NC3CCCC3)C=C2)N(C(C4=C(C)C=CC=C4F)=O)CCC1)NC5=CC=C(C)C(C(F)(F)F)=C5		
Formula	$C_{33}H_{35}F_4N_3O_2$	M.Wt	581.64
Solubility	DMSO : ≥ 10.1 mg/mL (17.36 mM);Water : < 0.1 mg/mL (insoluble)	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	Avacopan		

Protocol

Animal experiment:

Mice: Human C5aR knock-in mice are dosed with vehicle (PEG-400/solutol-HS15 70:30, 5 mL/kg) or CCX168 by oral gavage. One hour after dosing, C5a (20 μg/kg, 0.1 mL dose volume) is injected intravenously and blood samples collected from retro-orbital eye bleeds. Blood leukocyte levels are analyzed by flow cytometry[1].

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References:

[1]. Bekker P, et al. Characterization of Pharmacologic and Pharmacokinetic Properties of CCX168, a Potent and Selective Orally Administered Complement 5a Receptor Inhibitor, Based on Preclinical Evaluation and Randomized Phase 1 Clinical Study. PLoS One. 2016 Oct 21;11(10):e0164646.
[2]. Xiao H, et al. C5a receptor (CD88) blockade protects against MPO-ANCA GN. J Am Soc Nephrol. 2014 Feb;25(2):225-31.

Background

Avacopan (CCX168) is a potent, selective and orally available complement 5a receptor inhibitor with an IC50 of 0.1 nM.

CCX168 displaces [125I]-C5a binding to C5aR on a human myeloid cell line (U937) with a potency (IC50) of 0.1 nM. CCX168 inhibits C5a-mediated chemotaxis of U937 cells with a potency (the concentration of CCX168 that produces a 2-fold right-shift in C5a activity) of 0.2 nM. CCX168 competitively and selectively blocked C5a-induced calcium mobilization in purified human neutrophils, with an IC50 value of 0.2 nM. CCX168 inhibited C5a-induced release of reactive-oxygen species from isolated neutrophils, and is able to completely block respiratory burst in these neutrophils[1].

CCX168 is shown to be well tolerated across a broad dose range (1 to 100 mg) and it showed dose-dependent pharmacokinetics. An oral dose of 30 mg CCX168 given twice daily blocked the C5a-induced upregulation of CD11b in circulating neutrophils by 94% or greater throughout the entire day, demonstrating essentially complete target coverage. In mice dosed orally with 0.03 mg/kg of CCX168, the resulting plasma CCX168 concentration of 15 nM (8.7 ng/mL) reduces the drop in circulating leukocytes from 53% to 25%. In mice administered 0.3 mg/kg of CCX168, the resulting plasma CCX168 concentration of 75 nM (44 ng/mL) reduces the drop in circulating leukocytes from 53% to only 10% relative to baseline ($p<0.05$ for CCX168 vs. vehicle control). Oral doses of CCX168 of either 3 or 30 mg/kg completely blocks C5a-induced leukopenia in hC5aR knock-in mice[1]. Oral CCX168, 30 mg/kg daily, reduces the severity of anti-MPO NCGN in hC5aR mice. Glomerular crescents are reduced from 30.4% to 3.3% with CCX168. Urine

hematuria, proteinuria, and leukocyturia are reduced in mice receiving CCX168, 30 mg/kg per day. The protection by CCX168 results in reduced crescents and necrosis[2].

References:
[1]. Bekker P, et al. Characterization of Pharmacologic and Pharmacokinetic Properties of CCX168, a Potent and Selective Orally Administered Complement 5a Receptor Inhibitor, Based on Preclinical Evaluation and Randomized Phase 1 Clinical Study. PLoS One. 2016 Oct 21;11(10):e0164646.
[2]. Xiao H, et al. C5a receptor (CD88) blockade protects against MPO-ANCA GN. J Am Soc Nephrol. 2014 Feb;25(2):225-31.