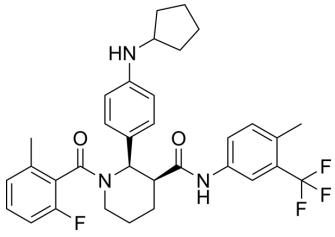
Avacopan

Cat. No.:	HY-17627
CAS No.:	1346623-17-3
Molecular Formula:	$C_{33}H_{35}F_4N_3O_2$
Molecular Weight:	581.64
Target:	Complement System
Pathway:	Immunology/Inflammation
Storage:	Powder -20°C 3 years 4°C 2 years In solvent -80°C 6 months -20°C 1 month



SOLVENT & SOLUBILITY

In Vitro

DMSO : ≥ 10.1 mg/mL (17.36 mM)

* "≥" means soluble, but saturation unknown.

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	1.7193 mL	8.5964 mL	17.1928 mL
5 mM	0.3439 mL	1.7193 mL	3.4386 mL
10 mM	0.1719 mL	0.8596 mL	1.7193 mL

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

BIOLOGICAL ACTIVITY

Description

Avacopan (CCX168) is a potent, selective and orally available complement 5a receptor (C5aR) inhibitor with an IC_{50} of 0.1 nM.

IC_{50} & Target

IC50: 0.1 nM (complement 5a receptor)[1]

In Vitro

CCX168 displaces [^{125}I]-C5a binding to C5aR on a human myeloid cell line (U937) with a potency (IC_{50}) 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 IC_{50} 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].

MCE has not independently confirmed the accuracy of these methods. They are for reference only.

In Vivo

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]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Animal Administration [1]	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]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Cell. 2023 Jun 22;186(13):2802-2822.e22.

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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.

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