Maraviroc

Cat. No.: HY-13004

CAS No.: 376348-65-1

Molecular Formula: $C_{29}H_{41}F_2N_5O$

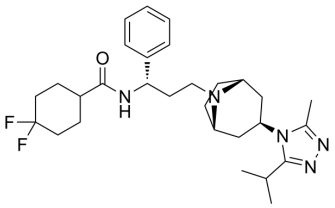
Molecular Weight: 513.67

Target: CCR; HIV

Pathway: GPCR/G Protein; Immunology/Inflammation; Anti-infection

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 : 50 mg/mL (97.34 mM; Need ultrasonic)

Ethanol : 6.5 mg/mL (12.65 mM; Need ultrasonic)

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	1.9468 mL	9.7339 mL	19.4678 mL
5 mM	0.3894 mL	1.9468 mL	3.8936 mL
10 mM	0.1947 mL	0.9734 mL	1.9468 mL

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

In Vivo

1. Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
   Solubility: ≥ 2.5 mg/mL (4.87 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.5 mg/mL (4.87 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (4.87 mM); Clear solution
4. Add each solvent one by one: 5% DMSO >> 40% PEG300 >> 5% Tween-80 >> 50% saline
   Solubility: ≥ 2.5 mg/mL (4.87 mM); Clear solution
5. Add each solvent one by one: 5% DMSO >> 95% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.5 mg/mL (4.87 mM); Clear solution
6. Add each solvent one by one: 1% DMSO >> 99% saline
   Solubility: ≥ 0.5 mg/mL (0.97 mM); Clear solution

BIOLOGICAL ACTIVITY

Description	Maraviroc (UK-427857) is a selective CCR5 antagonist with activity against human HIV.			
IC_{50} & Target	MIP-1α-CCR5 3.3 nM (IC_{50}, in HEK-293 cell membrane)	RANTES-CCR5 5.2 nM (IC_{50}, in HEK-293 cell membrane)	MIP-1β-CCR5 7.2 nM (IC_{50}, in HEK-293 cell membrane)	HIV-1 (Ba-L) 1.1 nM (IC_{50}, in PM-1 cells)
In Vitro	Maraviroc (UK-427857) is a selective CCR5 antagonist with potent anti-human immunodeficiency virus type 1 (HIV-1) activity. Maraviroc inhibits the downstream event of chemokine-induced intracellular calcium redistribution, with IC_{50}s ranging from 7 to 30 nM obtained against MIP-1β, MIP-1α and RANTES. Maraviroc (UK-427857) is active (IC_{90}) at low nanomolar concentrations against HIV-1 Ba-L (a lab-adapted R5 strain) when measured in a 5-day antiviral assay using either isolated multiple (pooled) donor PBMC (IC_{90}, 3.1 nM), single-donor PBMC (IC_{90}, 1.8 nM) or PM-1 cells (IC_{90}, 1.1 nM)[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.			
In Vivo	Clearance values are moderate to high in both rat and dog species following i.v. administration (74 and 21 mL/min/kg, respectively). Maraviroc also has a moderate volume of distribution in both species (4.3 to 6.5 liters/kg). The half-life values of maraviroc are 0.9 h in the rat and 2.3 h in the dog. Following oral administration (2 mg/kg) to the dog, the C_{max}(256 ng/mL) occurs 1.5 h. post-dose, and the bioavailability is 40%. For the rat, investigation of the concentrations obtain in the portal vein following oral administration indicated that approximately 30% of the administered dose is absorbed from the intestinal tract[1]. In the DSS/TNBS colitis and in the transfer model, Maraviroc attenuates development of intestinal inflammation by selectively reducing the recruitment of CCR5 bearing leukocytes[2] MCE has not independently confirmed the accuracy of these methods. They are for reference only.			

PROTOCOL

Kinase Assay [1]

Binding of ^{125}I-labeled MIP-1α, MIP-1β, and RANTES to CCR5 is measured essentially using intact HEK-293 cells stably expressing the receptor or membrane preparations thereof. Briefly, cells are resuspended in binding buffer (50 mM HEPES containing 1 mM $CaCl_2$, 5 mM $MgCl_2$, and 0.5% bovine serum albumin [BSA] and adjusted to pH 7.4) to a density of 2×10^6 cells/mL. For membrane preparations, phosphate-buffered saline (PBS)-washed cells are resuspended in lysis buffer (20 mM HEPES, 1 mM $CaCl_2$, 1 tablet COMPLETE per 50 mL, pH 7.4; Boehringer) prior to homogenization in a Polytron hand-held homogenizer, ultracentrifugation (40,000× g for 30 min), and resuspension in binding buffer to a protein concentration of 0.25 mg/mL (12.5 µg of membrane protein is used in each well of a 96-well plate). ^{125}I-radiolabeled MIP-1α, MIP-1β, and RANTES are prepared and diluted in binding buffer to a final concentration of 400 pM in the assay. Appropriate maraviroc dilutions are added to each well to a final volume of 100 µL, the assay plates incubated for 1 h, and the contents filtered through preblocked and washed Unifilter plates which are counted following overnight drying[1].

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Cell Assay [1]

HEK-293 cell aliquots (100 µL at 1×10^6 cells/mL) are plated into poly-D-lysine-coated plates and incubated at 37°C overnight. A 1:1 mix of soluble recombinant human CD4 (sCD4) (diluted to 4.5 nM in culture medium) and HIV-1 gp120 is incubated at room temperature for 15 min prior to its addition to PBS-washed cells in the presence of dilutions of maraviroc to enable IC_{50} determination. The assay plates are incubated at 37°C for 1 h and washed. Eu^{3+}-labeled anti-gp120 antibody (1/500 dilution in assay buffer) is added to each well (50 µL) and incubated for 1 h. The plate is washed three times with wash buffer prior to the addition of enhancement solution (200 µL/well) and measurement of Eu^{3+} fluorescence (Victor^{2}multilabel counter; “Europium” protocol). Nonspecific binding is taken as the fluorescence measured for gp120 incubated with cells in the absence of preincubation with sCD4[1].

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Animal Administration [1][2]

Rats and Dogs[1]

Preclinical pharmacokinetic studies are carried out with maraviroc following a single intravenous and oral administration to both male Sprague-Dawley rats (1 mg/kg of body weight given intravenously [i.v.] and 10 mg/kg given orally [p.o.]; n=2) and male beagle dogs (0.5 mg/kg i.v. and 2 mg/kg p.o; n=4). Plasma samples are taken for up to 24 h postdose, and the concentrations of unchanged maraviroc are determined using a specific high-performance liquid chromatography-tandem

mass spectrum assay.

Mice[2]

Splenocytes are collected from 6-10 week old $CCR5^{-/-}$ mice or wild-type controlmice (n=8 per group) and naive $CD4^{+}$ $CD45RB^{high}$ T-cells are isolated by cell sorting. A total of 3×10^{5} $CD45RB^{high}$ cells are then injected intravenously into $Rag1^{-/-}$ mice that are subsequently weighed and assessed for fecal score every 20 days to evaluate IBD development. To investigate whether Maraviroc rescues from intestinal inflammation induced by transfer colitis, $Rag1^{-/-}$ mice are injected with $CD4^{+}$ $CD45RB^{-/-}$ T-cells and 34 days later randomized into either a control group (no further treatment, n=6) or treatment with Maraviroc, 50 mg/kg/d Maraviroc per os (n=4) for 3 weeks, 5 d/week.

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

CUSTOMER VALIDATION

- Cell. 2022 Jun 23;185(13):2234-2247.e17.
- Cell Mol Immunol. 2023 Jun 12.
- Nat Commun. 2021 Dec 8;12(1):7122.
- Nat Commun. 2020 Nov 25;11(1):5994.
- Int J Antimicrob Agents. 2019 Dec;54(6):814-819.

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REFERENCES

[1]. Dorr P, et al. Maraviroc (UK-427,857), a potent, orally bioavailable, and selective small-molecule inhibitor of chemokine receptor CCR5 with broad-spectrum anti-human immunodeficiency virus type 1 activity. Antimicrob Agents Chemother. 2005 Nov;49(11):472

[2]. Mencarelli A, et al. Highly specific blockade of CCR5 inhibits leukocyte trafficking and reduces mucosal inflammation in murine colitis. Sci Rep. 2016 Aug 5;6:30802.

[3]. Romero-Sánchez MC, et al. Effect of maraviroc on HIV-disease progression-related biomarkers. Antimicrob Agents Chemother. 2012 Nov;56(11):5858-64.

[4]. Huilin Mou, et al. NRSF and CCR5 Established Neuron-glia Communication during Acute and Chronic Stresses. Journal of Drug Metabolism & Toxicology. January 10, 2016.

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