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产品名称：Maraviroc
产品别名：UK-427857

生物活性：

Description	Maraviroc (UK-427857) is a selective CCR5 antagonist with activity against human HIV.	
IC_{50} & Target	MIP-1α-CCR5	MIP-1β-CCR5
	3.3 nM (IC_{50}, in HEK-293 cell membrane)	7.2 nM (IC_{50}, in HEK-293 cell membrane)
	RANTES-CCR5	HIV-1 (Ba-L)
	5.2 nM (IC_{50}, in HEK-293 cell membrane)	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 IC50s 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 (IC90, 1.1 nM)[1].	
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]	
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

*请根据产品在不同溶剂中的溶解度选择合适的溶剂配制储备液；一旦配成溶液，请分装保存，避免反复冻融造成的产品失效。

储备液的保存方式和期限：-80°C, 6 months; -20°C, 1 month。-80°C 储存时，请在 6 个月内使用，-20°C 储存时，请在 1 个月内使用。

In Vivo:

请根据您的实验动物和给药方式选择适当的溶解方案。以下溶解方案都请先按照 In Vitro 方式配制澄清的储备液，再依次添加助溶剂：

——为保证实验结果的可靠性，澄清的储备液可以根据储存条件，适当保存；体内实验的工作液，建议您现用现配，当天使用； 以下溶剂前显示的百分比是指该溶剂在您配制终溶液中的体积占比；如在配制过程中出现沉淀、析出现象，可以通过加热和/或超声的方式助溶

	1.请依序添加每种溶剂： 10% DMSO→40% PEG300 →5% Tween-80 → 45% saline Solubility: ≥ 2.5 mg/mL (4.87 mM); Clear solution 此方案可获得 ≥ 2.5 mg/mL (4.87 mM，饱和度未知) 的澄清溶液。 以 1 mL 工作液为例，取 100 μL 25.0 mg/mL 的澄清 DMSO 储备液加到 400 μL PEG300 中，混合均匀向上述体系中加入 50 μL Tween-80，混合均匀；然后继续加入 450 μL 生理盐水定容至 1 mL。 2.请依序添加每种溶剂： 10% DMSO→ 90% (20% SBE-β-CD in saline) Solubility: ≥ 2.5 mg/mL (4.87 mM); Clear solution 此方案可获得 ≥ 2.5 mg/mL (4.87 mM，饱和度未知) 的澄清溶液。 以 1 mL 工作液为例，取 100 μL 25.0 mg/mL 的澄清 DMSO 储备液加到 900 μL 20% 的 SBE-β-CD 生理盐水水溶液中，混合均匀。 3.请依序添加每种溶剂： 10% DMSO →90% corn oil Solubility: ≥ 2.5 mg/mL (4.87 mM); Clear solution 此方案可获得 ≥ 2.5 mg/mL (4.87 mM，饱和度未知) 的澄清溶液，此方案不适用于实验周期在半个月以上的实验。 以 1 mL 工作液为例，取 100 μL 25.0 mg/mL 的澄清 DMSO 储备液加到 900 μL 玉米油中，混合均匀。
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.

实验参考：

Cell Assay	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 (Victor²multilabel counter; “Europium” protocol). Nonspecific binding is taken as the fluorescence measured for gp120 incubated with cells in the absence of preincubation with sCD4[1].
	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

Animal Administration	[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.
Kinase Assay	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].
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.