



上海源叶生物科技有限公司
Shanghai yuanye Bio-Technology Co., Ltd
电话: 021-61312973 传真: 021-55068248
网址: www.shyuanye.com
邮箱: shyysw@sina.com

产品名称: **BX471**
产品别名: **ZK-811752**

生物活性:																				
Description	BX471 (ZK-811752) is an orally active, potent and selective non-peptide CCR1 antagonist with a Ki of 1 nM, and exhibits 250-fold selectivity for CCR1 over CCR2, CCR5 and CXCR4.																			
IC50 & Target	MIP-1α-CCR1	RANTES-CCR1	MCP-3-CCR1																	
	1 nM (Ki)	2.8 nM (Ki)	5.5 nM (Ki)																	
In Vitro	BX471 is a potent functional antagonist based on its ability to inhibit a number of CCR1-mediated effects including Ca2+ mobilization, increase in extracellular acidification rate, CD11b expression, and leukocyte migration. BX471 demonstrates a greater than 10,000-fold selectivity for CCR1 compared with 28 G-protein-coupled receptors[1]. BX471 is also able to displace 125I-MIP-1α/CCL3 binding to mouse CCR1 in a concentration-dependent manner with a Ki of 215±46 nM. Increasing concentrations of BX471 inhibits the Ca2+ transients induced by MIP-1α/CCL3 in both human and mouse CCR1 with IC50 of 5.8±1 nM and 198±7 nM, respectively[2]. BX471 (0.1-10 μM) shows a dose-dependent inhibition of RANTES-mediated and shear-resistant adhesion on IL-1β-activated microvascular endothelium in shear flow in isolated blood monocytes. BX471 also inhibits the RANTES-mediated adhesion of T lymphocytes to activated endothelium[4].																			
In Vivo	BX471 (4 mg/kg, p.o. or i.v.) is orally active with a bioavailability of 60% in dogs. Furthermore, BX471 effectively reduces disease in a rat experimental allergic encephalomyelitis model of multiple sclerosis[1]. BX471 (20 mg/kg, s.c.) reaches peak plasma levels of 9 μM by around 30 minutes, and this rapidly declines to approximately 0.4 μM after 2 hours. From 4 to 8 hours the drug plasma levels drops to 0.1 μM or lower. Mice treated with 20 mg/kg of BX471 for 10 days shows a reduction of interstitial CD45 positive leukocytes of approximately 55%. BX471 has a borderline significant effect on the number of CCR5-positive CD8 cells in the peripheral blood. BX471 reduces the amount of FSP1-positive cells by 65% in UUO kidneys as compared with vehicle control[2]. Pretreatment with BX471 reduces macrophage and neutrophil accumulation in kidney after ischemia-reperfusion injury[3].																			
<div>In Vitro:</div> <div>DMSO : ≥ 51 mg/mL (117.27 mM)</div> <div>* "≥" means soluble, but saturation unknown.</div> <table><tr><th rowspan="4">Preparing Stock Solutions</th><th>Solvent / Mass / Concentration</th><th>1 mg</th><th>5 mg</th><th>10 mg</th></tr><tr><th>1 mM</th><td>2.2994 mL</td><td>11.4972 mL</td><td>22.9943 mL</td></tr><tr><th>5 mM</th><td>0.4599 mL</td><td>2.2994 mL</td><td>4.5989 mL</td></tr><tr><th>10 mM</th><td>0.2299 mL</td><td>1.1497 mL</td><td>2.2994 mL</td></tr></table> <div>*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。</div> <div>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。</div> <div>In Vivo:</div> <div>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</div>				Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg	1 mM	2.2994 mL	11.4972 mL	22.9943 mL	5 mM	0.4599 mL	2.2994 mL	4.5989 mL	10 mM	0.2299 mL	1.1497 mL	2.2994 mL
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Solvent&Solubility	<p>备液, 再依次添加助溶剂:</p> <p>——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</p> <p>1.请依序添加每种溶剂: 10% DMSO→40% PEG300 →5% Tween-80 → 45% saline</p> <p>Solubility: ≥ 2.5 mg/mL (5.75 mM); Clear solution</p> <p>此方案可获得 ≥ 2.5 mg/mL (5.75 mM, 饱和度未知) 的澄清溶液。</p> <p>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。</p> <p>2.请依序添加每种溶剂: 10% DMSO→ 90% (20% SBE-β-CD in saline)</p> <p>Solubility: ≥ 2.5 mg/mL (5.75 mM); Clear solution</p> <p>此方案可获得 ≥ 2.5 mg/mL (5.75 mM, 饱和度未知) 的澄清溶液。</p> <p>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。</p> <p>3.请依序添加每种溶剂: 10% DMSO →90% corn oil</p> <p>Solubility: ≥ 2.5 mg/mL (5.75 mM); Clear solution</p> <p>此方案可获得 ≥ 2.5 mg/mL (5.75 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。</p> <p>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。</p>
References	<p>[1]. Liang M, et al. Identification and characterization of a potent, selective, and orally active antagonist of the CC chemokine receptor-1. J Biol Chem. 2000 Jun 23;275(25):19000-8.</p> <p>[2]. Anders HJ, et al. A chemokine receptor CCR-1 antagonist reduces renal fibrosis after unilateral ureter ligation. J Clin Invest. 2002 Jan;109(2):251-9.</p> <p>[3]. Furuichi K, et al. Chemokine receptor CCR1 regulates inflammatory cell infiltration after renal ischemia-reperfusion injury. J Immunol. 2008 Dec 15;181(12):8670-6.</p> <p>[4]. Horuk R, et al. A non-peptide functional antagonist of the CCR1 chemokine receptor is effective in rat heart transplant rejection. J Biol Chem. 2001 Feb 9;276(6):4199-204.</p>
实验参考:	
	<p>Fasted male beagle dogs (n=3 per treatment group) are given BX471 either by oral gavage or by intravenous injection via the cephalic vein at a dose of 4 mg/kg. The compound is dissolved in a vehicle of 40% aqueous cyclodextrin. Serial blood samples are collected utilizing an in-dwelling catheter in the jugular vein at the indicated time points up to 6 h post-dosing. EDTA is used as an anticoagulant. The samples are centrifuged (1000\times g for 10 min at 4°C), and plasma is stored frozen until analyzed for drug levels by HPLC-MS (electrospray mode operated under a positive ion mode). Plasma samples are thawed and denatured by the addition of four parts of ice-cold methanol containing a fixed amount of an internal standard to one part of plasma. The resulting protein precipitate is removed by centrifugation at 5000\times g, and the supernatants are analyzed directly. Concurrently plasma calibration standards of BX471 are prepared over the range of quantification,</p>



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Animal Administration	<p>processed, and analyzed under identical conditions. A FISIONS, VG Platform single quadrupole instrument is used in these analyses with an electrospray inlet operated at 3.57 kV.</p> <p>Chromatographic separation is accomplished using a YMC AQ octadecyl silane reversed phase column (4.6×250 mm) following a short isocratic elution method (35% methanol, 65% water containing 0.1% trifluoroacetic acid). The total column flow (1 mL/min) is split post-column to infuse 50 µL/min into the mass spectrometer. The chromatograms are collected over a total run time of 7.5 min/sample following a 50-µL injection on the column. The ions are collected in a single ion positive ionization mode. A calibration curve for quantification is generated by plotting ion current ratios between the internal standard peak and the analyte in the plasma standards over the quantification range. Calculations of percent oral availability is deduced from the area under curve measurements. Pharmacokinetic parameters are calculated using WinNonLin version 3.0. [1]</p>
References	<p>[1]. Liang M, et al. Identification and characterization of a potent, selective, and orally active antagonist of the CC chemokine receptor-1. J Biol Chem. 2000 Jun 23;275(25):19000-8.</p> <p>[2]. Anders HJ, et al. A chemokine receptor CCR-1 antagonist reduces renal fibrosis after unilateral ureter ligation. J Clin Invest. 2002 Jan;109(2):251-9.</p> <p>[3]. Furuichi K, et al. Chemokine receptor CCR1 regulates inflammatory cell infiltration after renal ischemia-reperfusion injury. J Immunol. 2008 Dec 15;181(12):8670-6.</p> <p>[4]. Horuk R, et al. A non-peptide functional antagonist of the CCR1 chemokine receptor is effective in rat heart transplant rejection. J Biol Chem. 2001 Feb 9;276(6):4199-204.</p>

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