BX471

Cat. No.: HY-12080

CAS No.: 217645-70-0

Molecular Formula: $C_{21}H_{24}ClFN_4O_3$

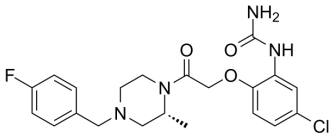
Molecular Weight: 434.89

Target: CCR

Pathway: GPCR/G Protein; Immunology/Inflammation

Storage:

Powder	-20°C	3 years
	4°C	2 years
In solvent	-80°C	2 years
	-20°C	1 year



SOLVENT & SOLUBILITY

In Vitro

DMSO : ≥ 100 mg/mL (229.94 mM)

H_2O : < 0.1 mg/mL (ultrasonic) (insoluble)

* "≥" means soluble, but saturation unknown.

Preparing Stock Solutions	Mass / Solvent / 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

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

In Vivo

1. Add each solvent one by one: 50% PEG300 >> 50% saline
   Solubility: 5 mg/mL (11.50 mM); Clear solution; Need ultrasonic
2. Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
   Solubility: ≥ 2.5 mg/mL (5.75 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.08 mg/mL (4.78 mM); Clear solution
4. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.08 mg/mL (4.78 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

BX471 (ZK-811752) is an orally active, potent and selective non-peptide CCR1 antagonist with a K_i of 1 nM, and exhibits 250-fold selectivity for CCR1 over CCR2, CCR5 and CXCR4.

IC_{50} & Target	MIP-1α-CCR1 1 nM (Ki)	RANTES-CCR1 2.8 nM (Ki)	MCP-3-CCR1 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 Ca^{2+} mobilization, increase in extracellular acidification rate, CD11b expression, and leukocyte migration. BX471 demonstrats a greater than 10,000-fold selectivity for CCR1 compared with 28 G-protein-coupled receptors[1]. BX471 is also able to displace ^{125}I-MIP-1α/CCL3 binding to mouse CCR1 in a concentration-dependent manner with a K_i of 215±46 nM. Increasing concentrations of BX471 inhibits the Ca^{2+} transients induced by MIP-1α/CCL3 in both human and mouse CCR1 with IC_{50} 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].

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

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 witih BX471 reduces macrophage and neutrophil accumulation in kidney after ischemia-reperfusion injury[3].

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PROTOCOL

Animal Administration [1]

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× 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× g, and the supernatants are analyzed directly. Concurrently plasma calibration standards of BX471 are prepared over the range of quantification, processed, and analyzed under identical conditions. A FISONS, VG Platform single quadrupole instrument is used in these analyses with an electrospray inlet operated at 3.57 kV. 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.

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

CUSTOMER VALIDATION

- Cancer Cell. 2021 Mar 8;39(3):423-437.e7.
- Cell Res. 2018 Mar;28(3):323-335.

- Signal Transduct Target Ther. 2021 Feb 28;6(1):91.
- Sci Adv. 2021 May 26;7(22):eabb5943.
- J Exp Clin Cancer Res. 2022 Mar 3;41(1):81.

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REFERENCES

[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.

[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.

[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.

[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.

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