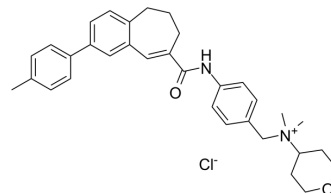


TAK-779

Cat. No.:	HY-13406
CAS No.:	229005-80-5
Molecular Formula:	C ₃₃ H ₃₉ ClN ₂ O ₂
Molecular Weight:	531
Target:	CCR; HIV; CXCR
Pathway:	GPCR/G Protein; Immunology/Inflammation; Anti-infection
Storage:	-20°C, sealed storage, away from moisture * In solvent : -80°C, 2 years; -20°C, 1 year (sealed storage, away from moisture)



SOLVENT & SOLUBILITY

In Vitro

DMSO : ≥ 25 mg/mL (47.08 mM)
 H₂O : 16.66 mg/mL (31.37 mM; Need ultrasonic and warming)
 * "≥" means soluble, but saturation unknown.

Preparing Stock Solutions	Solvent Concentration	Mass		
		1 mg	5 mg	10 mg
	1 mM	1.8832 mL	9.4162 mL	18.8324 mL
	5 mM	0.3766 mL	1.8832 mL	3.7665 mL
	10 mM	0.1883 mL	0.9416 mL	1.8832 mL

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

In Vivo

- Add each solvent one by one: PBS
Solubility: 50 mg/mL (94.16 mM); Clear solution; Need ultrasonic
- Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
Solubility: ≥ 2.58 mg/mL (4.86 mM); Clear solution
- Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
Solubility: ≥ 2.58 mg/mL (4.86 mM); Clear solution
- Add each solvent one by one: 10% DMSO >> 90% corn oil
Solubility: ≥ 2.58 mg/mL (4.86 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

TAK-779 is a potent and selective nonpeptide antagonist of CCR5 and CXCR3, with a K_i of 1.1 nM for CCR5, and effectively and selectively inhibits R5 HIV-1, with EC₅₀ and EC₉₀ of 1.2 nM and 5.7 nM, respectively, in MAGI-CCR5 cells.

IC₅₀ & Target

MIP-1α-CCR5 1 nM (IC ₅₀ , in CHO/CCR5)	MIP-1β-CCR5 1 nM (IC ₅₀ , in CHO/CCR5)	RANTES-CCR5 1.4 nM (IC ₅₀ , in CHO/CCR5)	MCP-1-CCR2b 27 nM (IC ₅₀ , in CHO/CCR5)
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	cells)	cells)	cells)	cells)
	R5 HIV-1 (Ba-L) 1.2 nM (EC ₅₀ , in MAGI-CCR5 cells)	R5 HIV-1 (KK) 1.6 nM (EC ₅₀ , in PBMCs)	R5 HIV-1 (HHA) 3.2 nM (EC ₅₀ , in PBMCs)	R5 HIV-1 (CTV) 3.5 nM (EC ₅₀ , in PBMCs)
	R5 HIV-1 (Ba-L) 3.7 nM (EC ₅₀ , in PBMCs)	R5 HIV-1 (Ba-L) 5.7 nM (EC ₉₀ , in MAGI-CCR5 cells)	R5 HIV-1 (HHA) 7.5 nM (EC ₉₀ , in PBMCs)	R5 HIV-1 (Ba-L) 12.8 nM (EC ₉₀ , in PBMCs)
	R5 HIV-1 (KK) 20.8 nM (EC ₉₀ , in PBMCs)	R5 HIV-1 (CTV) 27 nM (EC ₉₀ , in PBMCs)	mCXCR3 369 nM (IC ₅₀ , in PBMCs)	

In Vitro	<p>TAK-779 is a potent and selective nonpeptide antagonist of CCR5, with a K_i of 1.1 nM, and effectively and selectively inhibits R5 HIV-1, with EC₅₀ and EC₉₀ of 1.2 nM and 5.7 nM, respectively, in MAGI-CCR5 cells. TAK-779 less potently blocks the binding of [¹²⁵I]-monocyte chemotactic protein 1 to CCR2b in CHO/CCR2b cells, with an IC₅₀ for CCR2b of 27 nM. TAK-779 also completely inhibits the binding of [¹²⁵I]-RANTES to CHO/CCR5 cells with an IC₅₀ of 1.4 nM. TAK-779 (20 nM) selectively inhibits CCR5-mediated Ca²⁺-signaling. In addition, TAK-779 shows no inhibition on X4 HIV-1 strains^[1]. TAK-779 is an antagonist of CXCR3, and inhibits the migration of T cells but not T cell proliferation^[2].</p> <p>MCE has not independently confirmed the accuracy of these methods. They are for reference only.</p>
In Vivo	<p>TAK-779 (10 mg/kg per day, s.c.) significantly prolongs the allograft survival of the rat intestinal transplantation model. TAK-779 also decreases the number of CD4⁺ as well as CD8⁺ T cells in spleen, blood and recipient mesenteric lymph nodes (MLN)^[2]. TAK-779 (150 µg per mouse, s.c.) suppresses the development of experimental autoimmune encephalomyelitis (EAE) in myelin oligodendrocyte glycoprotein (MOG)-immunized C57BL/6 mice. TAK-779 decreases the infiltration of CXCR3 and CCR5 bearing leukocytes into the spinal cord. TAK-779 does not alter myelin oligodendrocyte glycoprotein (MOG)-specific immune responses or affect the potential of MOG-specific T cells to transfer experimental autoimmune encephalomyelitis (EAE)^[3].</p> <p>MCE has not independently confirmed the accuracy of these methods. They are for reference only.</p>

PROTOCOL

Cell Assay ^[1]

The anti-HIV-1 activities of the test compounds (TAK-779, etc.) are based on the inhibition of virus-induced infectious focus formation in MAGI-CCR5 cells and the reduction of p24 antigen production in PBMCs. In brief, MAGI-CCR5 cells (1 × 10⁴ cells per well) are cultured in a microtiter tray. After a 24-h incubation at 37°C, the culture supernatants are replaced with fresh culture media containing the virus (≈300 focus forming units per well) and various concentrations of the test compounds (TAK-779, etc.). After a 2-day incubation, the cells are fixed and stained with 5-bromo-4-chloro-3-indolyl-β-d-galactosidase. The number of infected (blue) cells is counted microscopically. For the PBMC assays, phytohemagglutinin-stimulated PBMCs (2.5 × 10⁵ cells per 500 µl) are infected with HIV-1 in the presence of various concentrations of the test compounds (TAK-779, etc.). The amounts of the virus used for infection are, depending on the replicability of each strain, generally 1-10 ng of p24 per 2.5 × 10⁵ cells. After an overnight incubation at 37°C, the cells are washed extensively to remove unadsorbed viral particles and are incubated further with culture media containing the same concentrations of the compounds as those used during viral adsorption. On day 6 after viral infection, the culture supernatants are collected and determined for their p24 antigen levels with a sandwich ELISA kit. The cytotoxicities of the compounds are evaluated in parallel with their antiviral activities. They are based on the viability and proliferation of mock-infected cells^[1].

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

Animal Administration ^[3]

Mice^[3]

The mice are immunized with MOG and are treated s.c. with TAK-779 or vehicle. The mice (N= 10) are injected s.c. with 150 µg TAK-779 (dissolved in 5% mannitol solution) in a volume of 100 µL, once daily after MOG immunization. TAK-779 injection is started from day 0 after immunization and continued once daily for 22 days. The dose of 150 µg is determined based on the observations in prior experiments that the dose of 50 µg per mouse can not produce inhibition, and a dose of more than

100 µg per mouse is required to produce significant inhibition. The dose of 150 µg per mouse has also been used in other mouse experimental models, and approximately the same dose is used in allograft rejection and asthma models. As a control, an equal volume of PBS containing 5% mannitol is injected daily in the control mice (N= 10)^[3]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- J Cell Mol Med. 2021 May 4.

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REFERENCES

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- [4]. Gao P, et al. The unique target specificity of a nonpeptide chemokine receptor antagonist: selective blockade of two Th1 chemokine receptors CCR5 and CXCR3. *J Leukoc Biol*. 2003 Feb;73(2):273-80.

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