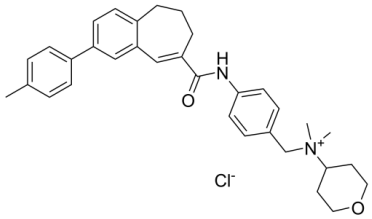
Data Sheet

Product Name:	TAK-779
Cat. No.:	CS-2026
CAS No.:	229005-80-5
Molecular Formula:	$C_{33}H_{39}ClN_2O_2$
Molecular Weight:	531.13
Target:	CCR; CXCR; HIV
Pathway:	Anti-infection; GPCR/G Protein; Immunology/Inflammation
Solubility:	DMSO : ≥ 25 mg/mL;H_2O : 16.66 mg/mL (ultrasonic;warming)



BIOLOGICAL ACTIVITY:

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 **EC_{50}** and **EC_{90}** of 1.2 nM and 5.7 nM, respectively, in MAGI-CCR5 cells. IC50 & Target: Ki: 1.1 nM (CCR5)[1]

EC50: 1.2 nM (R5 HIV-1, in MAGI-CCR5 cells)[1]

EC90: 5.7 nM (R5 HIV-1, in MAGI-CCR5 cells)[1]

CXCR[2] ***In Vitro:*** 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 EC_{50} and EC_{90} of 1.2 nM and 5.7 nM, respectively, in MAGI-CCR5 cells. TAK-779 less potently blocks the binding of [^{125}I]-monocyte chemotactic protein 1 to CCR2b in CHO/CCR2b cells, with an IC_{50} for CCR2b of 27 nM. TAK-779 also completely inhibits the binding of [^{125}I]-RANTES to CHO/CCR5 cells with an IC_{50} of 1.4 nM. TAK-779 (20 nM) selectively inhibits CCR5-mediated Ca^{2+}-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]. ***In Vivo:*** 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.) supppresses 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].

PROTOCOL (Extracted from published papers and Only for reference)

Cell Assay: TAK-779 is dissolved in DMSO, and diluted in medium[1].[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 (1×10^4 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 (2.5×10^5 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 **2.5×10^5 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].

Animal Administration: TAK-779 is dissolved in 5% mannitol solution[3].[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].

References:

[1]. Baba M, et al. A small-molecule, nonpeptide CCR5 antagonist with highly potent and selective anti-HIV-1 activity. Proc Natl Acad Sci U S A. 1999 May 11;96(10):5698-703.

[2]. Takama Y, et al. Effects of a calcineurin inhibitor, FK506, and a CCR5/CXCR3 antagonist, TAK-779, in a rat small intestinal transplantation model. Transpl Immunol. 2011 Jul;25(1):49-55.

[3]. Ni J, et al. The chemokine receptor antagonist, TAK-779, decreased experimental autoimmune encephalomyelitis by reducing inflammatory cell migration into the central nervous system, without affecting T cell function. Br J Pharmacol. 2009 Dec;158(8):2046-56.

[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.

CAIndexNames:

2H-Pyran-4-aminium, N-[[4-[[[6,7-dihydro-2-(4-methylphenyl)-5H-benzocyclohepten-8-yl]carbonyl]amino]phenyl]methyl]tetrahydro-N,N-dimethyl-, chloride (1:1)

SMILES:

C[N+](C)(CC1=CC=C(NC(C2=CC3=CC(C4=CC=C(C)C=C4)=CC=C3CCC2)=O)C=C1)C5CCOCC5.[Cl-]

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