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# 产品名称：TAK-779
# 产品别名：Takeda 779

| 生物活性： | | |
|---|---|---|
| **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 $EC_{50}$ and $EC_{90}$ of 1.2 nM and 5.7 nM, respectively, in MAGI-CCR5 cells. | |
| **$IC_{50}$ & Target** | MIP-1α-CCR5 | MIP-1β-CCR5 |
| | 1 nM ($IC_{50}$, in CHO/CCR5 cells) | 1 nM ($IC_{50}$, in CHO/CCR5 cells) |
| | RANTES-CCR5 | MCP-1-CCR2b |
| | 1.4 nM ($IC_{50}$, in CHO/CCR5 cells) | 27 nM ($IC_{50}$, in CHO/CCR5 cells) |
| | R5 HIV-1 (Ba-L) | R5 HIV-1 (Ba-L) |
| | 1.2 nM ($EC_{50}$, in MAGI-CCR5 cells) | 5.7 nM (EC90, in MAGI-CCR5 cells) |
| | R5 HIV-1 (Ba-L) | R5 HIV-1 (Ba-L) |
| | 3.7 nM ($EC_{50}$, in PBMCs) | 12.8 nM (EC90, in PBMCs) |
| | R5 HIV-1 (KK) | R5 HIV-1 (KK) |
| | 1.6 nM ($EC_{50}$, in PBMCs) | 20.8 nM (EC90, in PBMCs) |
| | R5 HIV-1 (HHA) | R5 HIV-1 (HHA) |
| | 3.2 nM ($EC_{50}$, in PBMCs) | 7.5 nM (EC90, in PBMCs) |
| | R5 HIV-1 (CTV) | R5 HIV-1 (CTV) |
| | 3.5 nM ($EC_{50}$, in PBMCs) | 27 nM (EC90, in PBMCs) |
| | mCXCR3 | |
| | 369 nM ($IC_{50}$, in PBMCs) | |
| **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]. | |
| | ***In Vitro:***<br>**DMSO : ≥ 25 mg/mL (47.07 mM)** | |

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**Solvent&Solubility**

**$H_2O$ : 16.66 mg/mL (31.37 mM;** Need ultrasonic and warming)

* "≥" means soluble, but saturation unknown.

| Preparing Stock Solutions | Solvent / Mass / Concentration | 1 mg | 5 mg | 10 mg |
|---|---|---|---|---|
| | 1 mM | 1.8828 mL | 9.4139 mL | 18.8278 mL |
| | 5 mM | 0.3766 mL | 1.8828 mL | 3.7656 mL |
| | 10 mM | 0.1883 mL | 0.9414 mL | 1.8828 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: ≥ 2.58 mg/mL (4.86 mM); Clear solution

此方案可获得 ≥ 2.58 mg/mL (4.86 mM，饱和度未知) 的澄清溶液。

以 1 mL 工作液为例，取 100 μL 25.8 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: ≥ 2.58 mg/mL (4.86 mM); Clear solution

此方案可获得 ≥ 2.58 mg/mL (4.86 mM，饱和度未知) 的澄清溶液。

以 1 mL 工作液为例，取 100 μL 25.8 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: ≥ 2.58 mg/mL (4.86 mM); Clear solution

此方案可获得 ≥ 2.58 mg/mL (4.86 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 25.8 mg/mL 的澄清 DMSO 储备液加到 900 μL 玉米油中，混合均匀。

**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.

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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. |

**实验参考：**

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| **Cell Assay** | 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 ($1 \times 10^4$ 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 ($2.5 \times 10^5$ 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 $2.5 \times 10^5$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** | Mice[3]<br>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.<br>[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.<br>[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.<br>[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. |