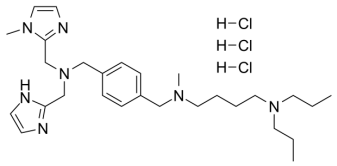
KRH-3955 hydrochloride

Cat. No.:	HY-122058A
CAS No.:	2253744-59-9
Molecular Formula:	$C_{28}H_{48}Cl_3N_7$
Molecular Weight:	589.09
Target:	CXCR; HIV
Pathway:	GPCR/G Protein; Immunology/Inflammation; Anti-infection
Storage:	Please store the product under the recommended conditions in the Certificate of Analysis.



BIOLOGICAL ACTIVITY

Description	KRH-3955 hydrochloride is an orally bioavailable CXCR4 antagonist. KRH-3955 hydrochloride inhibits SDF-1α binding to CXCR4 with an IC_{50} of 0.61 nM. KRH-3955 hydrochloride is also a highly potent and selective inhibitor of X4 HIV-1, with an EC_{50} of 0.3 to 1.0 nM[1].

IC_{50} & Target	SDF-1α-CXCR4	X4 HIV-1_{NL4-3}
	0.61 nM (IC_{50})	0.3-1.0 nM (EC50)

In Vitro

KRH-3955 inhibits the replication of NL4-3 in activated peripheral blood mononuclear cells (PBMCs) from eight different donors with the EC_{50} ranging from 0.23 to 1.3 nM[1].

KRH-3955 inhibits the infection of CD4/CXCR4 cells by these recombinant drug-resistant viruses, including viruses resistant to PIs, NRTIs, or NNRTIs, multidrug-resistant viruses and T20-resistant viruses, with the IC_{50} ranging from 0.4 to 0.8 nM[1].

KRH-3955 (10-100 nM) inhibits the SDF-1α-induced increase in the intracellular Ca^{2+} concentration in a dose-dependent manner[1].

KRH-3955 (0.1-1000 nM) binding sites are located in a region composed of all three extracellular loops (ECLs) of CXCR4[1].

KRH-3955 (10 nM) has a strong binding affinity for CXCR4 and a slow dissociation rate[1].

KRH-3955 inhibits MAb 12G5 binding to CXCR4 mutants, with the IC_{50} ranging from 0.5 to 14.1 nM[1].

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

In Vivo

KRH-3955 (10 mg/kg; a single p.o.) efficiently suppresses X4 HIV-1 infection in hu-PBL-SCID mice[1].

KRH-3955 (10 mg/kg; a single p.o.) exhibits moderate oral bioavailability (25.6%) and C_{max} (86.3 ng/mL)[1].

KRH-3955 (10 mg/kg; a single i.v.) exhibits terminal elimination half-lives (99 h) due to high plasma clearance (3.9 liters/h/kg) combined with large volumes of distribution (374 liters/kg)[1].

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

Animal Model:	C.B-17 SCID mice engrafted with human PBMCs and injected with infectious X4 HIV-1 (NL4-3)[1]
Dosage:	10 mg/kg
Administration:	A single p.o. administration
Result:	Four of five mock-treated mice were infected whereas only one of five mice treated with KRH-3955 was infected.

Animal Model:	Male Sprague-Dawley rats[1]
Dosage:	10 mg/kg (Pharmacokinetic Analysis)
Administration:	A single p.o. or i.v. administration
Result:	Well absorbed and the absolute oral bioavailability in rats was calculated to be 25.6%. The half time ($T_{1/2}$) of 99.0±13.1 h. Stable in human hepatic microsomes, and no significant inhibition of CYP450 liver enzymes by this compound was observed.

REFERENCES

[1]. Tsutomu M, et, al. The Novel CXCR4 Antagonist KRH-3955 Is an Orally Bioavailable and Extremely Potent Inhibitor of Human Immunodeficiency Virus Type 1 Infection: Comparative Studies With AMD3100. Antimicrob Agents Chemother. 2009 Jul; 53(7): 2940-8.

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