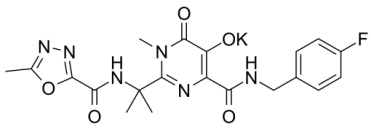
Data Sheet

Product Name:	Raltegravir (potassium)
Cat. No.:	CS-3263
CAS No.:	871038-72-1
Molecular Formula:	$C_{20}H_{20}FKN_6O_5$
Molecular Weight:	482.51
Target:	HIV; HIV Integrase
Pathway:	Anti-infection; Metabolic Enzyme/Protease
Solubility:	DMSO : 20.83 mg/mL (43.17 mM; ultrasonic and warming and heat to 60°C); H2O : 25 mg/mL (51.81 mM; Need ultrasonic)



BIOLOGICAL ACTIVITY:

Raltegravir (MK 0518) potassium is a potent **integrase (IN)** inhibitor, used to treat HIV infection. **In Vitro:** PFV IN carrying the S217H substitution is 10-fold less susceptible to Raltegravir with IC_{50} of 900 nM. PFV IN displays 10% of WT activity and is inhibited by Raltegravir with an IC_{50} of 200 nM, indicating a appr twofold decrease in susceptibility to the IN strand transfer inhibitor (INSTI) compared with WT IN. S217Q PFV IN is as sensitive to Raltegravir as the WT enzyme[1]. Raltegravir is metabolized by glucuronidation, not hepatically. Raltegravir has potent in vitro activity against HIV-1, with a 95% inhibitory concentration of 31±20 nM, in human T lymphoid cell cultures. Raltegravir is also active against HIV-2 when Raltegravir is tested in CEMx174 cells, with an IC_{95} of 6 nM. Raltegravir metabolism occurs primarily through glucuronidation. Drugs that are strong inducers of the glucuronidation enzyme, UGT1A1, significantly reduce Raltegravir concentrations and should not be used. Raltegravir exhibits weak inhibitory effects on hepatic cytochrome P450 activity. Raltegravir does not induce CYP3A4 RNA expression or CYP3A4-dependent testosterone 6-β-hydroxylase activity[2]. Raltegravir cellular permeativity is reduced in the presence of magnesium and calcium[3]. Raltegravir and related HIV-1 integrase (IN) strand transfer inhibitors (INSTIs efficiently block viral replication[4]. In acutely infected human lymphoid $CD4^+$ T-cell lines MT-4 and CEMx174, SIVmac251 replication is efficiently inhibited by Raltegravir, which shows an EC_{90} in the low nanomolar range[5]. **In Vivo:** Raltegravir induces viro-immunological improvement of nonhuman primates with progressing SIVmac251 infection. One non-human primate shows an undetectable viral load following Raltegravir monotherapy[5].

PROTOCOL (Extracted from published papers and Only for reference)

Cell Assay: [5]Human MT-4 cells are infected for 2 hours with the SIVmac251, HIV-1 (IIIB) and HIV-2 (CDC 77618) stocks at a multiplicity of infection of, approximately, 0.1. Cells are then washed three times in phosphate buffered saline, and suspended at 5×10^5/mL in fresh culture medium (to primary cells 50 units/mL of IL-2 are added) in 96-well plates, in the presence or absence of a range of triplicate raltegravir concentrations (0.0001 μM-1 μM). Untreated infected and mock-infected controls are prepared too, in order to allow comparison of the data derived from the different treatments. Viral cytopathogeniciy in MT-4 cells is quantitated by the methyl tetrazolium (MTT) method (MT-4/MTT assay) when extensive cell death in control virus-infected cell cultures is detectable microscopically as lack of capacity to re-cluster. The capability of MT-4 cells to form clusters after infection. Briefly, clusters are disrupted by pipetting; and, after 2 hours of incubation at 37°C, the formation of new clusters is assessed by light microscopy (100× magnification). Cell culture supernatants are collected for HIV-1 p24 and HIV-2/SIVmac251 p27 core antigen measurement by ELISA. In CEMx174-infected cell cultures, which show a propensity to form syncytia induced by the virus envelope glycoproteins, syncytia are counted, in blinded fashion, by light microscopy for each well at 5 days following infection.

References:

[1]. Hare, S., et al., Molecular mechanisms of retroviral integrase inhibition and the evolution of viral resistance. Proc Natl Acad Sci U S A, 2010. 107(46): p. 20057-62.

[2]. Hicks C, et al. Raltegravir: the first HIV type 1 integrase inhibitor. Clin Infect Dis. 2009 Apr 1;48(7):931-9

[3]. Moss DM, et al. Divalent metals and pH alter raltegravir disposition in vitro. Antimicrob Agents Chemother. 2012 Jun;56(6):3020-6

[4]. Hare S, et al. Structural and functional analyses of the second-generation integrase strand transfer inhibitor dolutegravir (S/GSK1349572). Mol Pharmacol. 2011 Oct;80(4):565-72.

[5]. Lewis, M.G., et al. Response of a simian immunodeficiency virus (SIVmac251) to raltegravir: a basis for a new treatment for simian AIDS and an animal model for studying lentiviral persistence during antiretroviral therapy. Retrovirology, 2010. 7: p. 21.

CAIndexNames:

4-Pyrimidinecarboxamide, N-[(4-fluorophenyl)methyl]-1,6-dihydro-5-hydroxy-1-methyl-2-[1-methyl-1-[[(5-methyl-1,3,4-oxadiazol-2-yl)carbonyl]amino]ethyl]-6-oxo-, potassium salt(1:1)

SMILES:

O=C(C(N=C(C(NC(C1=NN=C(C)O1)=O)(C)C)N2C)=C(O[K])C2=O)NCC3=CC=C(F)C=C3

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