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Potent and Selective Inhibition of HIV-1 and HIV-2 Replication by a Novel Class of Bicyclams Targeted at Viral Uncoating

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A variety of macrocyclic polyamines were synthesized and analyzed for activity against human immunodeficiency virus (HIV). Bicyclams, where the two cyclam units were linked in various ways, particularly JM1657 and JM2763, were found to be inhibitory to the replication of various HIV-1 and HIV-2 strains in various human T-cell systems, including peripheral blood lymphocytes, at a concentration of 0.1-1 μg/ml, without being toxic to the host cells at a concentration of 1.5 mg/ml. JM2763 was also active against azidothymidine (AZT)-resistant HIV-1 strains but not simian immunodeficiency virus (SIV). JM2763 did not inhibit HIV-1 binding to the cells; it did not prevent the formation of giant cells in a direct syncytium formation assay; it did not interact with the CD4 cell receptor or viral gp120 glycoprotein; and it did not prove inhibitory to either HIV-1 or HIV-2 reverse transcriptase, or HIV protease. Mechanism of action studies revealed the virion capsid uncoating as the presumable target for the anti-HIV action of JM2763, which thus represents the first example of an antiviral agent postulated to interact with the uncoating of retroviruses.

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HIV-1 Specific Phenylacetamide Derivatives: A Novel Class of Reverse Transcriptase Inhibitors with Potent and Selective Antiviral Activity *in vitro*

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High-flux *in vitro* screening of chemical libraries has led to the discovery of a new family of HIV-1 inhibitors. Through lead optimization several phenylacetamide derivatives have been identified that inhibit HIV-1 (strain III_B, RF, NDK or HE) replication in a variety of host cell types at concentrations which are 10,000 to 100,000 times lower than their cytotoxic concentrations. The 50% inhibitory concentration (IC_{50}) of the prototype phenylacetamide derivative R89439 for HIV-1 cytopathicity in MT-4 cells was 1-5 ng/ml. The median 90% inhibitory concentration (IC_{90}) was 11 ng/ml. This inhibition was found to be stereospecific. The phenylacetamide derivatives were not active against HIV-2 (strain ROD or EHO) or SIV (strain MAC_{251}). Synergism with 3'-azidothymidine (AZT) or 2',3'-dideoxyinosine (DDI) was demonstrated in cell culture. R89439 was inhibitory to virion-derived and recombinant reverse transcriptase (RT) of HIV-1, but not HIV-2. Stereospecific RT binding was observed with radiolabeled R89439. RT inhibition was dependent upon the template-primer used. The IC_{50} of R89439 in a poly(C).oligo(dG)-directed RT reaction was 74 ng/ml. Our findings indicate that these phenylacetamide derivatives inhibit HIV-1 RT by a mechanism that is similar of that of TIBO, HEPT, dipyridodiazepinone, pyridinone and BHAPs [bis(heteroaryl)piperazine] derivatives.