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Antiviral Properties of BMS 182,193, an Aminoalcohol Inhibitor of HIV Protease
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Human immunodeficiency virus (HIV) encodes for a protease which cleaves viral structural proteins. It is essential for production of infectious virus and therefore represents an important target for antiviral therapy. A series of aminoalcohol inhibitors were identified using an in vitro peptide cleavage assay. The compound BMS 182,193 protected cells against acute HIV-1 and HIV-2 infections with $IC_{50}$s of 0.06 μM to 0.33 μM, respectively and 50% cytotoxic concentrations of 5-10 μM. BMS 182,193 had similar antiviral activity against the replication of HIV-1 IIIB in peripheral blood mononuclear cells. In a time of addition assay, BMS 182,193 could be added as late as 26 hours after infection and still retain activity. To directly show that the culture efficacy of BMS 182,193 was due to inhibition of proteolytic cleavage, chronically infected 8E5 cells were treated with compound. Levels of HIV gag precursor (p55) and its processed protein (p24) in cell lysates were determined by Western Blot analysis. Results indicated that BMS 182,193 blocked the processing of p55 in a dose dependent manner ($IC_{50}$s of 0.4 μM). To examine the reversibility of a related aminoalcohol inhibitor, HIV-1 RF/CEM-SS cells were treated with drug and virions purified from culture medium. Incubation of virion particles in drug-free medium indicated that inhibition of p55 proteolysis was slowly reversible. The selective inhibitory activities of this compound against both acute and chronic HIV infections warrant its further development.

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**Potent Inhibition of Human Immunodeficiency Virus (HIV) Replication by Aromatic Linked Bis-Azamacrocycles: Synthesis and Effects of Macrocyclic Ring Size.**

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A novel series of phenylenebis(methylene) linked bis-azamacrocycles with ring sizes of 9-22 members and 3-6 nitrogen atoms have been synthesized and tested for anti-HIV activity. Potent anti-HIV activity of the bis-azamacrocycles was found to be specific for 12-14 membered ring systems but with varying cytotoxicity to the host cells. A study of the anti-HIV activity of dimers containing non-identical azamacrocycles will also be described. The optimum selectivity was achieved with JM 3100, a 14-membered bis-tetraazamacrocycle which inhibited the replication of several strains of HIV-1 and HIV-2 in various cell lines at an $IC_{50}$ of 1-10 ng/ml with a cytotoxic concentration greater than 500 μg/ml. The synthetic methodology leading to bis-azamacrocycles of different ring sizes will be discussed.