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Potent Inhibition of Human Immunodeficiency Virus (HIV) Replication by Aromatic Linked Bis-Azamacrocycles: Synthesis and Effects of Substitution at the Aromatic Linker.

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We have previously described that the bicyclam JM 3100, in which the cyclam (1,4,8,11-tetraazacyclotetradecane) moieties are tethered *via* an aromatic phenylenebis(methylene) linker, is a potent (IC_{50} of 1-10 ng/ml) and selective HIV inhibitor. A variety of bicyclams substituted at the aromatic linker were synthesized and analyzed for activity against human immunodeficiency virus (HIV). Several bicyclam derivatives were shown to retain both the potency and selectivity of JM 3100. For example, JM 3165, JM 3167 and JM 3207 were found to inhibit the replication of several strains of HIV-1 and HIV-2 in various cell lines at an IC_{50} of 1.3 - 7.6 ng/ml which is at least 30,000 - fold lower than the cytotoxic concentration (> 250 μg/ml). In the examples studied the *p*-substituted linker was at least an order of magnitude more potent than the corresponding *m*-substituted linker. Furthermore, the activity and selectivity were found to be sensitive to the electronic and steric nature of the substituents on the aromatic linker. The synthetic methodology leading to derivatives of JM 3100 will be discussed.

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The bicyclam derivative JM 2763 in which two cyclam rings are linked through an aliphatic propyl group is a potent and selective inhibitor of several strains of HIV-1 and HIV-2 with a unique target of action, tentatively assigned as a viral uncoating event [Proc. Natl. Acad. Sci. USA 89: 5286-5290 (1992)]. We have also described a 100-fold increase in potency observed when the cyclam moieties are linked via a phenylenebis(methylene) linker as in JM 3100, which inhibits the replication of HIV-1 (III_B) and HIV-2 (ROD) at an IC_{50} of 1-10 ng/ml while remaining non-toxic to the host cells at concentrations exceeding 500 μg/ml [Antiviral Res. 20 (Suppl. 1): Abst. 3, 1993]. By synthesizing a large variety of bis-azamacrocycles containing a phenylenebis(methylene) linker we have identified the key structural features which provide compounds of high potency and selectivity. Macrocyclic ring size, substituents on the aromatic linker and the point of attachment (C and N linked) all have a dramatic effect on the anti-HIV activity and cytotoxicity. The anti-HIV activity of transition metal complexes of JM 3100 will also be discussed.