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Synthesis and Structure-Activity Relationships in a Novel Class of Polyamines that Inhibit HIV-1 and HIV-2 Replication

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A large variety of known multidentate ligands, acyclic and macrocyclic polyamines and bicyclic polyamines were tested for anti-HIV activity, using the MT-4/MTT assay. All multidentate ligands and acyclic amines were found inactive and toxic to the host cells, whereas the monocyclic 1,4,8,11-tetra-azacyclotetradecane (cyclam, JM1498) exhibited marginal anti-HIV-1 and anti-HIV-2 activity (HTLV-III_B; IC_{50}: 44 μg/ml; SI= 8). However, bis-macrocycles containing the cyclam moiety were found to be potent inhibitors. The anti-HIV activity of the bicyclams appeared to be highly dependent upon the nature of coupling the cyclam rings. For example, against HIV-1 (HTLV-III_B), 2,2'-bicyclam (JM1657; IC_{50}: 0.1 μg/ml; SI= 2318) proved more potent than 6,6'-cyclam (JM1635; IC_{50}: 0.3 μg/ml; SI= 176) and in the N,N'-linked bicyclams, the compound containing a propyl linker (JM2763; IC_{50}: 0.1 μg/ml; SI= 3391) displayed superior activity over the analog containing an ethyl linker (JM2762; IC_{50}: 8.5 μg/ml; SI= 36). Mechanistic studies have suggested inhibition of viral uncoating as the presumable target for the anti-HIV activity of bicyclam analogs. Results of the anti-HIV-1 and HIV-2 assays for the range of compounds tested and synthetic strategies used for preparation of bis-macrocycles will be presented.

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Synthesis and *in vitro* anti-HIV activity of 2',3'-dideoxy-2',3'-methanonucleosides and of 3'-deoxy-2',3'-(difluoromethano)thymidine.

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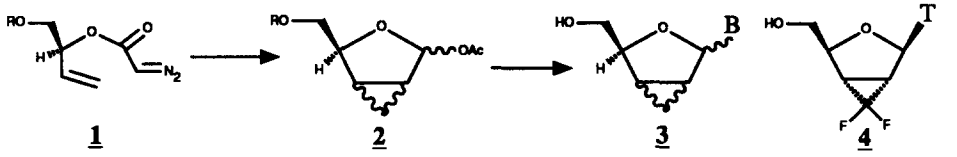
Many 2',3'-dideoxynucleosides possess potent anti-HIV activity and some have been investigated clinically, e.g. ddI and ddC. In addition the unsaturated analog of thymidine, 2',3'-didehydro-3'-deoxythymidine (D4T), has been pursued as a clinical candidate. Cyclopropano analogs are structurally related compounds and thus could also display potent anti-HIV activity. We report here on our general synthetic approach to this class of compounds starting with D-glyceraldehyde. The key step involved the construction of the cyclopropane moiety by a copper-(II) catalyzed decomposition of diazoester 1 to provide, through a intramolecular carbene, addition a pair of diastereomeric lactones. Reduction to the lactols followed by acetylation to the acetates 2, and Lewis acid catalyzed condensation with silylated bases provided mixtures of the α and β nucleosides 3 (B = A, T, C, G). None of these compounds had appreciable anti-HIV activity *in vitro*. In contrast, the bisfluoro thymidine analog 4, prepared in low yield by addition of difluorocarbene to N^3,$O^{5'}$-dibenzoyl-D4T, displayed significant *in vitro* anti-HIV activity (IC_{50}= 11 μM).



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