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New Approaches For Synthesizing Antiviral Nucleosides.

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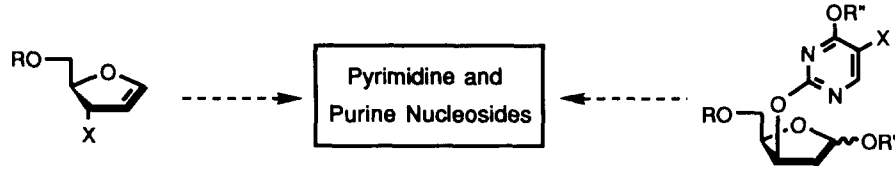
We have developed several complementary methods for synthesizing antiviral nucleosides. These approaches appear to be quite general and utilize inexpensive, acyclic precursors. Two of the methods to be discussed involve: (a) electrophilic additions to glycals; (b) 3' to 1' base transfers. The use of these methods for preparing several important antiviral nucleosides will be discussed.



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Inhibition of HIV replication by Cyclosporin derivatives: lack of correlation with immunosuppression.

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It has been argued that immunosuppression may have a beneficial effect in AIDS. It would block T4-cell activation which is necessary for HIV-replication and would thus have indirect antiviral activity; furthermore the autoimmune processes which presumably lead to killing of T4-cells would be inhibited. We tested Cyclosporin A, a large number of derivatives, FK 506 and several derivatives for inhibition of HIV-1 induced cytopathic effect in the T4-cell line MT4. Most of the CsA derivatives were inhibitory at a concentration below the cytotoxic concentration. On the other hand, FK 506 and derivatives were not active in this assay. The most potent CsA derivatives inhibited HIV-1 replication in MT4 cells at concentrations of 0.03 to 0.1 µg/ml, but impaired cell proliferation only at concentrations of 3 to 10 µg/ml. Anti-HIV activity, surprisingly, did not correlate with the immunosuppressive capacity of the derivatives but with Cyclophilin binding. FK 506 - as expected for an immunosuppressive drug - was able to block HIV replication in primary T4 lymphocytes when added simultaneously with PHA, i.e. before activation, but not when given after stimulation. Immunosuppressive as well as non-immunosuppressive Cyclosporin derivatives, on the other hand, were able to inhibit HIV when given before activation and also proved active when given 24 hours after PHA stimulation. The antiviral activity of selected immunosuppressive as well as non-immunosuppressive Cyclosporin derivatives was demonstrated in furhter T4 cell lines, in the promonocytic cell line U937, in HeLa CD4 cells, and in primary monocytes. The compounds proved equally active against laboratory strains of HIV-1 and against a set of clinical isolates from different geographic locations. Evidence was obtained that the step of virus replication which is inhibited by Cyclosporin derivatives is after penetration but before or at integration of the provirus.