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Synthesis of Carbocyclic Nucleosides, Nucleotides and Analogues Possessing anti-HIV Activity

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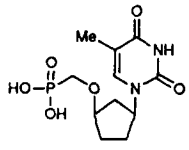
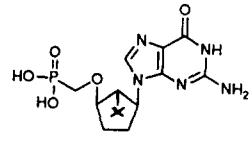
We have synthesised carbocyclic nucleosides and nucleotides of various types, for example in the deoxyribo, 2',3'-dideoxy-, and 2',3'-dideoxy-2',3'-didehydro-series. Recently we have prepared phosphonates of type (1) and (2) and we have shown that the pyrophosphate derivatives are potent inhibitors of HIV-reverse transcriptase. A full description of the syntheses and biological activities will be given.



(1)



(2) X = H or F

Reference: D.M. Coe, S.M. Roberts and R. Storer, *J.C.S. Perkin Trans. 1*, 1992, 2695.

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Highly Selective and Potent Inhibition of Human Immunodeficiency Virus (HIV) by the Novel Bicyclam Derivative JM3100

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We have previously described that bicyclams, in which the cyclam (1,4,8,11-tetraazacyclotetradecane) moieties are tethered *via* an aliphatic bridge (i.e. propylene as in JM2763) are potent and selective HIV inhibitors [Proc. Natl. Acad. Sci. USA 89: 5286-5290 (1992)]. We have now found that the bicyclam JM3100, in which the cyclam moieties are tethered by an aromatic phenylenebis(methylene) bridge, inhibits the replication of several strains of HIV-1 and HIV-2 in various cell lines at an IC_{50} of 1-10 ng/ml, that is about 100-fold lower than the concentration required for JM2763 to inhibit HIV replication, and at least 100,000-fold lower than the cytotoxic concentration (> 300 μg/ml). From time of addition experiments JM3100 appeared to interact with a viral uncoating event, and this was further corroborated by an uncoating assay in which RNase sensitivity of [^{3}H-5]uridine-labelled virions was monitored. JM3100 was also found to interfere directly with virus-induced syncytium formation, albeit at a higher concentration (1-2 μg/ml) than required for inhibition of viral replication. *In vivo*, following subcutaneous injection at 10 mg/kg to rabbits, JM3100 generated serum drug levels exceeding, for at least 6 hours, by > 100-fold the IC_{50} required to inhibit HIV replication *in vitro*. JM3100 is a highly selective and potent HIV inhibitor with a unique mode of action apparently targeted at a virus-associated uncoating process.