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

S.M. Roberts, Department of Chemistry, Exeter University, Exeter, Devon EX4 4QD, U.K.

We have synthesised carbocyclic nucleosides and nucleotides of various types, for example in the deoxyribo, 2',3'-dideoxy-, and 2',3'-dideoxy-2',3'-didehydroseries. 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.

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

3

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

E. De Clercq¹, N. Yamamoto¹, R. Pauwels¹, M. Witvrouw¹, K. De Vreese¹, Z. Debyser¹, R. Skerlj³, D. Thornton², G. Bridger³, G. Henson³ and M. Abrams³ Rega Institute for Medical Research, Katholieke Universiteit Leuven, B-3000 Leuven, Belgium; ²Johnson Matthey Technology Centre, Sonning Common, Reading RG4 9NH, United Kingdom; and ³Johnson Matthey Pharmaceutical Research, West Chester, Pennsylvania 19380, USA

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 IC50 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 $\mu\text{g}/\text{ml})\text{.}$ 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 [3H-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.