160

Novel Synthetic Approaches to Acyclic Phosphonate Analogues of Nucleotides. Structure-Activity Studies.

A.Holý, H.Dvořáková, J.Jindřich, P.Alexander, I.Rosenberg, M.Otmar and J.Balzarini, R.Snoeck, E.De Clercq
Institute of Organic Chemistry and Biochemistry, Czechoslovak Academy of Sciences, CS-166 10 Praha 6 (Czechoslovakia) and Rega Institute for Medical Research, Katholic University Leuven, B-3000 Leuven (Belgium).

Our foregoing investigation in the field of acyclic nucleotide analogues unveiled three main structural types of antivirals which warrant an utmost attention: N-(3-hydroxy-2-phosphonomethoxypropyl)(HPMP), N-(2-phosphonomethoxy ethyl)(PME) and N-(3-fluoro-2-phosphonomethoxypropyl)(FPMP) derivatives of purine and pyrimidine bases. Our determined effort resulted in the development of novel synthetic approaches which now permit efficient syntheses of miscellaneous derivatives bearing altered structural parameters. Novel methods will be demonstrated which make possible enantiospecific preparation of HPMP and FPMP compounds. Continued structure-specificity investigation which was based upon the exploitation of these synthetic capacities regards both modification of the heterocyclic base as well as absolute configuration at C-2 of the side--chain, and the role of the 3-OH group in HPMP derivatives which seems to determine whether the antiviral activity of diverse base-substituted and base--modified analogues will be directed against DNA viruses or retroviruses. Particular attention will be focused on aza and deaza derivatives in all three structural series, as well on relative activity of the singular enantiomers in the HPMP and FPMP series.