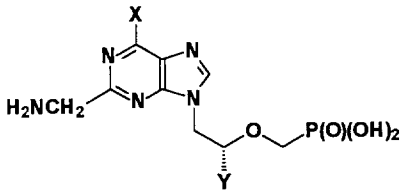
147

SYNTHESIS OF ACYCLIC NUCLEOTIDE ANALOGUES DERIVED FROM 2-(AMINOMETHYL)PURINE BASES.

A.Holý[a], M.Hocek[a], J.Balzarini[b] and E.De Clercq[b]

[a]Institute of Organic Chemistry & Biochemistry, Academy of Sciences, 16610 Prague, Czech Republic; [b]Rega Institute for Medical Research, Katholieke Universiteit Leuven, B-3000 Leuven, Belgium.

9-(2-Phosphonomethoxyalkyl)-2-(aminomethyl)purines were synthesized by selective alkylation of Cb-protected 2-(aminomethyl)adenine with bis(2-propyl) esters of phosphonomethoxyalkyl chlorides and tosylates at the 9-position. The resulting protected 2-aminomethyladenine derivatives were deaminated to the corresponding hypoxanthine derivatives (guanine nucleotide analogs).Iodotrimethylsilane treatment completely deprotected both Cb and 2-propyl functions giving the title compounds. None of these compounds showed any significant antiviral (HSV-1,HSV-2, VZV,CMV, VV, HIV-1, HIV-2) or cytostatic activity, nor any considerable cell toxicity.



X=NH$_2$, OH ; Y= H, CH$_3$, CH$_2$OH

148

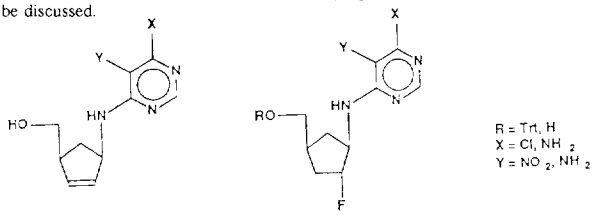
SYNTHESIS AND BIOLOGICAL EVALUATION OF NEW CARBOCYCLIC 2'3'-DIDEHYDRO-2',3'-DIDEOXY AND 3'-DEOXY-2'-FLUORO PYRIMIDINE AND PURINE NUCLEOSIDES

R.GUEDJ, E.E.E.SUHAS, P.R.T. FROGIER, R. CONDOM, S.R. CHALLAND, A. KIRN, A.M. AUBERTIN.

I) Purpose of the study : Carbocyclic nucleoside analogues exhibit antiviral activity against several viruses (HSV-1&2, HIV, HCMV, HBV). Therefore, the synthesis of carbocyclic 2',3'-didehydro-2'3'-dideoxy and 3'-deoxy-2'-fluoro pyrimidine and purine nucleosides has been realised in order to obtain new potential antiviral products.

II) Methods : Synthetic routes to these new classes of analogues utilise fonctionnalized cyclopentylamine and cyclopentenylamine as key intermediates. They are converted into carbocyclic analogues by further condensation with 4-nitro or 4-amino 2,6-dichloro-pyrimidines and ring closure presence of triethylorthoformate. 4-hydroxymethyl cyclopent-2-enylamine was prepared from 2-azabicyclo [2.2.1] hept-5-en-3-one in 4 steps : acid hydrolysis of the lactame, silylation of the acid and amino functions, reduction of the ester by aluminium lithium hydride and removal of the silyl protecting group of the amino function. The trityl derivative of 4-hydroxymethyl 2-fluoro cyclopentylamine was obtained from the isomeric *anti* epoxide by azide ion attack of the oxirane ring to give with very high selectivity the acohol, trityl portection of the primary hydroxyl, treatment of the azido-alcohol with DAST, reduction of the azide with hydrogen and Lindlar catalyst.

III) Summary of results : The synthesized carbocyclic (2'3'-didehydro-2'3'-dideoxy) and (3'deoxy-2'-fluoro) pyrimidine nucleosides have been evaluated for their activity against HSV-1, VZV, Influenza virus, HCMV and HIV. The results will be discussed.



IV) Conclusions : A short synthetic route to 4-hydroxymethyl cyclopent-2-enylamine was developed. Furthermore, a convenient synthesis of 4-hydroxymethyl 2-fluoro cyclopentylamine was realised. These two synthons are interesting for further condensation with different kinds of bases to yield new antiviral drugs.