Oral Session II: Herpesvirus Infections I

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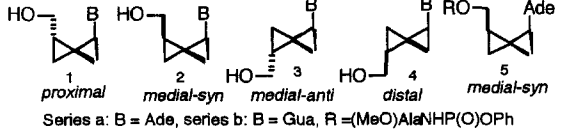
SPIROPENTANE ANALOGUES OF NUCLEOSIDES: CHEMISTRY AND ANTIVIRAL ACTIVITY. J. Zemlicka[1], H.-P. Guan[1], Y.-C. Cheng[2], J. C. Drach[3], E. R. Kern[4]. [1]Karmanos Cancer Institute, Wayne State University School of Medicine, Detroit, MI; [2]Yale University School of Medicine, New Haven, CT; [3]School of Dentistry, University of Michigan, Ann Arbor, MI; [4]University of Alabama School of Medicine, Birmingham, AL.

A new series of spiropentane analogues of 2'-deoxyadenosine and 2'-deoxyguanosine will be described. All possible isomeric forms in the adenine (1a - 4a) and guanine (1b - 4b) series were synthesized. The lipophilic prodrug 5 was also prepared. Biological activity was detected in all isomeric series. Thus, *proximal* and *medial-syn* isomers 1a and 2a were



Series a: B = Ade, series b: B = Gua, R =(MeO)AlaNHP(O)OPh

inhibitors of HCMV (EC_{50} 28 and 20 μM), CC_{50} >100 μM in HFF cells and EBV (EC_{50} 4.8 and 22 μM), CC_{50} 15 and >202 μM in Daudi cells. The guanine *distal* isomer 4b was also effective against EBV/Daudi (EC_{50} 6.0 μM, CC_{50} >199 μM). The *medial-anti* isomer 3a was devoid of antiviral activity but it was a substrate for adenosine deaminase. Conversion of *medial-syn* isomer 2a to lipophilic phenylphosphoralaninate 5 increased the antiviral potency of 2a. Thus, compound 5 inhibited HCMV (EC_{50} 0.38 μM, CC_{50} 100 μM), HSV-1/BSC-1 (EC_{50} 7.0 μM, CC_{50} 70 μM in KB cells) and HBV/2.2.15 (EC_{50} 3.1 μM, CC_{50} 27 μM in CEM cells). It was also a potent but cytotoxic inhibitor of EBV (EC_{50} 2.8 μM, CC_{50} 7.6 μM). Activity of 5 indicates that phosphorylation is necessary for activation of 2a. Supported by NIH grants RO1-CA32779, RO1-44358, U19-AI31718, RO1-AI33332 and NO1-AI-35177.

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Antiviral Activity of D- and L-Enantiomers of Cyclohexenyl Guanine

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The D- and L-cyclohexenyl guanine (G) nucleosides were synthesized in a stereospecific manner starting from R-(H)-carvone. Both enantiomers exhibited a potent and selective activity against herpesviruses (HSV-1 and HSV-2, VZV and HCMV). Their adenine counterparts showed very low antiviral activity. Both D- and L-cyclohexenyl G displayed similar activity against HSV-1 (IC_{50}: 0.002-0.004 μg/ml); they were slightly less active against HSV-2 (IC_{50}: 0.05-0.1 μg/ml). These results are comparable to those obtained with the reference drug acyclovir. Against VZV and HCMV, the potency of L-cyclohexenyl G (IC_{50}: 1.5 and 1.6 μg/ml, respectively) was about 2-fold lower than that of D-cyclohexenyl G (IC_{50}: 0.47 and 0.7 μg/ml, respectively). The activity of the latter against HCMV was similar to that obtained for the reference drug ganciclovir in the same conditions. The L- and D-cyclohexenyl G nucleosides retained activity against the TK^- strains of HSV-1 and VZV, albeit to a lesser extent than for the wild-type. In addition, both enantiomers remained active against several strains of HCMV that were resistant to either ganciclovir or foscavir. D- and L-cyclohexenyl G represent the most potent antiviral nucleosides containing a six-membered carbohydrate moiety that have ever been reported. Furthermore, they are the first example of enantiomeric nucleosides, both show similar activity against HSV, VZV and HCMV. Further studies are ongoing to elucidate the mechanism of action of D- and L-cyclohexenyl G, particularly against HCMV.