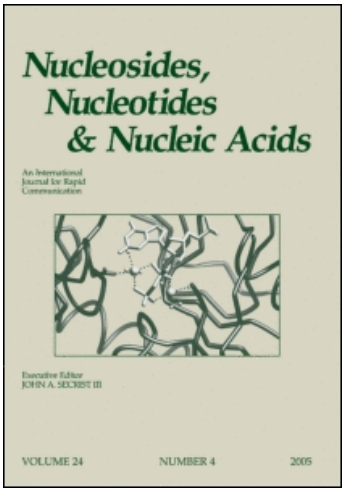

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D-xylo and Lyxofuranonucleosides Reviewed: Some Suggestions on The Mechanism of Activity of Antiviral Nucleosides

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D-XYLO AND LYXOFURANONUCLEOSIDES REVIEWED : SOME SUGGESTIONS ON THE MECHANISM OF ACTIVITY OF ANTIVIRAL NUCLEOSIDES

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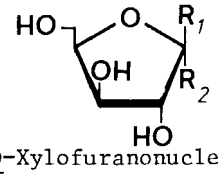
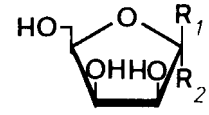
INTRODUCTION : D-Xylo and Lyxofuranonucleosides have not been extensively studied. Therefore in order to perform a systematic Structure-Antiviral Activity Relationship of the nucleoside analogs we have first synthesized their α and β anomers, some of them being unknown or their structure doubtful in the literature.



D-Xylofuranonucleosides



D-Lyxofuranonucleosides

R_1 = base, R_2 = H ⟶ β anomer ; R_1 = H, R_2 = base ⟶ α anomer (base = 9-adenine or guanine and 1-cytosine, thymine or uracil)

Here we present results concerning the antiviral effect of these analogs in cell culture as well as assays of reversion of this effect by natural nucleosides. With data currently available in the literature for other compounds, it seems possible to formulate some remarks on the relationship between the chemical structure and the antiviral activity of nucleoside analogs.

RESULTS : ANTIVIRAL ACTIVITY and ASSAYS OF REVERSION OF THE ANTIHERPETIC ACTIVITY OF D-XYLO and LYXOFURANONUCLEOSIDES (virus cultivated on Hela cells at a high multiplicity of infection ; analogs always used at the uniform concentration of 0.1 mg/ml. Natural antagonist nucleosides, when used, are at a 10-fold higher concentration, i.e. 1.0 mg/ml).

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1) ANTIVIRAL ACTIVITY :

- All tested analogs were inactive on a positive-stranded RNA-virus (Polio-2) and on a negative-stranded RNA-virus (Vesicular Stomatitis Virus).

- Four analogs showed good activity on a DNA-virus (Herpes Simplex Virus type 1) : 9-β-D-xylofuranosyladenine and guanine (β-D-XyloA and G), 1-β-D-xylofuranosylcytosine (β-D-xyloC) and 9-α-D-lyxofuranosyladenine (α-D-lyxoA).

2) REVERSION OF THE ANTIHERPETIC ACTIVITY of the four active analogs :

- β-D-XyloA was reversed by Adenosine (not by 2'-deoxyadenosine) and α-D-LyxoA was reversed by Thymidine, Uridine or 2'-deoxycytidine ; this denotes a competitive mechanism.

- β-D-XyloG and β-D-XyloC were not reversed by any of the natural nucleosides tested.

DISCUSSION : The results so far shown and other data from the literature seem to suggest some remarks concerning the relationship between the chemical structure and the antiviral activity of nucleoside analogs.

1) PURINE NUCLEOSIDE KINASES (Virus induced Purine Nucleoside Kinases are not known ⟶ Involved purine kinases must be cellular) :

- To be a Substrate for Adenosine or Deoxyadenosine Kinases ⟹ The base must be Adenine and the sugar anomeric form must be β.

. For Adenosine Kinase the sugar must bear on C-2' an OH-trans relatively to the base (Ex : β-D-XyloA and 3'-deoxyA).

. For Deoxyadenosine Kinase the sugar must fulfil two negative conditions : no OH-Trans on C-2' and no OH-Cis on C-3' (Ex : β-D-AraA, 2',3'-dideoxyA).

- The situation is different for Guanosine and Deoxyguanosine Kinases since : 1) β-D-AraG has practically no biological activity, and 2) β-D-XyloG has a potent antiviral and cytostatic effect which is irreversible.

2) PYRIMIDINE NUCLEOSIDE KINASES : The scheme is more complicated due to the occurrence of virus induced enzymes which are interve-

ning concurrently to cellular enzymes. For instance : a) Herpes, Pox and Adenovirus have virus-coded Thymidine Kinase. b) Not only Thymidine but also β-D-2'-deoxyC, AraC and T, α-D-LyxoA and Acyclovir could be substrate for the Herpetic Thymidine Kinase. So the base is not necessary a pyrimidine but is nature is depending from the structure of the sugar : Guanine in Acyclovir, Adenine in α-D-LyxoA.

3) POLYMERASES : When phosphorylation can process up to the 5'-triphosphates, these last compounds can behave as inhibitor or substrate for RNA and/or DNA Polymerases. To date, most of substances having shown an antiviral effect solely acts on the multiplication of DNA viruses. Only few nucleoside analogs, always with the β-D-Ribo configuration, are substrate for viral RNA Polymerases.

CONCLUSION : The reported data let us believe that nucleoside analogs active on RNA viruses could very probably be found only observing one or both of the following conditions :

. Modified base with β-D-Ribose.

. Modified or natural base with a sugar having a spatial configuration similar to β-D-Ribose (2' and 3'-groups in Trans with regard to aglycone). Ex : 2' as 3'-amino as 2',3'-diaminoRibose ; perhaps dihydroxypropylNucleosides. We are wanting to stress that our conclusion must be considered as suggestions to be further conforted by experiments.