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## Nucleosides, Nucleotides and Nucleic Acids

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### 3'-(N-Hydroxyimino)-2',3-dideoxynucleosides and Their Derivatives: Synthesis, Broad Spectrum Antiviral Properties and Synthetical Application for the Preparation of Other Nucleoside Analogues

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**3'-(N-HYDROXYIMINO)-2',3'-DIDEOXYNUCLEOSIDES AND THEIR  
DERIVATIVES: SYNTHESIS, BROAD SPECTRUM ANTIVIRAL PROPERTIES  
AND SYNTHETICAL APPLICATION FOR THE PREPARATION OF OTHER  
NUCLEOSIDE ANALOGUES**

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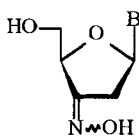
**ABSTRACT:** A series of 3'-(N-hydroxyimino)-2',3'-dideoxynucleosides bearing different nucleic bases has been prepared. *In vitro* antiviral activity studies showed that among these compounds the thymine derivative possesses significant activity against HIV, HSV, EBV and HBV. Conveniently 5'-protected 3'-(N-hydroxyimino)-2',3'-dideoxythymidine was further used as a synthon for the preparation of other nucleoside analogues.

In order to prepare novel 3'-substituted-2',3'-dideoxynucleosides with potential antiviral activity we have previously reported the synthesis of 3'-(N-hydroxyimino)-2',3'-dideoxythymidine (ODT) (I) [1], which showed significant activity against HIV, HSV, HBV [1] and EBV [2]. More recently, we have also prepared a series of related analogues bearing different natural and non-natural nucleic bases (I-IX).

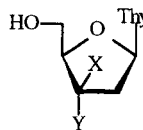
Appropriately 5'-protected ODT derivatives appeared to be convenient synthons for the preparation of other nucleoside analogues. Thus, oxidation of such a ODT

synthon with  $\text{CF}_3\text{COOOH}$ , followed by 5'-deprotection afforded the 3'-nitro derivative (**X**) [1, 3], and reduction with  $\text{NaBH}_4$  gave a diastereomeric mixture of the respective *threo*- and *erythro*- 3'-N-hydroxyamino- derivatives (**XI**, **XII**) which have already been previously reported [4]. Treatment of a ODT synthon with DAST gave a mixture of compounds containing a six-member ring product of Beckman rearrangement (**XIII**), as well as two diastereomeric fluorinated products with a restricted bond at the 3',4' positions of the sugar moiety (**XIV**-**XV**). The structure of **XIII** was confirmed by X-ray analysis.

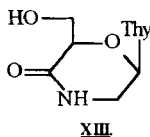
Some analogues of ODT, namely compounds **II**, **IV**, **VI** as well as the *threo*- and *erythro*- 3'-N-hydroxyamino derivatives **XI** and **XII** showed moderate activity against HIV, but were devoid of activity against HSV and HBV. The compounds containing uracil base (**III**) or non-natural nucleic bases (**VI**-**IX**) did not show any activity against the investigated DNA and RNA viruses. The difference in the antiviral activity spectrum of ODT and compounds **XI** and **XII** suggests that the latter are not subject of intracellular oxidation to ODT. The antiviral properties of the compounds **XIII**-**XV** is currently under investigation.



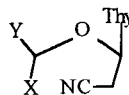
B =  
**I**. Thy (ODT), **II**. Cyt, **III**. Ura,  
**IV**. Ade, **V**. Gua, **VI**. Ura(5F)  
**VII**. Ura(5CF<sub>3</sub>), **VIII**. Ura(5I), **IX**. Ura(5Et),



**X**. X = H, Y = NO<sub>2</sub>  
**XI**. X = H, Y = NHOH  
**XII**. X = NHOH, Y = H



**XIII**



**XIV**. X = F, Y = CH<sub>2</sub>OH  
**XV**. X = CH<sub>2</sub>OH, Y = F

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