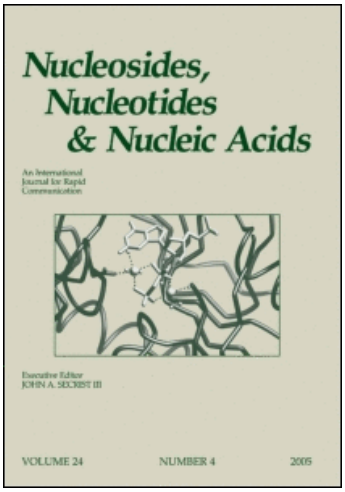

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3'-(N-Hydroxyimino)-2',3-dideoxynucleosides and Their Derivatives: Synthesis, Broad Spectrum Antiviral Properties and Synthetical Application for the Preparation of Other Nucleoside Analogues

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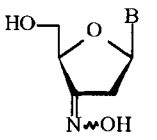
ABSTRACT: A series of 3'-(N-hydroxyimino)-2',3'-dideoxynucleosides bearing different nucleic bases has been prepared. *In vitro* antiviral activity studies showed that among these compounds the thymine derivative possesses significant activity against HIV, HSV, EBV and HBV. Conveniently 5'-protected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

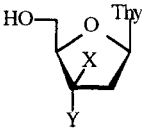
Appropriately 5'-protected ODT derivatives appeared to be convenient synthons for the preparation of other nucleoside analogues. Thus, oxidation of such a ODT

synthon with CF_3COOOH, followed by 5'-deprotection afforded the 3'-nitro derivative (X) [1, 3], and reduction with $NaBH_4$ 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.

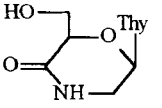
Some analogues of ODT, namely compounds II, IV, VI as well as the *threo-* and *erythro-* 3'-N-hydroxyamino derivatives XI and XII showed moderate activity against HIV, but were devoid of activity against HSV and HBV. The compounds containing uracil base (III) or non-natural nucleic bases (VI-IX) did 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.



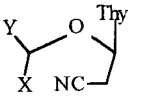
B=
I. Thy (ODT), II. Cyt, III. Ura,
IV. Ade, V. Gua, VI. Ura(5F)
VII. Ura(5CF3), VIII. Ura(5I), IX. Ura(5Et),



X. X= H, Y= NO_2
XI. X= H, Y= NHOH
XII. X= NHOH, Y= H



XIII.



XIV. X= F, Y= CH_2OH
XV. X= CH_2OH, Y= F

REFERENCES

1. Fedorov, I.I.; Kazmina, E.M.; Gurskaya, G.V.; Jasko M.V.; Zavodnic, V.E.; Balzarini, J.; De Clercq, E.; Faraj, A.; Sommadossi, J.-P.; Imbach J.-L.; Gosselin, G. *J. Med. Chem.*, **1997**, 40, 486-494.
2. Meerbach, A.; Holy, A.; Wutzler, P.; De Clercq, E.; Neyts, J.; *Antiviral Chem. Chemother.*, **1998**, 9, 275-282.
3. Hossain, N; Papchikhin, A.; Garg, N.; Fedorov, I.; Chattopadhyaya J. *Nucleosides Nucleotides*, **1993**, 12, 499-528.
4. Tronchet, J.M.J.; Zsely, M.; Capek, K; Komaromi, I.; Geoffroy, M.; De Clercq, E.; Balzarini, J. *Nucleosides Nucleotides*, **1994**, 13, 1871-1889.