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## Nucleosides, Nucleotides and Nucleic Acids

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## SYNTHESIS OF AZT- $\alpha$ -BORANO-5'-DIPHOSPHO-HEXOSES

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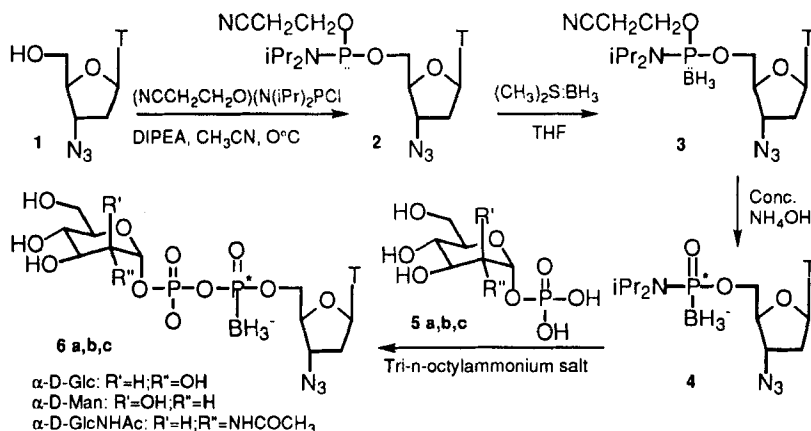
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**ABSTRACT :** 3'-Azido-3'-deoxythymidine- $\alpha$ -borano-5'-diphospho-hexoses have been synthesized. Their diastereoisomers were separated by HPLC.

3'-Azido-3'-deoxythymidine (AZT) was the first drug in clinical use for the treatment of infection with the human immunodeficiency virus (HIV)<sup>1</sup>, the etiologic agent of the acquired immunodeficiency syndrome (AIDS)<sup>2</sup>. More than ten years ago, Schinazi et al.<sup>3</sup> prepared various 5'-diphosphohexoses AZT, and many of these compounds had antiviral, including anti-HIV, activity. In this proceeding, we reported the synthesis and the evaluation of anti-HIV effects in HIV-1-LAI-infected peripheral blood mononuclear cells (PMBC) of the 5'- $\alpha$ -boranophosphate analogs.

Most of the chemical synthesis of sugar diphosphate nucleosides involve the coupling of a glycosyl phosphate with an activated nucleoside monophosphate (NMP)<sup>4a,b</sup>. The AZT  $\alpha$ -borano-5'-diphospho-hexoses **6a,b,c** were prepared according to the following scheme: AZT **1** was phosphitylated giving **2**. Compound **2** was then oxidised into the AZT boranophosphate cyanoethylester **3** by reaction with an excess of dimethyl sulfide-borane<sup>5</sup>. Compound **3** reacted with conc. NH<sub>4</sub>OH, hydrolysing the cyanoethyl group to give **4**. Reaction of **4** with trioctylammonium salt glycosyls phosphate respectively ( $\alpha$ -D-glucose 1-P **5a**,  $\alpha$ -D-mannose 1-P **5b** and  $\alpha$ -D-N-acetyl-glucosamine 1-P **5c**) afforded the corresponding title compounds **6a,b,c**. The boron-modified P-diastereoisomers of **6a,b,c** were separated in 1:1 ratio by RP-HPLC on a C<sub>18</sub> column eluted by a 0.01M solution of triethylammonium acetate containing 5 to 25% of acetonitrile, to give for the

mannose couple, as an example, **6b-1** (7.18 min) and **6b-2** (8.20 min) are the faster and slower eluting diastereoisomers, respectively.



Molecules were tested towards phytohemagglutinin (PHA)-P-activated PBMC infected with 100 TCID<sub>50</sub> of the lymphotropic reference HIV-1-LAI strain. HIV replication was assessed by the dosage of reverse transcriptase (RT) activity in cell culture supernatants. Cells were one-hour pre-treated and maintained all along the culture.

None of the six tested AZT derivatives demonstrated higher antiviral activity than AZT.. The closest antiviral activity was observed with compound **6a-1** (ED<sub>50</sub> **6a-1**: 75 nM vs. ED<sub>50</sub> AZT 3 nM). Nevertheless, these molecules are of interest because 1) unlike other nucleotides, they may cross the plasma membrane, and 2) they are able to liberate  $\alpha$ -borano AZTMP and AZTDP inside the cells and, as a consequence, the two first steps of phosphorylation, probably the most limiting for dideoxynucleoside efficiency, are avoided.

## REFERENCES

- 1 Fischl, M.A.; Richman, D.D.; Grieco, M.H.; Gottlieb, M.S.; Volberding, P.A.; Laskin, O.L.; Leedom, J.M.; Groopman, J.E.; Milvan, D.; Scooley, R.T.; Jackson, G.G.; Durach, D.T.; King, D. *Eng. J. Med.*, **1987**, 317, 188-191.
- 2 Barré-Sinoussi, F.; Chermann, J.C.; Rey, R.; Rey, F.; Nugeyre, M.T.; Chamaret, S.; Gruest, J.; Dautet, C.; Axler-Blin, C.; Vezinet-Brun, F.; Rouzioux, C.; Rozenbaum, W.; Montagnier, L. *Science*, **1983**, 220, 868-871.
- 3 Schinazi, R.F.; Shafer, W.M.; Sommadossi, J.P.; Chu, C.K. PCT Int. Appl. WO 91 00, 867.
- 4 a-Heidlas, J.E.; Williams, K.W.; Whitesides, G.M. *Acc. Chem. Res.*, **1992**, 25, 307-314. b- Kochetkov, N.K.; Shibaiev, V.N. *Adv. Carbohydr. Chem. Biochem.*, **1973**, 28, 307-399.
- 5 Sood, A.; Shaw, B.R.; Spielvogei, B.F. *J. Am. Chem., Soc.*, **1990**, 112, 9000-9001.