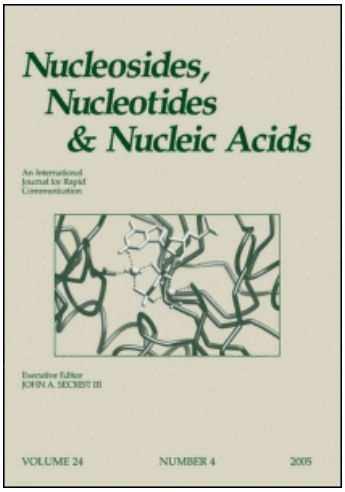

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Investigations of Nucleoside *H*-Phosphonamidate in the Design of Nucleotide Prodrug

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ABSTRACT

The synthesis, anti-HIV activity and stability studies of a *H*-phosphonamidate derivative of 3′-azido-2′,3′-dideoxythymidine (AZT) incorporating a *N*,*N*-diisopropylamino residue as first model of alkylamino group are reported. The results demonstrate that such phosphorylated structure exerts its biological effects via chemical hydrolysis into the corresponding *H*-phosphonate, precursor of the parent nucleoside.

Key Words: Prodrug; Mononucleotide; Bioconversion.

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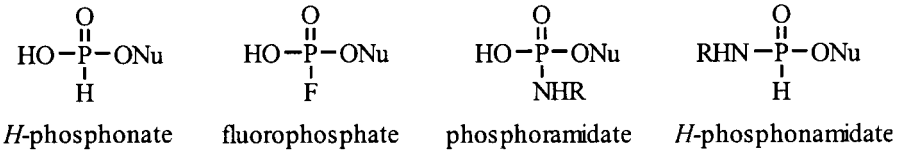
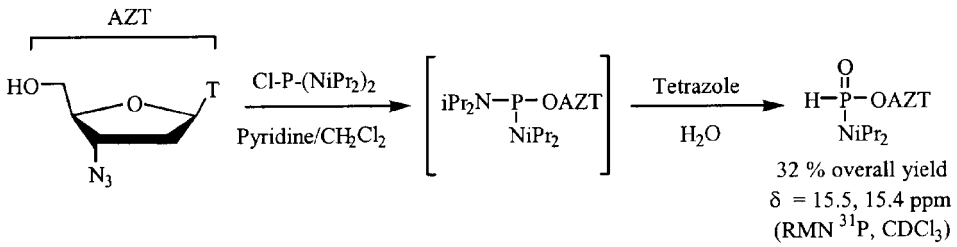


Figure 1.

The use of structurally phosphate modified nucleotides is one of the strategies envisaged to improve the therapeutic efficiency of nucleoside analogues. Such entities would be expected to act as mononucleotide prodrugs (pronucleotides) leading to the delivery of the corresponding mononucleotides inside infected cells.[1] This approach has been particularly illustrated by the study of nucleoside *H*-phosphonate,[2] fluorophosphate[3] or phosphoramidate[4] monoester derivatives (Fig. 1).

As part of our ongoing research on this topic, we decided to evaluate the potentialities of new series of *H*-phosphonate derivatives having a nitrogen atom linked to the phosphorus center, i.e., nucleoside *H*-phosphonamidate (Fig. 1). Using AZT as nucleoside model, the synthesis of the *H*-phosphonamidate derivative incorporating a *N*,*N*-diisopropylamino residue was performed by coupling successively AZT with bis(*N*,*N*-diisopropylamino) chlorophosphine, and in situ hydrolysis in presence of tetrazole and water (Sch. 1).

In two human T_4-lymphoblastoid cell lines, the studied *H*-phosphonamidate derivative displayed an anti-HIV activity comparable to AZT, with an effective concentration about submicromolar range. In contrast, no antiretroviral activity was observed in thymidine kinase-deficient CEM cells indicating the unsuccessful intracellular release of the corresponding 5′-mononucleotide. This point was corroborated by stability studies in several media which showed that the *H*-phosphonamidate structure was hydrolysed to the corresponding *H*-phosphonate derivative, precursor of the parent nucleoside.[2]



Scheme 1.

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