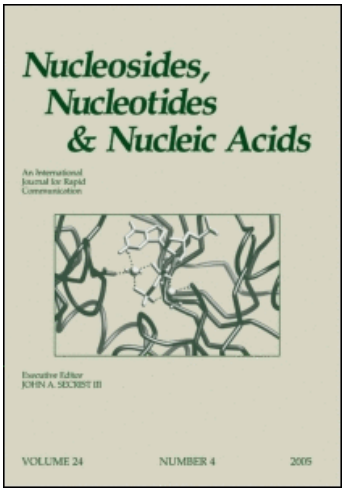

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New Series of Mixed Pronucleotides. Synthesis and Anti-HIV Activities of Mononucleoside Phenyl SATE Phosphotriesters

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NEW SERIES OF MIXED PRONUCLEOTIDES. SYNTHESIS AND ANTI-HIV ACTIVITIES OF MONONUCLEOSIDE PHENYL SATE PHOSPHOTRIESTERS

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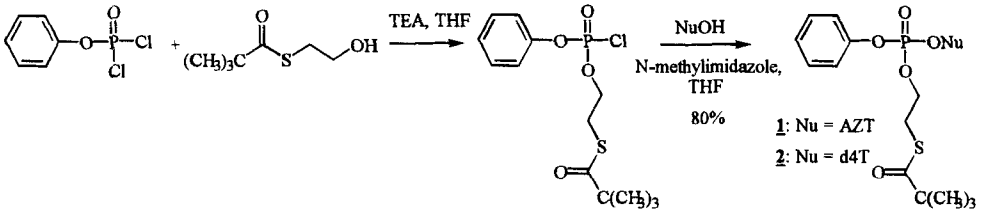
ABSTRACT: The synthesis and anti-HIV activities of phenyl *S*-pivaloyl-2-thioethyl (*t*BuSATE) phosphotriesters of AZT and d4T are reported. These compounds show similar activity compared to bis(*t*BuSATE) phosphotriesters and appear to be able to deliver the corresponding 5'-mononucleotides inside the cells.

Previous *in vitro* studies have shown that the anti-HIV activity of several nucleoside analogues can be enhanced by using their mononucleotide prodrugs (usually called pronucleotides)[1-3]. As part of our antiviral drug research program, we decided to evaluate the potentialities of new series of mixed phosphorylated derivatives involving two different enzymatic process in their decomposition pathways. Among the wide range of enzymatic systems present inside the cells, we were particularly interested on esterases and phosphodiesterases. Indeed, it has been reported that the binding domain, of the active site of some of them, has good affinity for aromatic substituants[4]. Consequently, we choose to design mononucleotide prodrugs which will bear one SATE group and an aryl phosphate protection. As preliminary models, we would like to describe herein the synthesis and the anti-HIV-1 activities of phenyl *t*BuSATE phosphotriester derivatives of AZT and d4T, **1** and **2**, respectively (Scheme).

Synthesis. The phenyl *t*BuSATE phosphotriester derivatives, **1** and **2**, were both prepared using P(V) chemistry (Scheme). The commercially available phenyl phosphorodichloridate

was reacted successively with *S*-pivaloyl-2-thioethanol, to give the phosphoromonochloridate, which was coupled without further purification with AZT or d4T. The expected phosphotriesters **1** and **2** were obtained as diastereoisomeric mixture after silica gel column chromatography with 80% overall yields and fully characterised.



Scheme. Synthesis of phenyl tBuSATE phosphotriesters of AZT **1** *and d4T* **2**.

Biological Results. Phenyl *t*BuSATE phosphotriesters **1** and **2** were evaluated for their inhibitory effects on the replication of HIV-1 in several cell lines including thymidine kinase-deficient CEM cells (CEM/TK$^-$). The tested compounds **1** and **2** exhibited a potent anti-HIV effect with IC_{50} at submicromolar concentrations, whereas the nucleosides are unactive for AZT, and poorly active for d4T.

The results presented here demonstrate, on the basis of phenyl *t*BuSATE phosphotriester derivatives of AZT and d4T as first models, that mixed phosphotriesters incorporating two different phosphate protections such as a SATE and an aryl groups allow the intracellular delivery of the parent 5'-mononucleotide. Work is currently in progress in order to synthesize and study various mixed phosphotriester derivatives.

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