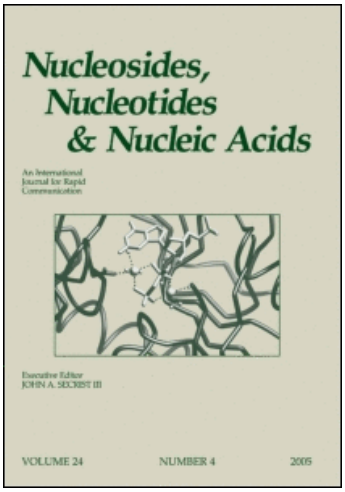

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Synthesis and Anti-HIV Activity of Some *S*-Acyl-2-thioethyl (SATE) Phosphoramidate Derivatives of 3'-Azido-2',3'-dideoxythymidine

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SYNTHESIS AND ANTI-HIV ACTIVITY OF SOME *S*-ACYL-2-THIOETHYL (SATE) PHOSPHORAMIDATE DERIVATIVES OF 3'-AZIDO-2',3'-DIDEOXYTHYMIDINE

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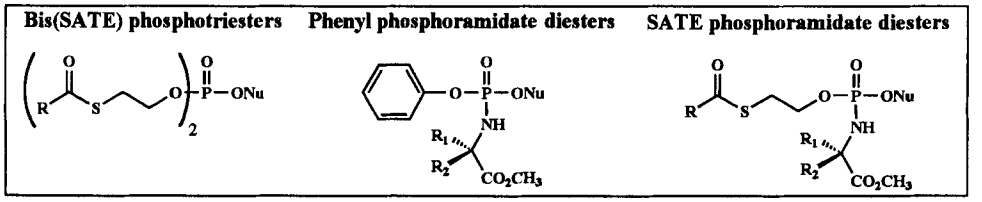
ABSTRACT: The synthesis and *in vitro* anti-HIV activity of *t*BuSATE phosphoramidate derivatives of AZT incorporating several methyl-esterified α-aminoacids are reported. The biological evaluation strongly supports the hypothesis that such compounds exert their anti-HIV effects *via* intracellular delivery of the corresponding 5'-mononucleotide.

Many strategies have previously been envisaged to mask or to reduce the phosphate negative charges of nucleoside 5'-monophosphate analogues, thereby forming more lipophilic derivatives (pronucleotides) which would be expected to revert back to the corresponding 5'-mononucleotides inside the cell[1]. Among the various pronucleotide series, we have previously demonstrated that mononucleoside phosphotriesters incorporating two *S*-acyl-2-thioethyl (SATE) groups (FIG.) as enzyme-labile transient phosphate protections allow the intracellular delivery of 5'-mononucleotide[2]. Another attractive pronucleotide approach uses phenyl phosphoramidate diesters[3,4] containing methyl-esterified α-amino acids (FIG.). In this last series, the biological activity is highly depending on the nature of the amino acid[5].

In order to design new kinds of pronucleotides, we decided to combine these two strategies by synthesising and studying new mononucleotide prodrugs, namely SATE phosphoramidate diesters (FIG.). Using AZT as nucleoside moiety, we report here the synthesis and anti-HIV activities of phosphoramidate derivatives incorporating the *S*-pivaloyl-2-thioethyl (*t*BuSATE) group and various methyl-esterified α-amino acids.



Figure

The SATE phosphoramidate diester derivatives of AZT were prepared following a three step procedure: (i) the formation of the *t*BuSATE H-phosphonate monoester, (ii) synthesis of the corresponding *t*BuSATE AZT H-phosphonate diester, (iii) conversion of the H-phosphonate diester into the desired phosphoramidates via oxidative coupling with the corresponding methyl-esterified amino acids.

As expected AZT is inactive against HIV-1 replication in CEM/TK$^-$ cell line, whereas all the phosphoramidate derivatives proved to be markedly effective. At the opposite to the phenyl phosphoramidate series[5], the variation of the structure of the amino acid side-chain does not lead to notable change of the EC_{50} values, which are included between 2.3 and 8 μM. This result can be considered as evidence that SATE phosphoramidates allow the efficient delivery of the corresponding 5'-mononucleotide inside the cells.

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