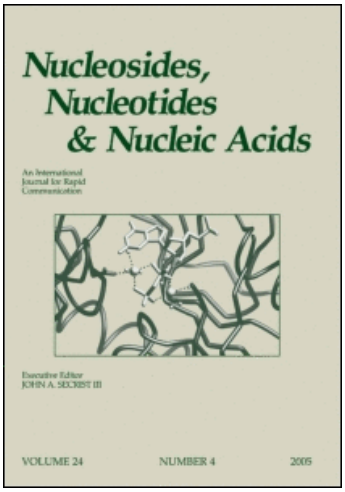

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Mononucleoside SATE Glucosyl Phosphorothiolates as a New Series of Pronucleotides

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ABSTRACT

The synthesis and the study of two phosphorothiolate derivatives of 3′-azido-2′,3′-dideoxythymidine (AZT) bearing a *S*-pivaloyl-2-thioethyl (*t*BuSATE) group and glucosyl residues associated to the phosphorus atom by a 2-oxyethyl link, are reported. These derivatives could be considered as prototypes of a new series of nucleotide prodrugs (pronucleotides).

Key Words: Prodrug; Mononucleotide; Glucosidase.

We have previously reported that the use of mononucleoside arylphosphotriester or phosphoramidate diester derivatives bearing one *t*BuSATE group (Fig. 1) leads to the intracellular delivery of the corresponding mononucleotide.[1,2] As part of our work in this field, the potentialities of a new series of mixed phosphorylated derivatives, namely SATE glucosylphosphorothiolates (Fig. 1), have been evaluated.

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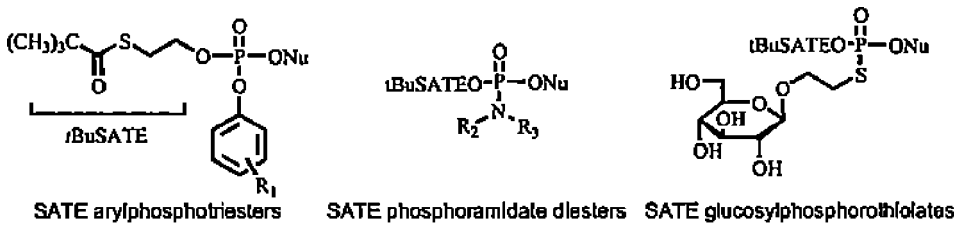
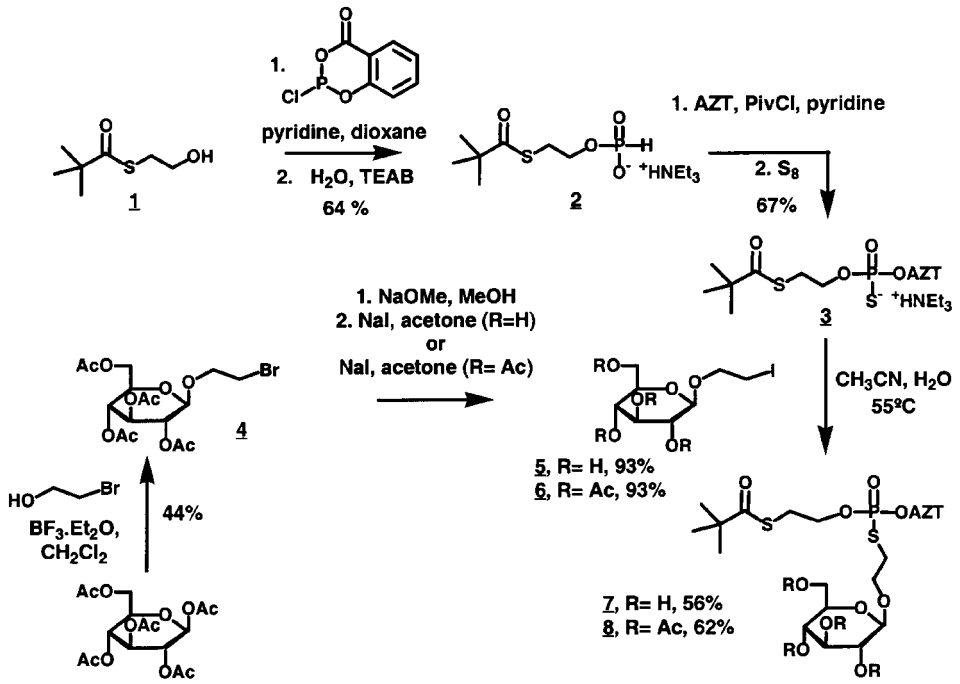


Nu = 3'-azido-2',3'-dideoxythymidin-5'-yl; R_1, R_2, R_3 = H, alkyl or aryl residues

Figure 1.



Scheme 1.

The synthesis of phosphorothiolate models **7** and **8** (Sch. 1) combined two common strategies using P^{III} and P^{V} intermediates. These derivatives were evaluated for their inhibitory effects on the replication of HIV-1 in several cell lines. In thymidine-kinase deficient (TK^-) CEM cells compounds **7** and **8** exhibited, in contrast to AZT, antiviral activity at micromolar concentration showing their ability to act as pronucleotides.

This point was corroborated by stability studies in various biological media as well as evaluation of substrate properties towards purified β-glucosidase. The proposed decomposition mechanism of these mixed pronucleotides involves successively two different enzymatic systems, i.e., esterases and glucosidases.

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