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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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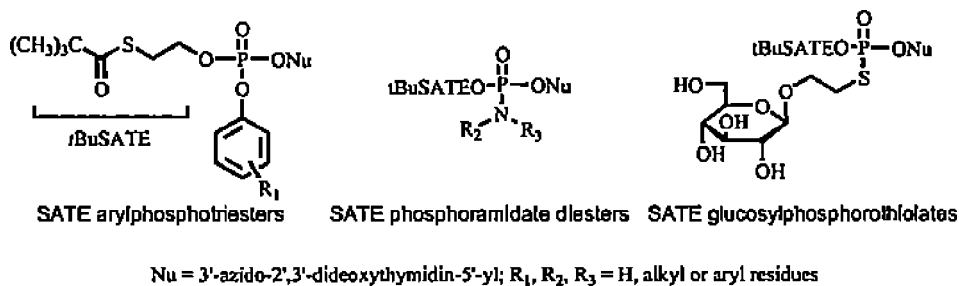
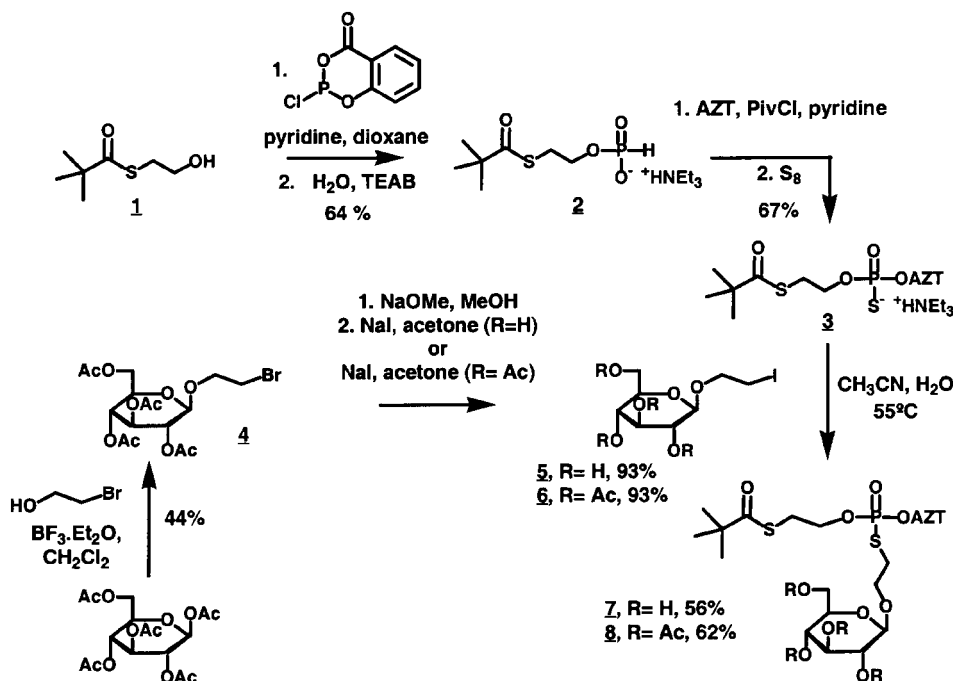


Figure 1.



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 pro-nucleotides.

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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