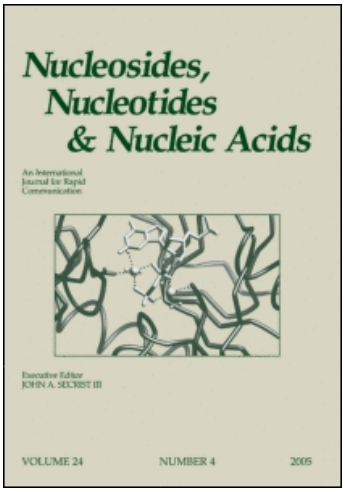

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SATE (Aryl) Phosphotriester Series. I. Synthesis and Biological Evaluation

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SATE (Aryl) Phosphotriester Series. I. Synthesis and Biological Evaluation

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ABSTRACT

Synthesis and biological activities of several phosphotriester derivatives of 3′-azido-2′,3′-dideoxythymidine (AZT) bearing a *S*-pivaloyl-2-thioethyl (*t*Bu-SATE) group and aryl residues derived from L-tyrosine are reported. All compounds showed marked anti-HIV activity in thymidine kinase-deficient CEM cells demonstrating their ability to deliver intracellularly the parent 5′-mononucleotide.

Key Words: Prodrug; Phosphotriester; AZT; HIV.

Preliminary studies have shown that aryl phosphotriester derivatives of AZT incorporating a tyrosinyl residue and a *t*BuSATE group as biolabile phosphate protections were able to release the corresponding 5′-mononucleotide selectively inside infected cells.[1,2] However, the presence of the carboxylate function on tyrosinyl residue (Fig. 1, compound **1**) seems to limit passive diffusion of the resulting phospho-

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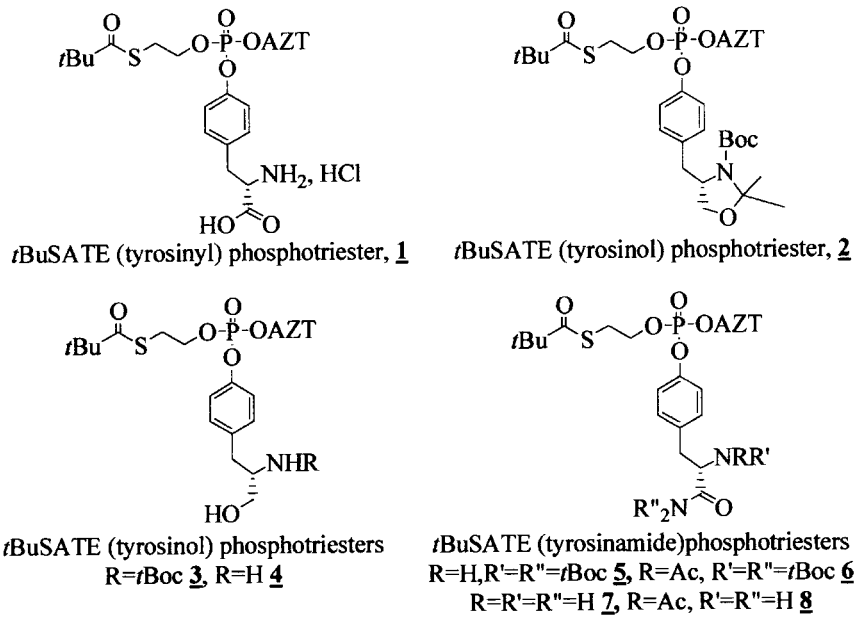

*t*BuSATE (tyrosinyl) phosphotriester, 1

*t*BuSATE (tyrosinol) phosphotriester, 2

*t*BuSATE (tyrosinol) phosphotriesters
R=*t*Boc 3, R=H 4

*t*BuSATE (tyrosinamide)phosphotriesters
R=H,R'=R"=*t*Boc 5, R=Ac, R'=R"=*t*Boc 6
R=R'=R"=H 7, R=Ac, R'=R"=H 8

Figure 1.

triester through cellular membrane leading to the loss of the anti-HIV activity in thymidine kinase-deficient (TK^-) CEM cells. Consequently, novel mixed phosphotriester structures (Fig. 1, compounds 2–8) bearing polar but not anionic functionality were designed to study the influence of the pending group of the aryl residue regarding anti-HIV activity, kinetic decomposition parameters and lipophilicity.

Compounds incorporating tyrosinol and tyrosinamide residues were synthesised using phosphoramidite chemistry, starting from the appropriate aryl precursors bearing acidolabile protecting groups on the alcohol, amino and amide functions.

These mixed phosphotriester derivatives of AZT were evaluated for their inhibitory effects on HIV-1 replication in three cell culture systems. The results demonstrate that compounds 2–8 allow the efficient intracellular delivery of the parent 5′-mononucleotide, with 50% effective concentration (EC_{50}) values at micromolar range in HIV-infected CEM/TK^- cells.

The decomposition mechanism of these mixed pronucleotides involves successively an esterase and a phosphodiesterase hydrolytic steps.[3]

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