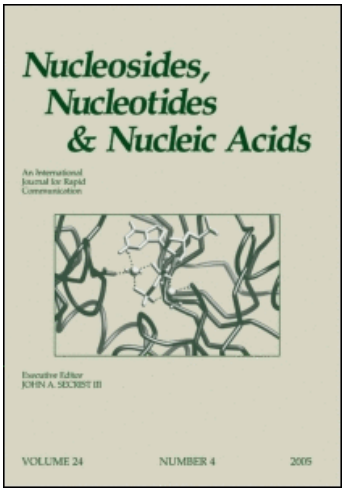

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SATE (Aryl) Phosphotriester Series. II. Stability Studies and Physicochemical Parameters

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ABSTRACT

The stability of phosphotriester derivatives of 3′-azido-2′,3′-dideoxythymidine (AZT) bearing a *S*-pivaloyl-2-thioethyl (*t*BuSATE) group and various aryl residues derived from L-tyrosine was evaluated in biological media. The results demonstrate that such compounds give rise to intracellular delivery of the parent mononucleotide through esterase and phosphodiesterase hydrolytic steps, successively.

Key Words: LC/MS; Prodrug; Mononucleotide; AZT.

The anti-HIV evaluation of phosphotriester derivatives of AZT **1**–**4** bearing a *t*BuSATE group and various tyrosinyl residues (Fig. 1) showed their ability to act as mononucleotide prodrugs (pronucleotides).[1] In order to determine the mechanism by which such constructs were selectively converted into the corresponding 5′-mononucleotide (AZTMP) inside infected cells, stability studies have been carried out in several media using an ''on-line cleaning HPLC/UV/MS'' methodology.[2]

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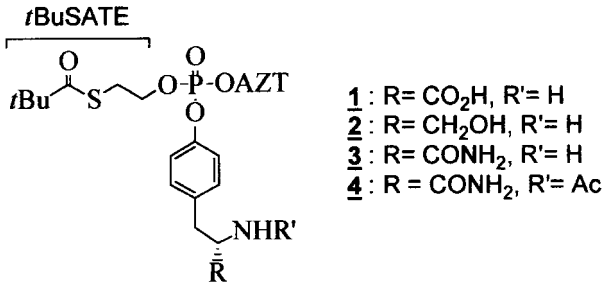

Figure 1.

Table 1.

Compound	First step	Second step	$t_{1/2}$ AZTMP formation	Log P	EC_{50} (μM) CEM/TK^-
1	1.2 h	25 h	25 h	0.24	29
2	2.5 h	43 h	42 h	0.64	7.6
3	23 min	33 h	38 h	1.18	4.0
4	1.9 h	13 h	16 h	1.52	6.7

The stability of these compounds was evaluated in total cell extracts (TCE) from CEM-SS cells used as mimic for the intracellular medium. Decomposition process of the *t*BuSATE(aryl) phosphotriesters **1**–**4** involves, firstly an esterase mediated activation leading to the loss of *t*BuSATE chain and formation of the corresponding arylphosphodiester derivative. This metabolite is then substrate for a second enzymatic activity giving rise to AZTMP. Additional studies in TCE either heat-inactivated or pre-incubated with EDTA strongly support the hypothesis that intracellular conversion of mononucleoside arylphosphodiesters is due to a type I phosphodiesterase activity. For all phosphotriesters, the half-life of the first step was shorter than the second one (Table 1). This last step (phosphodiesterase-mediated) seems to be the limiting one during the conversion of the phosphotriesters to AZTMP. Furthermore, the antiviral activity (EC_{50} in CEM/TK^- cells) seems to be closely related to the physicochemical properties (log P, kinetic data) of the pronucleotides.

The present results demonstrate that *t*BuSATE(aryl) phosphotriester derivatives of AZT **1**–**4** allow the intracellular delivery of parent 5′-mononucleotide through esterase and phosphodiesterase hydrolytic steps, successively. The large number of chemical modifications which could be envisaged on the aryl moiety opens the way to the search of antiviral pronucleotides with an adequate balance between aqueous solubility, lipophilicity and enzymatic stability needed to envisage in vivo pharmacological studies.

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