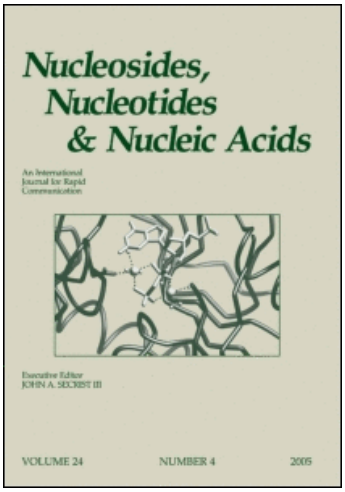

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Anti-HIV Pronucleotides: SATE Versus Phenyl as a Protecting Group of AZT Phosphoramidate Derivatives

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ANTI-HIV PRONUCLEOTIDES: SATE *versus* PHENYL as a PROTECTING GROUP of AZT PHOSPHORAMIDATE DERIVATIVES

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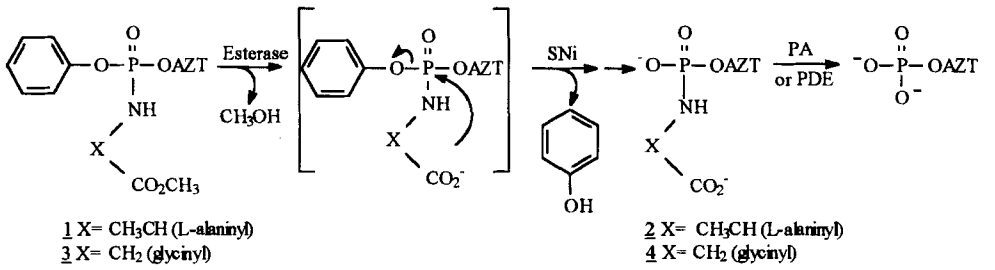
ABSTRACT: We comparatively studied the decomposition pathways in CEM cell extract of several PHENYL phosphoramidate diesters of AZT. A correlation between anti-HIV activities in TK$^-$ cell lines and pharmacokinetic data has been observed. This study would help to design corresponding SATE phosphoramidate diesters which revealed potent anti-HIV properties .

Firstly, the aryl phosphoramidate diester of AZT incorporating L-alanine (compound **1**) having shown anti-HIV activity in TK$^-$ cell lines [1], whereas the parent nucleoside is inactive, we were particularly interested in studying its decomposition pathway. In cell extract it has been shown to proceed through the formation of the corresponding L-alaninyl phosphoramidate monoester (compound **2**). Then the conversion of a phosphoramidate monoester derivative into the NuMP has been suggested to be mediated by phosphodiesterase(s) (PDE) or more likely phosphoramidase(s) (PA).

Surprisingly, the modification of the amino-acid residue in the aryl phosphoramidate series led to less active (compound **3**) or inactive compounds (compound **5**). Have examined the decomposition pathway of various aryl phosphoramidate diesters in CEM cell extract [2], where slight PDE and PA enzymatic activity was observed using HPLC/UV/MS technique [3]



1 X= CH_3CH (L-alaninyl)
3 X= CH_2 (glycinyl)

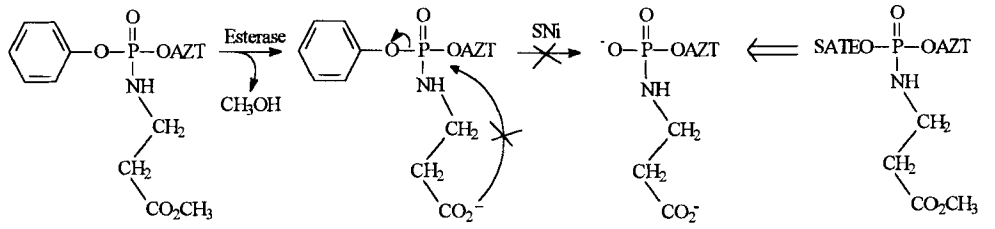
2 X= CH_3CH (L-alaninyl)
4 X= CH_2 (glycinyl)

Scheme 1

For the alaninyl (1) and glycinyl (3) derivatives, we confirmed that, the first observed metabolite is the corresponding phosphoramidate monoester (2, 4).

In the case of the β-alaninyl derivative(s), the phosphoramidate monoester (7) was not observed and, instead, the stable compound (6) was formed and stable. This stability could be explained though the formation of a six membered ring intermediate which was shown to be less thermodynamically favorable than a five membered ring.

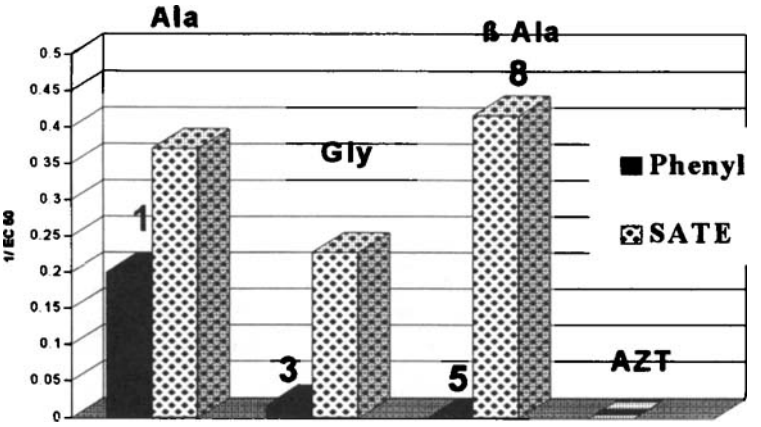
One could expect to by pass this limiting intramolecular mechanism (SNi) and so, deliver the ß-alanine phosphoramidate monoester (7) from the corresponding S-acyl-2-thioethyl (SATE) phosphoramidate diester (8).



Compound 5 (ß-alaninyl) | Compound 6 | Compound 7 | Compound 8

Scheme 2

The corresponding SATE phosphoramidate diesters were synthesized and their pharmacokinetic behavior in CEM cell extract were studied. We demonstrated that whatever the amino-acid residue used in the SATE PHOSPHORAMIDATE series, AZTMP was delivered *via* a phosphoramidate monoester intermediate. Note that SATE phosphoramidate diester incorporating ß-alanine(8) was active, contrary to the corresponding ARYL phosphoramidate diester(5).



$1/EC_{50}$: Reciprocal of the 50% effective concentration
(concentration required to inhibit the replication of HIV by 50%)

It appears a nice correlation between the anti-HIV activity and the ability of the prodrug to convert to a phosphoramidate monoester.

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