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

T. Beltran^a; D. Egron^a; I. Lefebvre^a; C. Périgaud^a; A. Pompon^a; G. Gosselin^a; A-M. Aubertin^b; J-L. Imbach^a

^a Laboratoire de Chimie Bioorganique, UMR CNRS-USTL 5625, Université Montpellier II, Montpellier Cedex 5, France ^b Université Louis Pasteur, Institut de Virologie, Strasbourg, France

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

T. Beltran, D. Egron, I. Lefebvre*, C. Périgaud, A. Pompon, G. Gosselin,
A.-M. Aubertin ^a and J.-L. Imbach

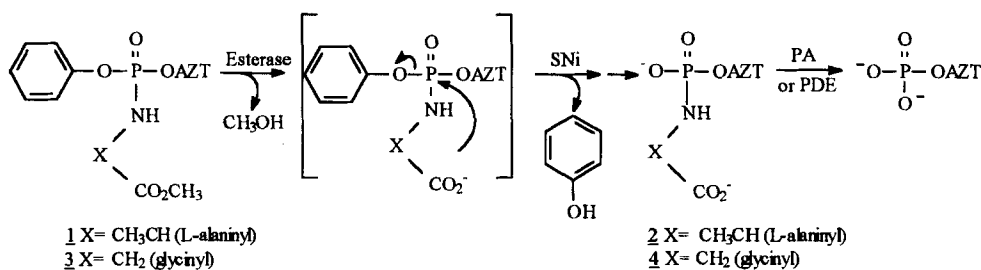
Laboratoire de Chimie Bioorganique, UMR CNRS-USTL 5625, Université Montpellier
II, Case courrier 008, Place E. Bataillon, 34095 Montpellier Cedex 5, France

^aUniversité Louis Pasteur, Institut de Virologie, INSERM U74,
67000 Strasbourg, France

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

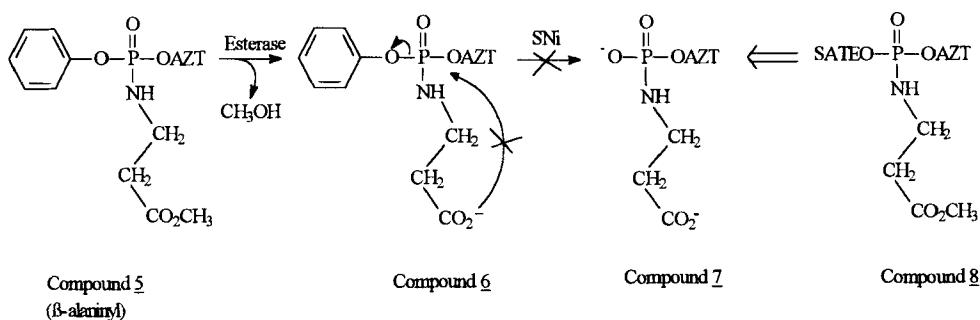


Scheme 1

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

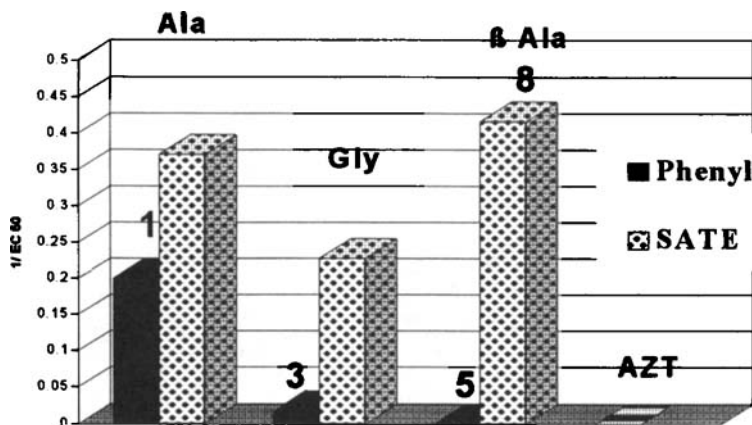
In the case of the β -alaninyl derivative(s), the phosphoramidate monoester (**7**) was not observed and, instead, the stable compound (**6**) was formed and stable. This stability could be explained though the formation of a six membered ring intermediate which was shown to be less thermodynamically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

One could expect to by pass this limiting intramolecular mechanism (S_Ni) and so, deliver the β -alanine phosphoramidate monoester (**7**) from the corresponding S-acyl-2-thioethyl (SATE) phosphoramidate diester (**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 β -alanine(**8**) was active, contrary to the corresponding ARYL phosphoramidate diester(**5**).



1/EC₅₀: 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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