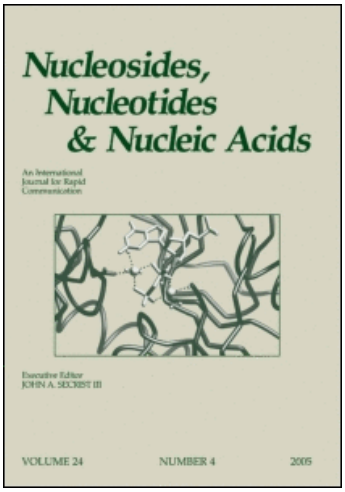

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Synthesis, Anti-HIV Activity and Stability Studies of 3'-Azido-2',3'-dideoxythymidine-5'-fluorophosphate

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SYNTHESIS, ANTI-HIV ACTIVITY AND STABILITY STUDIES OF 3'-AZIDO-2',3'-DIDEOXYTHYMIDINE 5'-FLUOROPHOSPHATE

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ABSTRACT: The synthesis, *in vitro* anti-HIV activity, and stability studies of AZT 5'-fluorophosphate (F-AZTMP) are reported. The present results demonstrate that such compound is a bioprecursor of its parent 5'-mononucleotide (AZTMP) but its biotransformation does not allow its selective intracellular delivery. Moreover, several attempts were carried out in order to improve the biological activity of this compound by the use of a SATE prodrug strategy.

In recent years, several attempts have been made to improve the therapeutic potential of nucleoside analogues by the use of nucleotide prodrugs (pronucleotides)[1,2]. As an original class of modified anti-HIV nucleotide analogues, nucleoside 5'-fluorophosphates emerged as potent antiviral compounds. Particularly, the AZT derivative F-AZTMP (FIG. 1) has been described to exhibit an anti-HIV activity higher than that of its parent nucleoside AZT in cell culture experiments[3].

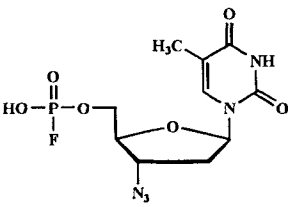
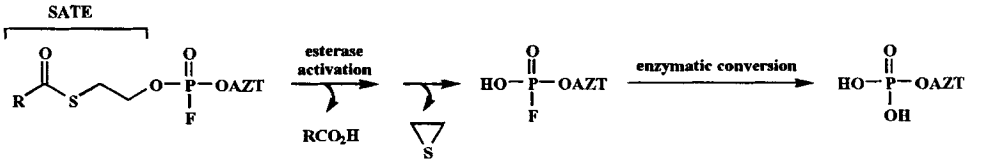


FIG. 1. *Structure of AZT 5'-fluorophosphate (F-AZTMP)*

In order to determine the mode of action of F-AZTMP, we decided to extend the biological evaluation of this compound to human T4-lymphoblastoid CEM-SS cell line deficient in cytosolic thymidine kinase (CEM/TK$^-$). As previously reported[3], F-AZTMP proved to be markedly active in inhibiting the HIV-1 replication in CEM-SS (0.005 μM) and MT-4 (0.032 μM) cell lines. In contrast, this compound exhibited a very low antiretroviral activity in CEM/TK$^-$ cells (60 μM). This result demonstrates that F-AZTMP is not able to deliver AZTMP inside the cells. Moreover, stability studies in different biological media have shown that F-AZTMP is able to be converted into AZTMP through enzymatic process, but this biotransformation is not selective of the intracellular media. Finally, several attempts were carried out in order to improve the antiviral activity of this compound by the use of a SATE prodrug strategy (Scheme 1).



Scheme 1. *The SATE prodrug strategy applied to F-AZTMP*

The fluorophosphosphodiester derivative has been obtained but its chemical instability in common organic solvents has not allowed us to isolate this compound with high purity.

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