

This article was downloaded by:

On: 26 January 2011

Access details: *Access Details: Free Access*

Publisher *Taylor & Francis*

Informa Ltd Registered in England and Wales Registered Number: 1072954 Registered office: Mortimer House, 37-41 Mortimer Street, London W1T 3JH, UK



## Nucleosides, Nucleotides and Nucleic Acids

Publication details, including instructions for authors and subscription information:

<http://www.informaworld.com/smpp/title~content=t713597286>

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

D. Egron<sup>a</sup>; A. A. Arzumanov<sup>b</sup>; N. B. Dyatkina<sup>b</sup>; A. Krayevsky<sup>b</sup>; J-L. Imbach<sup>a</sup>; A-M. Aubertin<sup>c</sup>; G. Gosselin<sup>a</sup>; C. Périgaud<sup>a</sup>

<sup>a</sup> Laboratoire de Chimie Bioorganique, UMR CNRS-USTL 5625, Université Montpellier II, Montpellier Cedex 5, France <sup>b</sup> Engelhardt Institute of Molecular Biology, Russian Academy of Sciences, Moscow, Russia <sup>c</sup> Université Louis Pasteur, Institut de Virologie, Strasbourg, France

**To cite this Article** Egron, D. , Arzumanov, A. A. , Dyatkina, N. B. , Krayevsky, A. , Imbach, J-L. , Aubertin, A-M. , Gosselin, G. and Périgaud, C.(1999) 'Synthesis, Anti-HIV Activity and Stability Studies of 3'-Azido-2',3'-dideoxythymidine-5'-fluorophosphate', *Nucleosides, Nucleotides and Nucleic Acids*, 18: 4, 983 — 984

**To link to this Article:** DOI: 10.1080/15257779908041621

**URL:** <http://dx.doi.org/10.1080/15257779908041621>

PLEASE SCROLL DOWN FOR ARTICLE

Full terms and conditions of use: <http://www.informaworld.com/terms-and-conditions-of-access.pdf>

This article may be used for research, teaching and private study purposes. Any substantial or systematic reproduction, re-distribution, re-selling, loan or sub-licensing, systematic supply or distribution in any form to anyone is expressly forbidden.

The publisher does not give any warranty express or implied or make any representation that the contents will be complete or accurate or up to date. The accuracy of any instructions, formulae and drug doses should be independently verified with primary sources. The publisher shall not be liable for any loss, actions, claims, proceedings, demand or costs or damages whatsoever or howsoever caused arising directly or indirectly in connection with or arising out of the use of this material.

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

D. Egron<sup>1</sup>, A.A. Arzumanov<sup>2</sup>, N.B. Dyatkina<sup>2</sup>, A. Krayevsky<sup>2</sup>, J.-L. Imbach<sup>1</sup>, A.-M. Aubertin<sup>3</sup>, G. Gosselin<sup>1</sup>, C. Périgaud<sup>1\*</sup>

<sup>1</sup>Laboratoire de Chimie Bioorganique, UMR CNRS-USTL 5625, Université Montpellier II, CC 008, Place E. Bataillon, 34095 Montpellier Cedex 5, France; <sup>2</sup>Engelhardt Institute of Molecular Biology, Russian Academy of Sciences, 32 Vavilov str., Moscow 117984, Russia; <sup>3</sup>Université Louis Pasteur, Institut de Virologie, INSERM U 74, 67000 Strasbourg, France

**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)<sup>1,2</sup>. 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<sup>3</sup>.

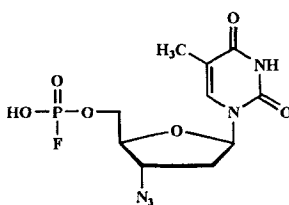
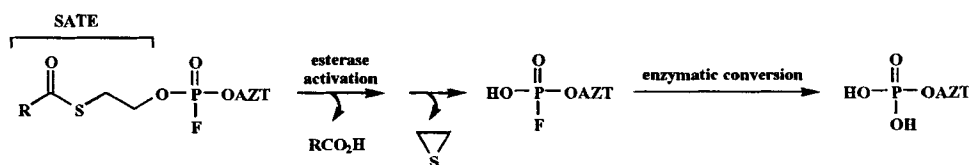


FIG. 1. Structure of AZT 5'-fluorophosphate (F-AZTMP)

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<sup>-</sup>). As previously reported<sup>3</sup>, F-AZTMP proved to be markedly active in inhibiting the HIV-1 replication in CEM-SS (0.005  $\mu$ M) and MT-4 (0.032  $\mu$ M) cell lines. In contrast, this compound exhibited a very low antiretroviral activity in CEM/TK<sup>-</sup> cells (60  $\mu$ M). 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 fluorophosphodiester derivative has been obtained but its chemical instability in common organic solvents has not allowed us to isolate this compound with high purity.

*This work was supported by grants from CNRS and "Agence Nationale de Recherches sur le SIDA" (ANRS, France).*

## REFERENCES

1. Arzumanov, A. A.; Dyatkina, N. B. *Russ. J. Bioorg. Chem.* **1996**, *22*, 777-794.
2. Périgaud, C.; Girardet, J.-L.; Gosselin, G.; Imbach, J.-L. In *Advances in Antiviral Drug Design*; De Clercq, E., Ed.; JAI Press: London, **1996**; Vol. 2, pp 147-172.
3. Dyatkina, N.; Arzumanov, A.; Krayevsky, A.; O'Hara, B.; Gluzman, Y.; Baron, P.; MacLow, C.; Polsky, B. *Nucleosides Nucleotides* **1994**, *13*, 325-337.