

Nucleosides, Nucleotides and Nucleic Acids

Publication details, including instructions for authors and subscription information:

<http://www.tandfonline.com/loi/lncn20>

SYNTHESIS OF NEW HOMO AND HETERODINUCLEOSIDES CONTAINING THE 2',3'-DIDEOXYNUCLEOSIDES AZT AND D4T

M. Taourirte , H. B. Lazrek , J. J. Vasseur ^a , M. Ferrero , S. Fernandez & V. Gotor

^a CNRS-Université Montpellier II, Lab. Chimie Organique Biomoléculaire de Synthèse, UMR 5625, France

Published online: 07 Feb 2007.

To cite this article: M. Taourirte , H. B. Lazrek , J. J. Vasseur , M. Ferrero , S. Fernandez & V. Gotor (2001) SYNTHESIS OF NEW HOMO AND HETERODINUCLEOSIDES CONTAINING THE 2',3'-DIDEOXYNUCLEOSIDES AZT AND D4T, Nucleosides, Nucleotides and Nucleic Acids, 20:4-7, 959-962

To link to this article: <http://dx.doi.org/10.1081/NCN-100002468>

PLEASE SCROLL DOWN FOR ARTICLE

Taylor & Francis makes every effort to ensure the accuracy of all the information (the "Content") contained in the publications on our platform. However, Taylor & Francis, our agents, and our licensors make no representations or warranties whatsoever as to the accuracy, completeness, or suitability for any purpose of the Content. Any opinions and views expressed in this publication are the opinions and views of the authors, and are not the views of or endorsed by Taylor & Francis. The accuracy of the Content should not be relied upon and should be independently verified with primary sources of information. Taylor and Francis shall not be liable for any losses, actions, claims, proceedings, demands, costs, expenses, damages, and other liabilities whatsoever or howsoever caused arising directly or indirectly in connection with, in relation to or arising out of the use of the Content.

This article may be used for research, teaching, and private study purposes. Any substantial or systematic reproduction, redistribution, reselling, loan, sub-licensing, systematic supply, or distribution in any form to anyone is expressly forbidden. Terms & Conditions of access and use can be found at <http://www.tandfonline.com/page/terms-and-conditions>

SYNTHESIS OF NEW HOMO AND HETERODINUCLEOSIDES CONTAINING THE 2',3'-DIDEOXYNUCLEOSIDES AZT AND D4T

M. Taourirte,¹ H. B. Lazrek,^{2,*} J. J. Vasseur,³ M. Ferrero,⁴
S. Fernandez,⁴ and V. Gotor⁴

¹Faculty of Sciences and Techniques Gueliz, BP : 618, 40 000,
Marrakech, Morocco

²Lab. of Bioorganic chemistry, Faculty of Sciences Semlalia,
Marrakech, Morocco

³Lab. Chimie Organique Biomoléculaire de Synthèse, UMR 5625
CNRS-Université Montpellier II, France

⁴Lab. of Bioorganic Chemistry, Faculty of Chemistry, Oviedo, Spain

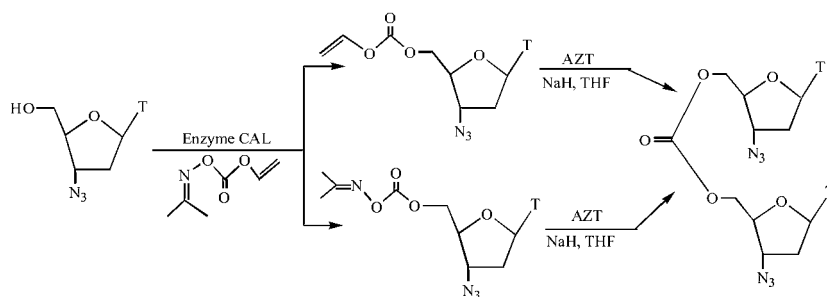
ABSTRACT

The synthesis of new dinucleosides of AZT and D4T is described.

The rapid spread of the human immunodeficiency virus (VIH), mainly HIV-1, the etiological agent of Acquired immunodeficiency syndrome (AIDS) is urging scientists to develop new drugs that can interrupt the viral life cycle. Efficient vaccine development is still faced with the ongoing mutational events of HIV that enable it to evade the immune system. Efforts are now focused on the design of new drugs that will arrest the viral life cycle. Some drugs such as AZT, D4T, DDC and DDI have been approved so far. These nucleosides analogues are incorporated into the retroviral DNA by the reverse transcriptase resulting in chain termination.

In fact, the main benefits of a combination therapy against HIV-infections, is to prevent emergence of virus drug resistance and the reduction of toxicity (1). Other results suggest that anti-HIV activity is principally dependent on lipophilicity

*Corresponding author.



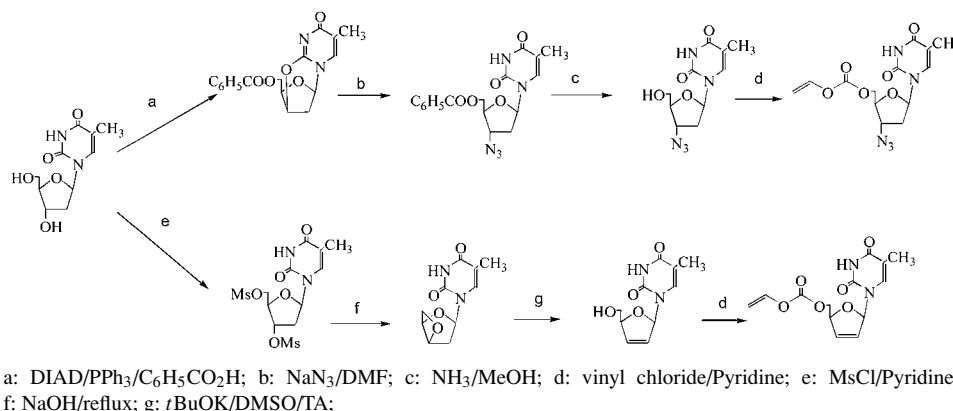
Scheme 1.

of the drug (2). The latter can easily penetrate the cell membrane either by a passive diffusion or by structural membrane deformation if the drug contain a lipophilic group (linker). According to these remarks, an interesting alternative approach to combination therapy, would be the use of dimers. For these investigations we have selected as models the homodimers (AZT-CO-NH-(CH₂)_n-NH-CO-AZT and D4T-CO-NH-(CH₂)_n-NH-CO-D4T) and an heterodimer (AZT-CO-NH-(CH₂)_n-NH-CO-D4T) in the aim to combine the inhibitory capacity of these two drugs (AZT, D4T) and to increase their lipophilicity.

The starting nucleosides AZT and D4T were prepared according to the literature (2). A general methodology was then successfully tried to give homo dimers of AZT (Scheme 1). The synthetic scheme is based on the 5' directed intermolecular nucleophilic substitutions at the 5'-activated position of AZT.

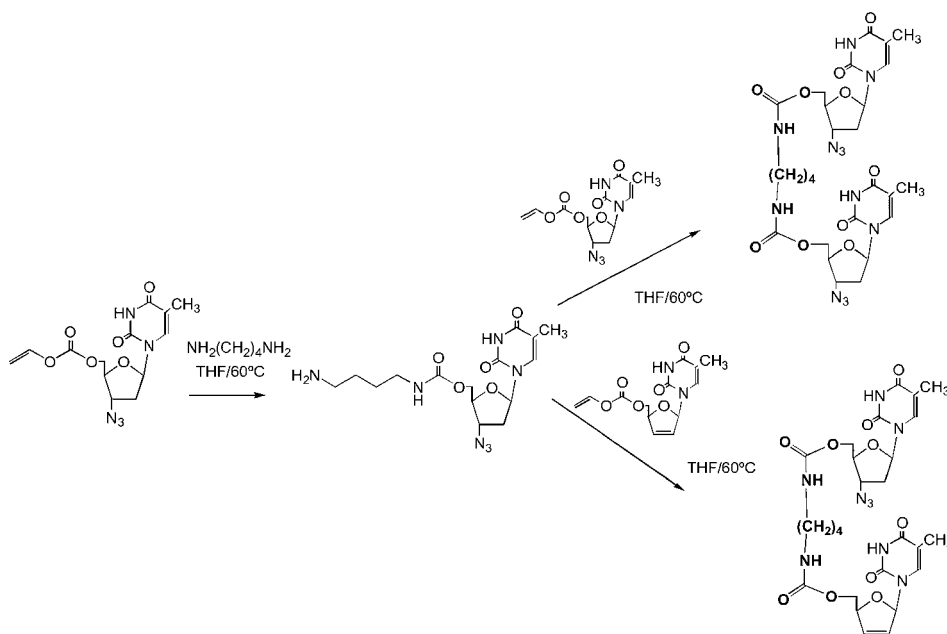
To study the effect of the spacer chain on the antiviral activity and the lipophilicity, we carried out the synthesis of some homo and heterodimers with a higher chain-length. The preparation of these dimers was achieved as described in Schemes 2, 3 and 4.

The methodology described here allowed us to prepare various homo and heterodimers characterized by the presence of one or two drugs used in clinical

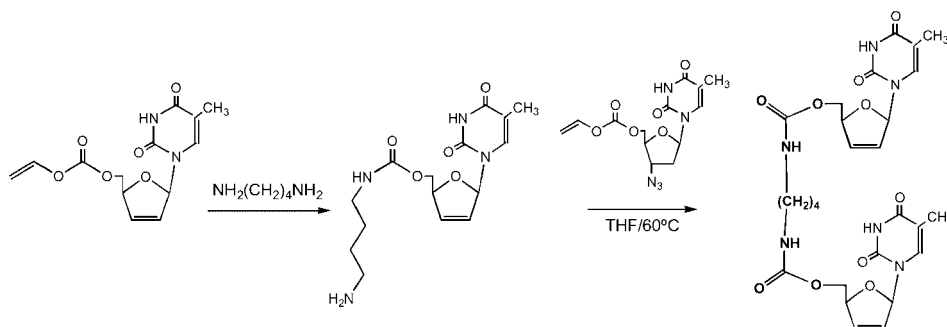


Scheme 2. Synthesis of activated precursors of AZT and D4T.





Scheme 3. Synthesis of the homodimer of AZT and the heterodimer of AZT and D4T.



Scheme 4. Synthesis of the homodimer of D4T.

treatment and connecting residues of various lengths with carbonate and carbamate functionality susceptible to hydrolyze in biological environment upon esterase activation releasing the active nucleosides.

The biological activities concerning the inhibition of the multiplication of the HIV-1 and 2 are under investigations.

ACKNOWLEDGMENTS

We thank the CNR (Morocco), the CNRS (France) and the Moroccan-Spanish Commission for financial support.

REFERENCES

1. Schott, H.; Ludwig, P.S.; Immelmann, A.; Schwendener, R.A. *Eur. J. Med. Chem.* **1999**, *34*, 343–352 and references cited therein.
2. Siddiqui, A.Q.; Mc Guigan, C.; Ballatore, C.; Zuccotto, F.; Gilbert, I.H.; De Clercq, E.; Balzarini, J. *J. Med. Chem.* **1999**, *42*, 4122–4128 and references cited therein.



Request Permission or Order Reprints Instantly!

Interested in copying and sharing this article? In most cases, U.S. Copyright Law requires that you get permission from the article's rightsholder before using copyrighted content.

All information and materials found in this article, including but not limited to text, trademarks, patents, logos, graphics and images (the "Materials"), are the copyrighted works and other forms of intellectual property of Marcel Dekker, Inc., or its licensors. All rights not expressly granted are reserved.

Get permission to lawfully reproduce and distribute the Materials or order reprints quickly and painlessly. Simply click on the "Request Permission/Reprints Here" link below and follow the instructions. Visit the [U.S. Copyright Office](#) for information on Fair Use limitations of U.S. copyright law. Please refer to The Association of American Publishers' (AAP) website for guidelines on [Fair Use in the Classroom](#).

The Materials are for your personal use only and cannot be reformatted, reposted, resold or distributed by electronic means or otherwise without permission from Marcel Dekker, Inc. Marcel Dekker, Inc. grants you the limited right to display the Materials only on your personal computer or personal wireless device, and to copy and download single copies of such Materials provided that any copyright, trademark or other notice appearing on such Materials is also retained by, displayed, copied or downloaded as part of the Materials and is not removed or obscured, and provided you do not edit, modify, alter or enhance the Materials. Please refer to our [Website User Agreement](#) for more details.

[Order now!](#)

Reprints of this article can also be ordered at

<http://www.dekker.com/servlet/product/DOI/101081NCN100002468>