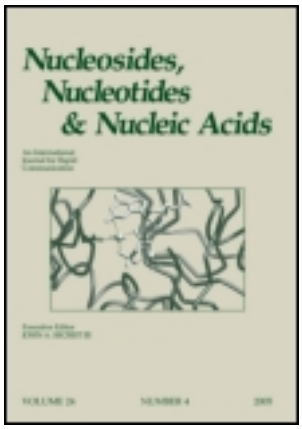

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M. Taourirte , H. B. Lazrek , J. J. Vasseur [a] , M. Ferrero , S. Fernandez & V. Gotor
[a] CNRS-Université Montpellier II, Lab. Chimie Organique Biomoléculaire de Synthèse, UMR 5625, France
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SYNTHESIS 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. Gotor[4]

[1]Faculty of Sciences and Techniques Gueliz, BP : 618, 40 000, Marrakech, Morocco
[2]Lab. of Bioorganic chemistry, Faculty of Sciences Semlalia, Marrakech, Morocco
[3]Lab. Chimie Organique Biomoléculaire de Synthèse, UMR 5625 CNRS-Université Montpellier II, France
[4]Lab. of Bioorganic Chemistry, Faculty of Chemistry, Oviedo, Spain

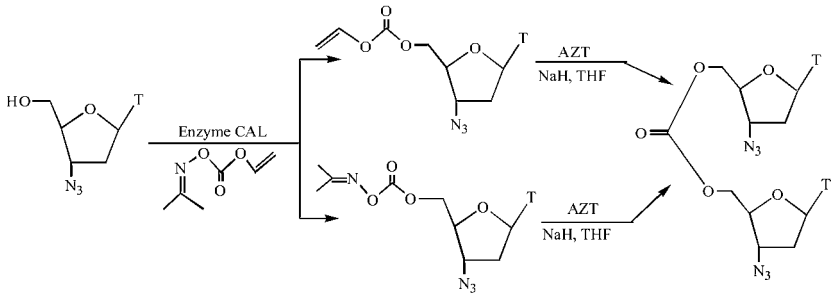
ABSTRACT

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 interrupts the viral life cycle. Efficient vaccine development is steal 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.



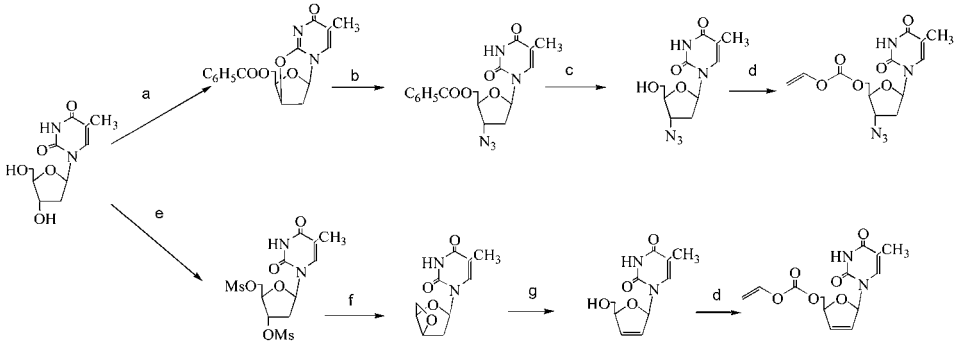
Scheme 1.

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



a: DIAD/PPh_3/$C_6H_5CO_2H$; b: NaN_3/DMF; c: NH_3/MeOH; d: vinyl chloride/Pyridine; e: MsCl/Pyridine; f: NaOH/reflux; g: *t*BuOK/DMSO/TA;

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

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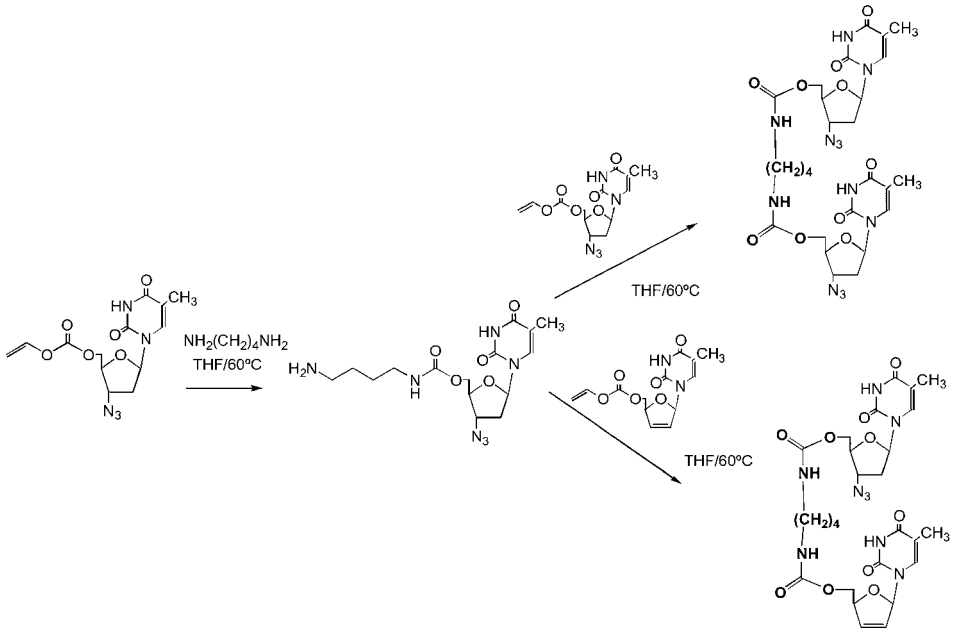
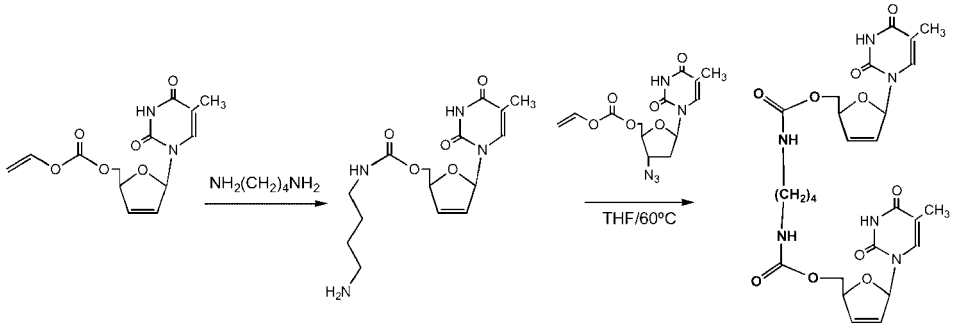


Scheme 3. Synthesis of the homodimer of AZT and the heterodimer of AZT and D4T.



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.

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