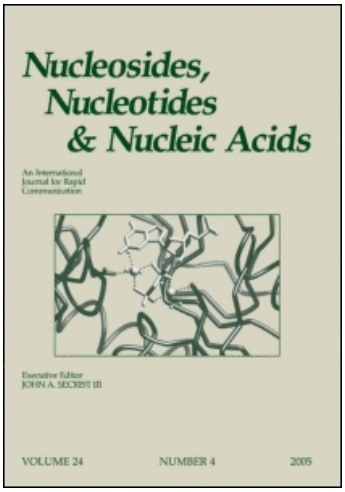

Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

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Online publication date: 09 August 2003

To cite this Article Mohamed, L. Ait , Taourirte, M. , Rochdi, A. , Lazrek, H. B. , Vasseur, J. J. , Engels, J. W. , Pannecouque, C. and De Clercq, E.(2003) 'Synthesis of New Homo and Heterodimers of 2',3'-Dideoxyinosine (ddi) Using Ester Linkages', Nucleosides, Nucleotides and Nucleic Acids, 22: 5, 829 — 831
To link to this Article: DOI: 10.1081/NCN-120022664
URL: http://dx.doi.org/10.1081/NCN-120022664

NUCLEOSIDES, NUCLEOTIDES & NUCLEIC ACIDS
Vol. 22, Nos. 5–8, pp. 829–831, 2003

Synthesis of New Homo and Heterodimers of 2′,3′-Dideoxyinosine (ddI) Using Ester Linkages

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ABSTRACT

A series of new homo and heterodimers of ddI has been synthesized. A glutarate diester spacer was used to covalently couple ddI onto ddI, AZT or d4T.

Key Words: Dimers; ddI; AZT; d4T.

INTRODUCTION

Intensive efforts are underway to develop chemotherapeutic agents against human immunodeficiency virus (HIV). Among the current diversity of compounds active against HIV, the 2′,3′-dideoxynucleosides (ddNs), are among the most potent.

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DOI: 10.1081/NCN-120022664
1525-7770 (Print); 1532-2335 (Online)

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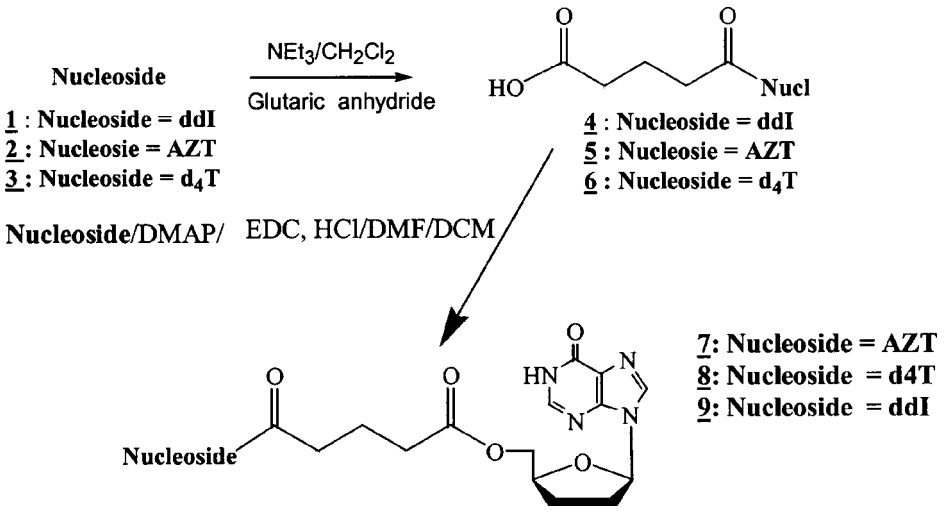
The most extensively studied of these agents are 3′-azido-2′,3′-dideoxythymidine (AZT); 2′,3′-dideoxy-2′,3′-didehydrothymidine (d4T) and 2′,3′-dideoxyinosine (ddI). On the other hand, encouraging results from studies of ddI combinations with AZT (ddI + AZT) or d4T (ddI + d4T) showed that people receiving (AZT + ddI) as combination therapy had a significantly larger and more sustained rise in CD_4^+ cell counts and more pronounced decrease in viral load compared to people receiving AZT alone.[1]

Previously, combination of AZT with other nucleoside analogues or with other classes of anti-HIV agents linked through a spacer chain have been reported.[2] Recently, we prepared [3] a series of homodimers and heterodimers of AZT and d4T, which contain carbonate (AZT-O-CO-OAZT and AZT-O-CO-O-$(CH_2)_4$-O-CO-AZT), carbamate (AZT-CO-NH-$(CH_2)_4$-NH-CO-AZT) and ester linkages (AZT-O-CO-$(CH_2)_3$CO-O-AZT). Continuing this program, we have now synthesized novel homodimers (ddI + ddI) and heterodimers (ddI + AZT) and (ddI + d4T) using an ester linkage (glutaric acid).

METHODOLOGY AND RESULTS

To investigate the properties of new homo and heterodimers of 2′,3′-dideoxyinosine (ddI)**7**–**9**, their syntheses were undertaken. DDI **1**, AZT **2**, and d4T **3**, were prepared according to the literature. AZT and d4T were converted into their half ester **5** and **6** by treatment with glutaric anhydride in dichloromethane with an excess of triethylamine at room temperature for 3 h (Sch. 1).[4]

As for ddI half ester **4** the mixture of dichloromethane and dimethylformamide was necessary to increase the solubility of ddI and longer time (overnight). All glutarates were obtained in good yield (85%). The preparation of hetrodimers **7**, **8** was



Scheme 1.

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performed by esterification of AZT-half ester **5** and d4T-half ester **6** with ddI. This reaction was carried out using EDC, HCl and DMAP in CH_2Cl_2/DMF. After work-up and purification on silica gel chromatography column, heterodimers **7** and **8** were obtained in 80% yield. The homodimer **9** was obtained by condensation of ddI half ester **4** with ddI in the presence of EDC, HCl and DMAP in DMF. The confirmation of the structure of all compounds was based on ^{1}H NMR, ^{13}C NMR and mass spectra.

CONCLUSION

The methodology described here will allow the preparation of several homo- and heterodimer ester conjugates.

ACKNOWLEDGMENTS

This work was supported by CNR (Morocco)/CNRS (France) and by CNR (Morocco)/DFG (Germany) program.

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