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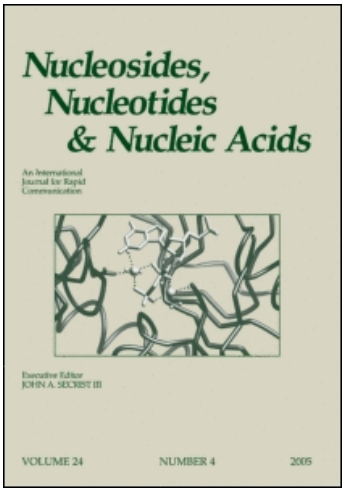

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A Glutaric Acid Ester as Carrier System for Sustained Delivery of Lamuvidine (3TC) Dimers

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A GLUTARIC ACID ESTER AS CARRIER SYSTEM FOR SUSTAINED DELIVERY OF LAMUVIDINE (3TC) DIMERS

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□ *We report the synthesis of homo and heterodimers of 3TC conjugates. All new dimers were screened for their ability to inhibit HIV-1 in MT4 cell line and were compared to AZT alone and showed marked antiviral activity.*

Keywords Glutaric acid ester; homodimer; heterodimer; 3TC conjugates; anti-HIV-1

INTRODUCTION

The past decade has seen remarkable progress in the development of drugs for HIV- infection. Currently, six out of the twenty antiretroviral drugs currently approved for the treatment of AIDS (AZT, ddC, ddI, 3TC, and abacavir) belong to reverse transcriptase (RT) inhibitors, NRTIs. Of these, 3TC (lamuvidine, Epivir) is also a drug for the treatment of hepatitis B virus (HBV) infection.[1] However, treatment with 3TC, rapidly induces resistance both in HIV and HBV infected individuals. Drug combinations offer additive or synergistic activity against the target enzymes or enhance activity

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by inhibiting several critical viral enzyme loci. They may improve pharmacodynamics and permit more tolerable, more active, and/or less frequent dosing. Unfortunately, because of their polar nature, ddNs are not able to cross the cell membrane efficiently, rapid elimination from the brain and high dose related toxicity. Besides, the combination of 3TC with other NRTIs, particularly with AZT, has been shown to reduce the emergence of 3TC resistant strains. This has been exploited in combination therapy, especially in a bis combination of AZT and 3TC (Combivir, 300 mg AZT+150 mg 3TC). The effectiveness of the 3TC/AZT combination is a very interesting example where resistance to one agent confers sensitivity to a companion drug.

As a result, one effort to improve the therapeutic potential of nucleoside analogues is the idea of temporarily masking the polar group of drug with neutral substituents (prodrugs). It has to be lipophilic enough for passive diffusion of the membrane and blood-brain barrier. It should be able to deliver the nucleoside hydrolytically or enzymatically leaving a non toxic masking group.[2] For example, an hydroxy, amino or carboxylic acid containing drug may be esterified, amidated, etc., to obtain a prodrug.[3] After administration, the prodrug can be converted to the active drug. Following all these remarks, it would be interesting to find whether combinations of 3TC with AZT, d4T and ddI at a variety of concentration are synergistic, additive or antagonistic in displaying their anti-HIV activity. Recently, we have started a programme directed to the synthesis of dimers conjugates of AZT, d4T and ddI linked with glutaric acid[4,5] (Table 1). Here we want to describe new dimers conjugates of 3TC with AZT, d4T and ddI (Figure 1) in the aim to compare their anti HIV activity with parent nucleosides.

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TABLE 1 In vitro anti-HIV activity and cytotoxicity of compounds 1–10 against HIV-1 from acutely infected MT-4 cells

Compound	IC_{50} (μM)	CC_{50} (μM)	TI
3TC-ester 1	4.65	>100	>21.5
AZT-ester 2	0.14	>100	714
d4T-ester 3	<0.32	>100	>313
	0.012	>1.0	>83.8
3TC-ester-AZT 4	<0.32	>100	>313
	0.03	>2.0	>72.7
3TC-ester-d4T 5	<0.32	>100	>313
	0.70	>4.0	>5.71
3TC-ester-ddI 6	0.51	7.11	13.9
3TC-ester-3TC 7	0.34	>100	>293
AZT 8	0.004	>0.5	>138
	0.002	>0.5	>209
3TC 9	0.4	>44	>107
D4T 10	0.8	>100	125

IC_{50} = 50% inhibitory concentration for HIV-1_{NL4-3} replication.
CC_{50} = 50% cytotoxic concentration for Hela-CD4-LTR-βgal cells.
TI = Therapeutic Index (TC_{50}/IC_{50}).

Drug(1)-O-CO-CH_2-CH_2-CH_2-CO-O-Drug(2)

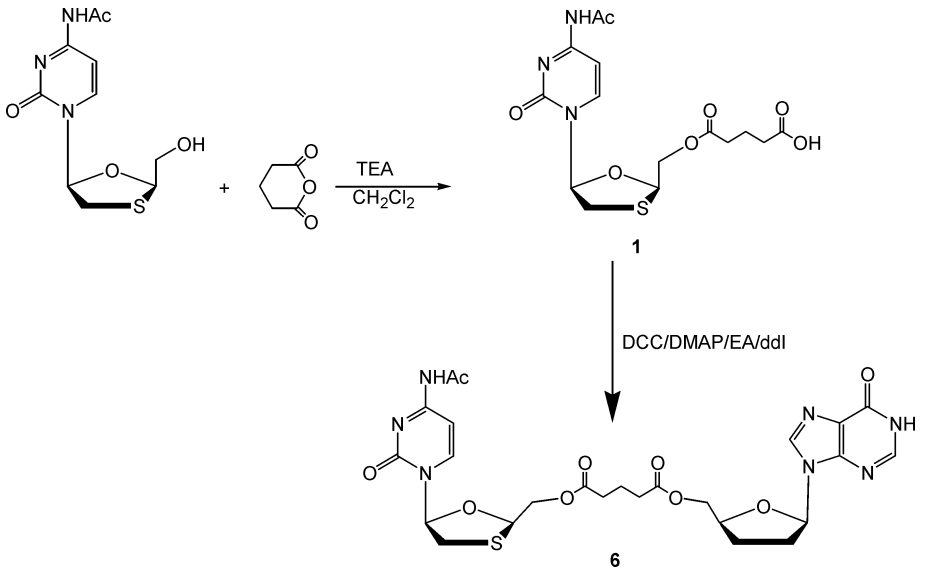
Drug : 3TC, AZT, d4T, ddI

FIGURE 1 Dimers conjugates general formula.

RESULTS AND DISCUSSION

To prepare homo- and heterodimer conjugates, protected 3TC[3] was directly converted into 5′-acid derivative **1** by treatment with glutaric anhydride in dichloromethane with an excess of triethylamine at room temperature.[5] 3TC 5′-monoester **1** was obtained in good yield (Scheme 1). The preparation of heterodimer 3TC-ester-ddI **6** was performed by esterification of 5′-acid derived of 3TC with ddI, in the presence of DCC, and DMAP in ethyl acetate. After work-up and purification on silica gel chromatography column, heterodimer 3TC-ester-ddI was obtained in satisfactory yield, all other dimers (3TC-ester-AZT, 3TC-ester-d4T, 3TC-ester-3TC) were prepared following the same procedure (Scheme 1).

Antiviral evaluation[6] of the new 3TC dimer conjugates was performed as their ability to inhibit HIV-1 in MT4 cell line, and it appeared that the dimers showed comparable activity (0.32 μM) and less toxicity (100 μM) than the parent nucleosides (Table 1). These results suggest that hydrolysis of homo and hetrodimers it happens from 3TC side (3TC-ester-AZT IC: 0.32 μM, 3TC IC: 0.4 μM and AZT IC: 0.004 μM), and the enzymatic hydrolysis takes place at the ester side chain of these prodrugs. The active



SCHEME 1 Heterodimer 3TC-ester-ddI **6** synthesis.

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dimers may exert their effects by extracellular or intracellular hydrolysis to the corresponding antiviral parent nucleosides. Further investigations are needed to explain these results. Other biological testing with these dimers is underway.

CONCLUSION

The above protocol for the preparation for 3TC dimer conjugates represents an efficient and general entry to this class of prodrug. Further study for intracellular uptake and metabolism of these prodrugs will be needed to determine the anti HIV mechanism.

REFERENCES

1. Gumina, G.; Song, G.Y.; Chu, C.K. L-Nucleosides as chemotherapeutic agents. *FEMS Microbiology Lett.* **2001**, 202, 9–15.
2. Cooperwood, J.S.; Gumina, G.; Boudinot, F.D.; Chu, C.K. Nucleosiode and nucleotide prodrugs, in *Recent Advances in Nucleosides: Chemistry and Chemotherapy*, Chu, C.K. ed., New York: Elsevier, 2002, pp. 91–147.
3. Charvet, A. S.; Camplo, M.; Faury, P.; Graciet, J.C.; Mourier, N.; Chermann, J.C.; Kraus, J.L. Inhibition of human immunodeficiency virus type 1 replication by phosphonoformate and phosphonoaceatate-2,3-Dideoxy-3-thiacytidine conjugates. *J. Med. Chem.* **1994**, 37, 2216–2223.
4. Aggarwal, S.K.; Gogu, S.R.; Rangan, S.R.S.; Agrawal, K.C. Synthesis and biological evaluation of prodrugs of Zidovudine. *J. Med. Chem.* **1990**, 33, 1505–1510.
5. Taourirte, M.; Lazrek, H.B.; Rochdi, A.; Vasseur, J.J.; Engels, J.W. Homo and heteroimers of ddI, d4T and AZT: influence of (5′-5′) Thiocarbonate-carbamate linkage on anti-HIV activity *Nucleosides, Nucleotides and Nucleic Acids* **2005**, 24, 523–525, and references cited therein.
6. Rey, F.; Barré-Sinoussi, F.; Schmidtmyerova, H.; Chermann, J.C. Detection and titration of neutralizing antibodies to HIV using an inhibition of the cytopathic effect of the virus on MT4 cells. *J. Virol. Methods* **1987**, 16, 239–249.

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