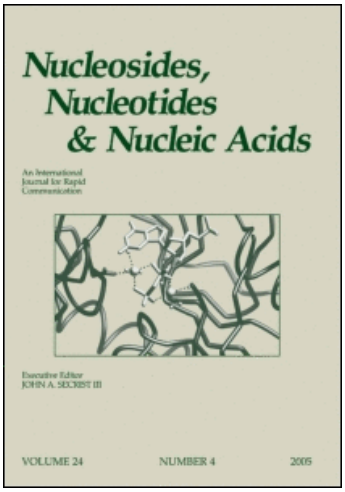


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# Homo and Heterodimers of ddI, d4T and AZT: Influence of (5'-5') Thiolcabonate-Carbamate Linkage on Anti-HIV Activity

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# HOMO AND HETERODIMERS OF DDI, D4T AND AZT: INFLUENCE OF (5′-5′) THIOLCABONATE-CARBAMATE LINKAGE ON ANTI-HIV ACTIVITY

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▫ *New homo and heterodimers of ddI, d4T and AZT with (5′-5′) thiolcarbonate-carbamate linkages have been prepared with the aim of testing them against wild type and NNRTI resistant HIV mutants. The prepared dimers showed a low activity in comparison to the parent drug.*

## INTRODUCTION

A common problem in the treatment of HIV-1 infected patients using a combination of nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs) is the failure of a drug regimen after a period of success. It has been shown that in many cases this problem is due to virus-drug resistance. In general, cellular resistance mechanisms account for an insufficient intracellular concentration of the active form of drugs, which results in the lack of anti-retroviral activity.[1] One alternative approach to combination therapy that has been suggested earlier is the use of dimers resulting from the linking of two anti-HIV agents through an appropriate spacer.[2,3] The expected advantages of these dimer prodrugs can be multiple: improvement in anti-HIV activity, synergetic interactions, enhancement of drug intracellular uptake, and decrease of toxicity. Dimers of NRTIs bearing spacer arms as transient protections

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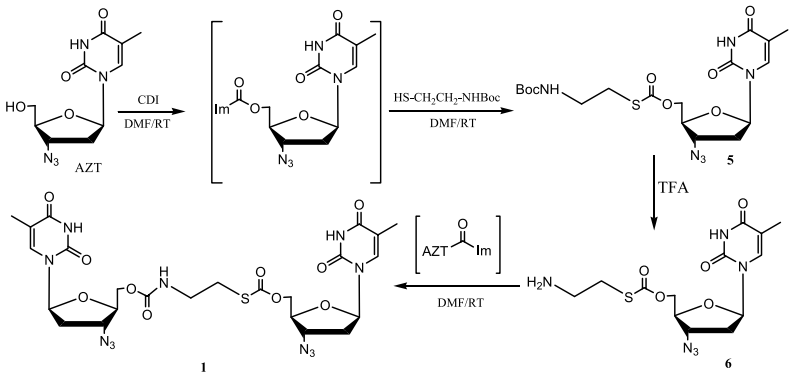


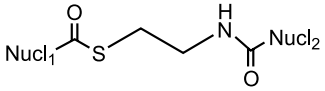

**SCHEME 1**

of their 5′-hydroxyl group were able to deliver the corresponding drugs inside the cell through hydrolysis and/or enzymatic cleavage.[4,5] We have developed a new concept for the synthesis of homo and heterodimers of NTRIs of the general formula $Nucl_1$-CO-X-$(CH_2)$n-Y-CO-$Nucl_2$ in attempts to improve the cellular uptake of dimers and to extend their therapeutic potency.

## RESULTS AND DISCUSSION

Recently, we reported the synthesis and anti-HIV activity of a series of homo- and heterodimers with carbamate, carbonate, and ester linkages.[4,5] In continuation of our program, we report herein the synthesis and anti-HIV activity of a series of homo and heterodimers of the general formula $Nucl_1$-CO-NH-$(CH_2)_2$-S-CO-$Nucl_2$. We have chosen AZT, d4T, and ddI as NRTIs. The synthetic route is illustrated in Scheme 1.

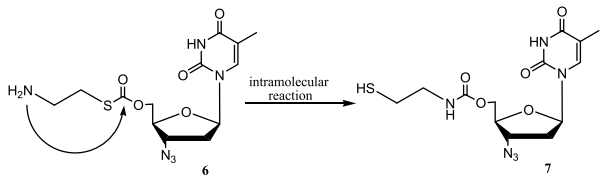
**TABLE 1** Anti-HIV Data Against Wild-Type and NNRTI Resistant HIV Mutants




| | | | | $EC_{50}$[b] | | | |
|---|---|---|---|---|---|---|---|
| Compound | Nucl1 | Nucl2 | $CC_{50}$[a] MT-4 | wt | $EFV^R$ | Y181C | K103N/Y181C |
| 1 | AZT | AZT | > 100 | 5 ± 0.8 | 1 ± 0.2 | 1 ± 0.3 | 5 ± 0.5 |
| 2 | AZT | ddI | > 100 | 1 | 0.2 | 0.2 | 1.2 |
| 3 | d4T | d4T | > 100 | 45 | 14 | 7 | > 20 |
| 4 | d4T | ddI | > 100 | 43 | > 20 | 13 | > 20 |
| AZT | — | — | 55 | 0.07 ± 0.02 | 0.02 | 0.02 ± 0.005 | 0.07 ± 0.01 |
| d4T | — | — | ≥ 100 | 1.7 | 0.4 | 0.4 | 1.8 |
| ddI | — | — | > 100 | 10 ± 0.3 | 1.2 | 3 ± 1 | 9 ± 0.5 |

[a]Compound concentration (μM) required to reduce the viability of mock-infected MT-4 cells by 50%, as determined by the MTT method.

[b]Compound concentration (μM) required to achieve 50% protection of MT-4 cells from the HIV-1 induced cytopathogeneticy, as determined by the MTT method.




**SCHEME 2**

AZT was first treated with 1,1-carbonyldiimidazole in DMF for 2 h at room temperature. After the addition of 2-N-Boc-ethanethiolamine, the reaction mixture was stirred overnight. After work-up and purification on silica gel column, the N-protected thiolcarbonate-AZT derivative **5** was obtained in a good yield. The N-Boc deprotection by TFA in $CH_2Cl_2$ gave 3′-azido-3′-deoxythymidin-5′-yl thiolcarbonate **6** in quantitative yield. The latter was condensed with activated 5′-O-imidazocarbonyl-AZT in DMF to give the homodimer thiolcarbonate-carbamate AZT-AZT **1** in 51% yield. Under the same conditions the condensation of the thiolcarbonate derivative of AZT **6** with 5′-imidazocarbonyl-ddI gave a mixture of two heterodimers AZT-CO-NH-$(CH_2)_2$-SCO-ddI and ddI-CO-NH-$(CH_2)_2$-S-CO-AZT **2** (Table 1). The formation of this mixture can be explained as occurring via rearrangement of **6** to **7** through intramolecular nucleophilic attack by the β-amino group of the thiolcarbonate function as depicted in Scheme 2.

Using the same procedure, we obtained homo and heterodimers d4T-d4T **3** and d4T-ddI **4**. The thiolcarbonate-carbamate dimers displayed low anti-HIV activities (Table 1). This may be due to the lack of hydrolysis inside the cell. Previously, we showed that the carbonate and ester dimers had activities similar to that of AZT.[4,5] These results suggest that the anti-HIV activity of heterodimers is primarily attributable to the action of the more potent ddN of the two coupled components. The antiviral efficacy of these dimers depends on many factors such as enzyme inhibition, extracellular stability, cell membrane permeability, and intracellular hydrolysis. Additional research is under way to understand the relation between (5′-5′) linkage and the antiviral activity of the prepared dimers.

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