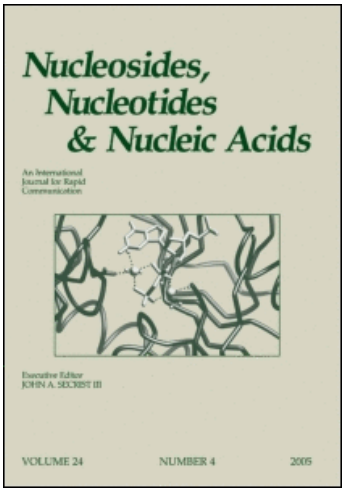

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Novel Series of [ddN]-[TSAO-T] Heterodimers as Potential Bi-Functional Inhibitors of HIV-1 RT. Studies in the Linker and ddN Region

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NOVEL SERIES OF [ddN]-[TSAO-T] HETERODIMERS AS POTENTIAL BI-FUNCTIONAL INHIBITORS OF HIV-1 RT. STUDIES IN THE LINKER AND ddN REGION

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ABSTRACT: Novel series of [ddN]-$(CH_2)_n$-[TSAO-T] heterodimers have been prepared and tested for their anti-HIV-1 and HIV-2 activity. The most active compound of this series was the [d4T]-$(CH_2)_3$-[TSAO-T] heterodimer (EC_{50} = 0.018 ± 0.03 μM).

Combination of anti-HIV agents is now being explored as therapeutic modalities to prevent emergence of virus-drug resistance.[1,2] An alternative approach to combination therapy, would be the use of heterodimers resulting from the linking of an HIV-1-specific non-nucleoside RT inhibitor (NNRTI) and a 2',3'-dideoxynucleoside (ddN) through an appropriate spacer, in an attempt to combine the inhibitory capacity of these two different classes of molecules. With this aim, we previously reported[3] the synthesis and evaluation for their anti-HIV activity of a series of heterodimers of the general formula [ddN]-$(CH_2)_n$-[NNRTI], which combine in their structure a ddN analogue (such as AZT) or the natural substrate (dThd) and a NNRTI such as TSAO-T or HEPT linked, through a polimethylene spacer, between the N-3 of the thymine base of both compounds. Although several [AZT]-$(CH_2)_n$-[TSAO-T] heterodimers proved markedly inhibitory to HIV-1 they were less potent inhibitors than the parent compounds from which they were derived. The most active compounds of this series were the [AZT or dThd]-$(CH_2)_3$-[TSAO-T] heterodimers.[3] Our biological results suggested that the activity of the heterodimers could be ascribed to the TSAO-T part of the molecule without any significant contribution from the ddN part of the heterodimer.

We have now prepared novel series of [ddN]-spacer-[TSAO-T] heterodimers in order to obtain better insights in the feasibility of this approach to increase the inhibitory efficacy of the test compounds against the HIV-1 RT. Four types of modifications have been addressed in the model heterodimers [[AZT or dThd]-$(CH_2)_3$-[TSAO-T]]: First, we focused on modifications of the spacer, including linkers of different length (**1**, and **4**),

conformational freedom (**11** and **12**) or aromatic nature (**13**). Second, we explored other attachment points of the spacer, by anchoring the linker at the C-5 position of thymine base of the ddN and at the N-3 position of the thymine base of TSAO-T (**14** and **15**). Third, we have also modified the nature of the ddN, consequently heterodimers in which the ddN was d4T (**2** and **3**) have been prepared. Finally, in order to circumvent the dependence of ddN moiety of the heterodimer on activation by the nucleoside kinases, we have prepared heterodimers of general formula [5'-MMP-ddN]-$(CH_2)_n$-[TSAO-T] in which the ddN was bearing at 5'-position a masked monophosphate group[4] (**5-10**).

[ddN]N^3–$(CH_2)_3$–N^3[TSAO-T]

1 ddN = AZT; n = 6
2 ddN = d4T; n = 3
3 ddN = d4T; n = 6
4 ddN = dThd; n = 6

[5'-MMP-ddN]N^3–$(CH_2)_3$–N^3[TSAO-T]

5 ddN = AZT; n = 3
6 ddN = AZT; n = 6
7 ddN = d4T; n = 3
8 ddN = d4T; n = 6
9 ddN = dThd; n = 3
10 ddN = dThd; n = 6

[AZT]N^3–Spacer–N^3[TSAO-T]

11 Spacer = $-(CH_2)_2-O-(CH_2)_2-$
12 Spacer = $-CH_2-C{=}C-CH_2-$
13 Spacer = $-CH_2-Ph-CH_2-$

[ddN]C^5–C≡C–CH_2–N^3[TSAO-T]

14 ddN = AZT
15 ddN = dThd

Figure 1

The shorter the methylene spacer, the higher the activity of the heterodimers against HIV-1 in CEM/0 and MT4 cells. None of the heterodimers showed anti-HIV-2 activity in CEM/0 cells. None of the heterodimers proved markedly cytotoxic to the MT4 cells at 100 μM. [5'-MMP-ddN]-$(CH_2)_n$-[TSAO-T] heterodimers showed a similar, or slightly lower activities than the corresponding [ddN]-$(CH_2)_n$-[TSAO-T]. Change in the ddN from AZT to d4T gave heterodimers with activities one order of magnitude higher than the parent heterodimer. Heterodimer **2** resulted the most active compound of this series (EC_{50} = 0.018 ± 0.03 μM).

The nature of the linker seems important for the activity of the heterodimers. Ether type (**11**) or double bond (**12**) linkers gave compounds with similar activity to the parent heterodimer. In contrast, introduction of an aromatic spacer (**13**) resulted in a markedly decreased activity. Change in the position of the linker in the ddN from N^3 to C^5 (**14** and **15**) gave compounds with similar or 5-9 fold lower activity than the parent N^3-N^3-heterodimer.

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