57

[AZT]-[TSAO-T] And [AZT]-[HEPT] Heterodimers as Potential Bi-Functional Inhibitors of HIV-1 Reverse Transcriptase. Synthesis , Structural Assignment and Anti-HIV Activity

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A common feature of the HIV-1-specific non-nucleoside RT inhibitors (NNRTIs) is that they lead to the rapid emergence of mutant HIV-1 strains that are resistant to these compounds. HIV-1 strains that are resistant to the non-nucleoside RT inhibitors are still sensitive to 2',3'-dideoxynucleosides (ddN) such as AZT or ddI, and, vice versa, HIV-1 strains selected for resistance against AZT or ddI are still sensitive to the NNRTIs. Combination of anti-HIV agents is now being explored as therapeutic modalities to prevent emergence of virus-drug resistance.

An alternative approach to combination therapy, would be the use of dimers resulting from the linking of an NNRTI and a ddN through an appropriate spacer, in an attempt to combine the inhibitory capacity of these two different classes of molecules. With this aim we have synthesized and evaluated for their anti-HIV activity several heterodimers of the general formula [ddN]-$(CH_2)_n$-[NNRTI], which combine in their structure a ddN analogue (such as AZT) and an NNRTI such as TSAO-T or HEPT linked through a spacer between the N-3 of the thymine base of both compounds. Several [TSAO-T]-$(CH_2)_n$-[AZT] dimers proved markedly inhibitory to HIV-1. Also, if AZT was replaced by thymidine in the dimer molecules, potent anti-HIV-1 activity was observed. None of the dimers showed anti-HIV-2 activity, thus pointing to the TSAO-T as the functional part of the dimers. In contrast with the TSAO-T monomers, none of the TSAO-T-containing dimers proved markedly cytotoxic to the cells. There was a clear trend toward decreased antiviral potency with lengthening the methylene spacer in the [TSAO-T]-$(CH_2)_n$-[AZT] dimers.

58

Optimization of antiviral and kinetic properties of PETT compounds, a class of potent non-nucleoside HIV-RT inhibitors.

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The PETT [N-(2-PhenylEthyl)-N'-(2-Thiazolyl)Thiourea] series[1] has been further developed. Extensive SAR studies, now including more than 800 compounds, have optimized compound with regard to activity against wild-type and mutant strains of HIV-1 RT, selectivity, time to resistance development and pharmacokinetic properties. Here the HIV-1 RT activities and kinetic data will be presented. The most active compounds now have IC_{50} of <1 ng/ml against wt RT IC_{50} and 3-5 ng/ml against Cys181 and Ile100 mutant RT. Good oral bioavailabilities have been found from kinetic screening in rats. The coordinates for a 2.2 Å resolution structure of HIV-1 RT[2] have been used for fitting PETT compounds into their binding site and these studies will also be described.

References

1) C. Åhgren et al. The PETT series: A new class of potent non-nucleoside inhibitors of human immunodeficiency virus type 1 reverse transcriptase. Antimicrobial Agents and Chemotherapy, Manuscript submitted (1994).
2) T. Unge et al. 2.2Å resolution structure of the amino-terminal half of HIV-1 reverse transcriptase (fingers and palm subdomains). Structure 2 (1994) 953-961.