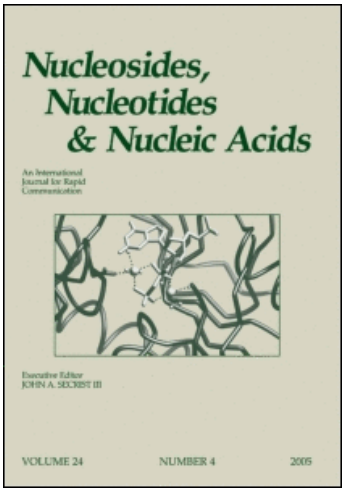

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R. Pontikis[a]; R. Note[a]; E. Dechaux[a]; J. Guillaumel[a]; A-M. Aubertin[b]; D. S. Grierson[a]; C. Monneret[a]
[a] Section Recherche, Institut Curie, Paris Cedex 05, France [b] Faculté de Médecine, Institut de Virologie, Strasbourg, France

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"MIXED INHIBITORS" OF HIV-REVERSE TRANSCRIPTASE: SYNTHESIS AND ANTIVIRAL ACTIVITY

R. Pontikis[1], R. Note[1], E. Dechaux[1], J. Guillaumel[1], A.-M. Aubertin[2], D.S. Grierson[1], C. Monneret[1] *

[1]Institut Curie, Section Recherche, UMR-176 CNRS-IC, 26 rue d'Ulm, 75248 Paris Cedex 05, France; [2] Institut de Virologie, U 74 INSERM, Faculté de Médecine, 3 rue Koeberlé, 67000 Strasbourg, France.

Abstract: Some "AZT-HEPT" and "ddC-HEPT" conjugates were designed, synthesized and evaluated for their anti-HIV activity.

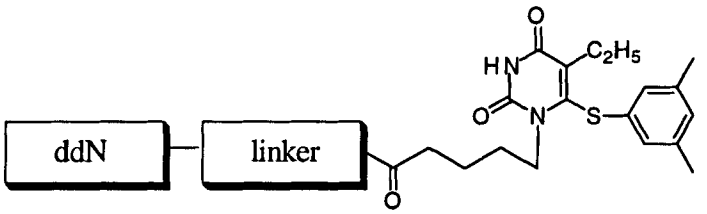
Suppression of human immunodeficiency virus (HIV) replication can be achieved through inhibition of reverse transcriptase (RT) activity. RT inhibitors include nucleoside analogs or NRTIs (such as AZT, ddC), and a class of structurally diverse compounds designed as the NNRTIs: HEPT, TIBO... Single-agent therapy has been associated with emergence of drug resistance. However, by the combination of NNRTIs with nucleoside analog(s), synergistic inhibition of HIV replication is often observed, and, in some cases, the onset of resistance may be delayed or reduced.[1] These results have shown that the complex interplay of different phenoma can be exploited towards therapeutic ends.

Structural analysis of HIV-1 RT complexed with different NNRTIs[2], has established that the various NNRTIs bind to a common hydrophobic pocket close to the RT polymerase catalytic site. Kinetic studies[3] indicated that these inhibitors lower the rate of incorporation of the dNTPs but without interfering with nucleotide binding. Because of the cooperative interaction between these two sites, derivatives combining the functionalities of a NNRTI and a nucleoside analog were postulated. With such conjugates, named "mixed inhibitors", one could expect an improvement of the antiviral properties and a lower rate of emergence of virus-drug resistance.

As ddN moieties we chose AZT and ddC. Owing to its potent activity, **1**, an HEPT analog bearing a 4-carboxybutyl substituent at N-1, was selected as NNRTI. Knowledge of the HIV-RT structure suggests a minimum distance of 10 Å between the two inhibitor binding sites, although this distance may reach 15 Å with some RT/NNRTI complexes.[4]

Therefore, in a first time, the two inhibitory entities were linked with a fifteen atoms arm. For the introduction of the linker on the nucleoside entity, C-5 and N-3 positions were selected for AZT, the exocyclic amino group for ddC. In that way, conjugates **2**, **3** and **4** were prepared by coupling the carboxylic derivative **1** with three nucleoside analogs, bearing a tether functionalized at the extremity by a primary amine.

Conjugates **2** and **3** showed effective activity against HIV-1 but probably not against HIV-2. Their activity must be ascribed only to the HEPT part of the molecule. The same results were obtained by Velázquez *et al.*[5] with dimers which combine in their structure AZT and TSAO-T (as NNRTI) linked *via* the N-3 of the thymine base of both entities. Conjugate **4** showed marked activity against HIV-1 and also against HIV-2. This suggests that **4** may inhibit HIV through an AZT-type mechanism. In this regard, the type of inhibition of this compound is currently under investigation.



Compounds			IC50 (μM)		
N°	ddN	linker	CEM-SS HIV-1 LAI	PBMC HIV-1 IIIB	PBMC HIV-2 D194
2	AZT N-3	$(CH_2)_2CONH(CH_2)_{10}NH$	2.8	5.5	>10
3	AZT C-5	$(CH_2)_2CONH(CH_2)_{10}NH$	1.7	5.1	>10
4	ddC N-4	$NH(CH_2)_{12}NH$	0.43	0.46	0.43
AZT			0.002	0.001	0.006
ddC			0.031	0.016	0.07
1	—	OCH_3	0.025	0.18	>10

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