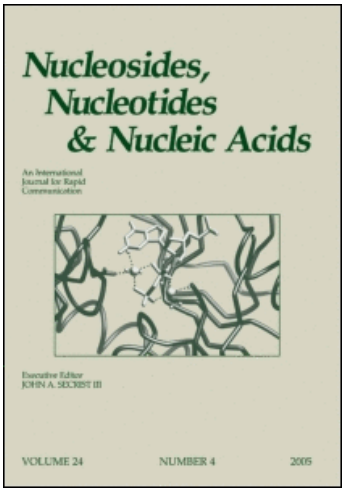

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Jean Dessolin[ab]; Pascale Galéa[b]; Patrick Vlieghe[ab]; Jean-Claude Chermann[b]; Jean-Louis Kraus[ab]
[a] Laboratoire de Chimie Biomoléculaire, Faculté des Sciences de Luminy, Université de la Méditerranée, Marseille Cédex 9, France [b] INSERM U 322 "Rétrovirus et Maladies Associées", Campus Universitaire de Luminy, Marseille Cédex 9, France

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NEW POLYAZAMACROCYCLE-NUCLEOSIDE CONJUGATES : SYNTHESIS, ANTI-HIV EVALUATION AND INTERACTION WITH CXCR-4 CORECEPTOR

Jean Dessolin,[1,2] Pascale Galéa,[2] Patrick Vlieghe,[1,2]
Jean-Claude Chermann[2] and Jean-Louis Kraus[1,2]*

1. Laboratoire de Chimie Biomoléculaire, Faculté des Sciences de Luminy, case 901, Université de la Méditerranée, 163 avenue de Luminy, 13288 Marseille Cédex 9, France.
2. INSERM U322 "Rétrovirus et Maladies Associées", Campus Universitaire de Luminy, BP 33, 13273 Marseille Cédex 9, France.

ABSTRACT : We report the synthesis of new conjugates that incorporate in their structure bis-tetraazamacrocycle coupled with AZT via enzymolabile bond.
Two series of bis-polyazamacrocycles-AZT conjugates were designed, synthesized and evaluated for their antiviral effect in vitro as well as their capability to bind to CXCR-4 coreceptor.

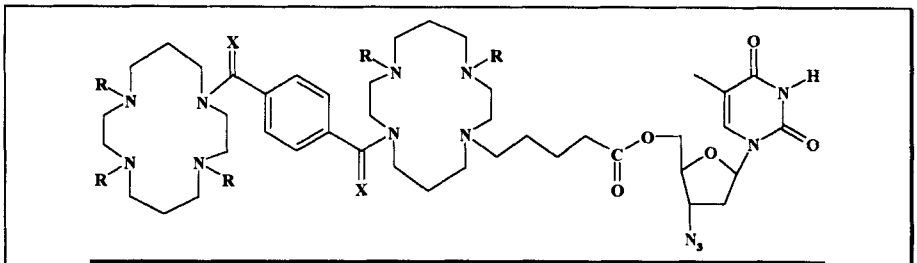
The emergence of polytherapy to control HIV infections has demonstrated the biological importance of nucleosides (anti-Reverse Transcriptase inhibitors) and pseudo-peptide analogues (protease inhibitors) in such treatments. However limitations due to toxicity, bioavailability or virus resistance suggests that there is an outgoing need to find new chemotherapeutic drugs.

Previous studies of our laboratory on 3-TC (Lamivudine, Epivir) have shown that linear polyamines could act as drug vector for anti-HIV nucleosides, allowing specific targeting of HIV-infected macrophages.[1] These conjugates were still efficient when tested against various nucleoside-resistant virus strains.[2]

Recently bicyclam compounds were reported to inhibit HIV-1 entry, specifically *via* the CXCR-4 coreceptor.[3] In the meantime, we were engaged in developing synthetic schemes in order to prepare new enzymolabile mono- and bis-tetraazamacrocyle-

nucleoside conjugates. We hoped that the cyclic polyamine moiety of these new compounds could act as nucleoside carrier.

Two series of bis-polyazamacrocycle-AZT conjugates were synthesized and their antiviral effect *in vitro* was compared to that of AZT alone. The two series differ in the linker between the two polyazamacrocyle subunits : terephtalyl and xylyl respectively for **a** and **b** series. As a result of our synthetic pathways, we first obtained the new conjugates as N-Boc protected compounds (**5a** and **5b**). The carbamate deprotection afforded the final desired compounds **6a** and **6b** without cleavage of the ester bond.



5a	**R = Boc**	**X = O**	**6a**	**R = H**	**X = O**
5b	**R = Boc**	**X = H_2**	**6b**	**R = H**	**X = H**

Antiviral evaluation of the new AZT-conjugates was performed as their ability to inhibit *syncytia* formation in the MT4 cell line, and it appeared that N-protected analogues were equipotent to AZT while N-deprotected compounds **6a** and **6b** demonstrated both higher activity and selectivity. Moreover, N-deprotected analogues (**6a** and **6b**) were antagonists to the mAb 12G5 binding until 0.05 µg/ml and 5 µg/ml respectively.

Further studies of the new AZT-bis-polyazamacrocycles on AZT-resistant strains as well as cellular uptake measurements are in progress. Improvement of the selective index of such prototype should have clinical potential in AIDS combinotherapy and could lead to a new class of antiviral drugs.

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