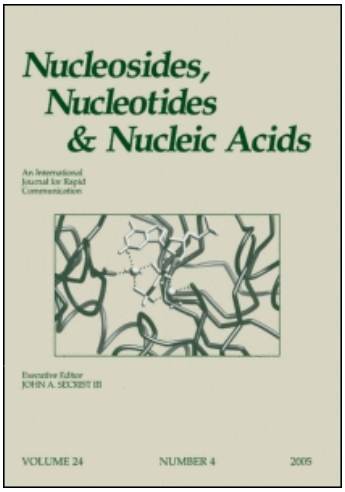

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2'5'-Phosphodiesterase Activity Studies with Xyloadenosine Analogs of 2-5A Cores

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2'5'-PHOSPHODIESTERASE ACTIVITY : STUDIES WITH XYLOADENOSINE ANALOGS OF 2-5A CORES

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Abstract. Sequential substitution of xyloadenosine into the trimeric and tetrameric 2-5A cores[1] allows evaluation of the importance of the 3' hydroxyl groups to 2',5'-phosphodiesterase (PDE) activity.

INTRODUCTION :

A study with 3'-deoxyadenosine analogs of 2-5A and 2',5'-phosphodiesterase (PDE) activity revealed that replacement of the 3'-hydroxyl moiety of the penultimate nucleotide of p5'A2'p5'A resulted in a high degree of resistance to 2',5'-PDE action.[2] To attempt to confirm and extend these observations, the ability of various xyloadenosine analogs of 2-5A cores to act as 2',5'-PDE substrates was examined.

METHODS :

Degradation studies were carried out in extracts of mouse L cells under conditions of protein synthesis. Aliquots were removed at 30, 60, 90 and 120 minutes, heat-treated, and analyzed by HPLC using 2-chloroadenosine as an internal standard. Xyloadenosine analogs of 2-5A were prepared as described previoulsly.[1]

RESULTS :

The oligonucleotides fell into two distinct groups in regard to their behaviour in the presence of the 2',5'-PDE.
The first group contained xyloadenosine at the 2'-termini and included

A2'p5'A2'p5'(xyloA) and A2'p5'A2'p5'A2'p5'(xyloA). These oligomers behaved as did their parent oligoadenylates in that they were equally sensitive to degradation by the 2',5'-PDE.

The second group of oligonucleotides bore a xyloadenosine residue in the penultimate nucleotide residue of the oligomer and included A2'p5'(xyloA)2'p5'(xyloA), (xyloA)2'p5'(xyloA)2'p5'(xyloA), A2'p5'A2'p5'(xyloA)2'p5'(xyloA) and (xyloA)2'p5'(xyloA)2'p5'(xyloA)2'p5'(xyloA). This group was quite resistant to 2',5'-PDE activity.

CONCLUSIONS :

i) A ribo configuration for the 3'-hydroxyl group in the penultimate nucleotide of the 2',5'-oligonucleotide substrate is a prerequiste for the 2',5'-PDE activity.

ii) Inversion of configuration at C-3' of the 2'-terminal residue of 2-5A core trimer or tetramer does not lead to 2',5'-PDE resistance.

iii) These results are in accord with the previous finding that 2',5'-PDE activity depended upon the presence of a 3'-hydroxyl in the penultimate position of the oligonucleotide substrate.[2]

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