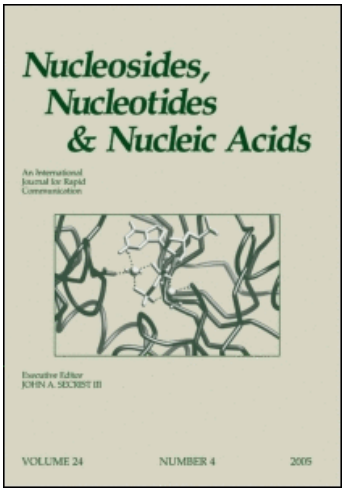

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Synthesis and Biological Activity of 3'-Modified 2'-5' Adenylate Trimers

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SYNTHESIS AND BIOLOGICAL ACTIVITY OF 3'-MODIFIED 2'-5'ADENYLATE TRIMERS

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One of the most important mediators in the mode of action of interferon is the $(2'-5')(A)_n$ synthetase-RNase L pathway. The 2'-5'oligoadenylates (2-5A), synthesized from ATP, activate a pre-existing endonuclease that cleaves single-stranded RNA. The biological activity of 2-5A is rapidly lost due to cleavage of the 2'-5' internucleotide bond by a specific 2'-5'-phosphodiesterase starting at the 3'end. This rapid cleavage and the poor uptake of 2-5A in intact cells limit the use of 2-5A as an antiviral or antineoplastic agent. Although several modified 2-5A analogues have been synthesized in order to improve the enzymatic stability, only few have proven to be resistant to degradation and still able to activate the 2-5A dependent endonuclease.[1-4] On the other hand, relative drastic methodology[5] such as calcium coprecipitation, microinjection and liposome encapsulation[5] has been used to introduce 2-5A into intact cells. Here, we present the synthesis and biological activity of oligoadenylates in which one or more adenosine residues were replaced by 9-(3-azido-3-deoxy-β-D-xylofuranosyl)adenine or 9-(3-amino-3-deoxy-β-D-xylofuranosyl)adenine. The oligonucleotides were synthesized by the phosphotriester method with triisopropylbenzenesulfonylchloride in the presence of N-methylimidazole as the condensing agent. The p-nitrophenylethyl group was used as the protecting group for the 2'-hydroxylfunction (carbonate), the internucleotide linkage (phosphate ester) and the exocyclic amino groups of the heterocyclic base (carbamate). Bis(p-nitrophenylethyl)phosphoromonochloridate was used to phosphorylate the 5'-hydroxyl group. All these blocking groups were removed with DBU in pyridine.

The antiproliferative activity of the compounds was determined by measuring the inhibition of murine leukemia L1210 cell growth. The L1210 cells were allowed to proliferate for 47 hours in Eagle's minimum essential medium (EMEM) supplemented with 10 % fetal calf serum and varying concentrations of the test compounds. At the end of this incubation period the cells were enumerated with the coulter counter. The ID_{50} value (50 % inhibitory dose) was defined as the concentration (μM) of compound required to reduce the cell increment by 50 %. The 3'-azido substituted 2-5A analogues were about equally active as the natural 2-5A core (ID_{50} : 27, 29, 20, 45 μM for compounds 1, 2, 3 and 4, respectively, as compared to 29 μM for the 2-5A core), whereas the 3'-amino substituted compound (5) was found not to inhibit L1210 cell growth at a concentration of 200 μM.

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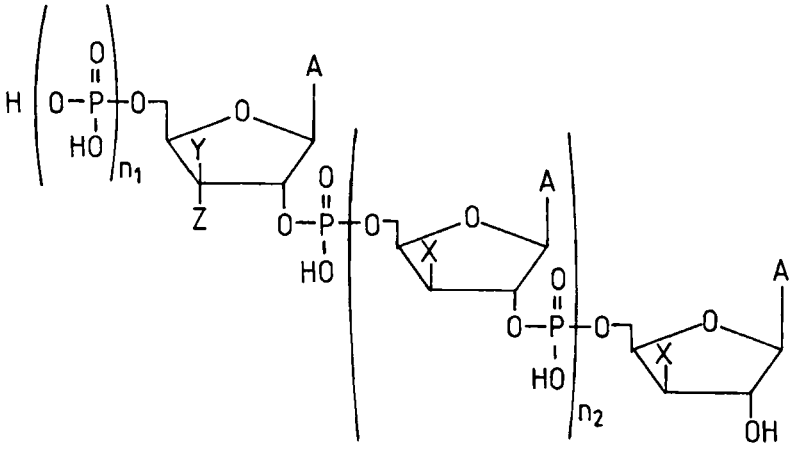

X	Y	Z	n_1	n_2	Compound
N_3	N_3	H	0	1	1
N_3	N_3	H	1	1	2
N_3	N_3	H	0	2	3
N_3	H	OH	0	1	4
NH_2	NH_2	H	0	1	5

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