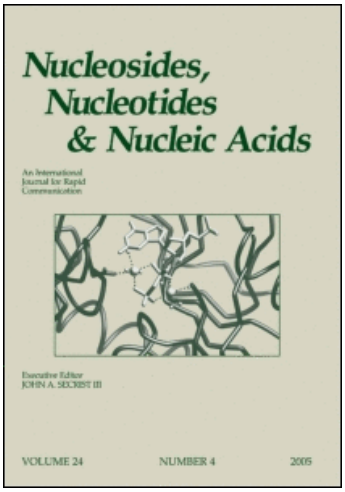

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Synthesis and Biological Activity of 2',5'-Oligoadenylate Trimers Containing 5'-Terminal 5'-Amino-5'-deoxy- and 5'-Amino-3',5'-dideoxyadenosine Derivatives

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SYNTHESIS AND BIOLOGICAL ACTIVITY OF 2',5'-OLIGOADENYLATE TRIMERS CONTAINING 5'-TERMINAL 5'-AMINO-5'-DEOXY- AND 5'-AMINO-3',5'-DIDEOXYADENOSINE DERIVATIVES

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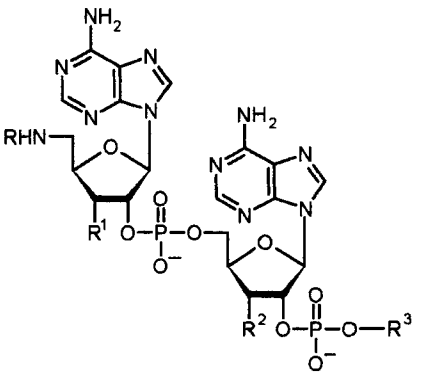
ABSTRACT: Some new 2',5'-oligonucleotide trimers containing 5'-terminal 5'-amino-5'-deoxy- and 5'-amino-3',5'-dideoxyadenosine derivatives have been synthesized. Some of the trimers showed biological inhibitions of HIV-1 reverse transcriptase (RT),HIV-1 induced syncytia formation and PCR amplification.

The major disadvantage in the therapeutic application of 2',5'-oligoadenylates are their polar character which does not allow them to penetrate through the cell membrane and the sensitivity to nucleases leading to rapid degradation of oligomers[1]. Many attempts have been made to overcome these problems by chemical modification of 2',5'-oligoadenylates. It was shown that the attachment of lipophilic groups to the 2',5'-oligoadenylates[2] or substitution of the 5'- or 3'(2')-terminal hydroxyl groups by the amino group results in improvement of biological properties of such oligomers[3]. To investigate the antiviral properties of modified 2',5'-oligoadenylates we have synthesized some of the title compounds **1-10**, containing 5'-amino-5'-deoxyadenosine, 5'-amino-3',5'-dideoxyadenosine or their lipophilic 5'-deoxy-5'-hexadecanoylamido- derivatives at the 5'-terminus, adenosine and 3'-deoxyadenosine at the penultimate position, as such as cordycepin and 9-[(2-hydroxyethoxy)-methyl]adenine (A-ether), respectively, at the 2'-terminal end of the trimers.

The 2',5'-linked triadenylates **1-10** have been prepared by the phosphoramidite method, and isolated by ion-exchange chromatography in 30-50% overall yields .



	R	R^1	R^2	R^3
1	palm	H	OH	Ado
2	palm	H	H	3'dAdo
3	palm	OH	H	Ado
4	palm	OH	OH	3'dAdo
5	palm	OH	OH	A-ether
6	H	OH	OH	Ado
7	H	OH	OH	A-ether
8	H	H	OH	Ado
9	H	H	H	3'dAdo
10	H	OH	H	Ado

The synthesized trimers **1-7** were tested in 100 μM concentration for inhibition of RT, HIV-1 induced syncytia formation and PCR amplification. Summarized data are presented in the following table.

TABLE. Biological activity of the synthesized trimers **1-7**.

Comp.	Syn.[a]	RT[b]	PCR[c]
1	81.0	61.9	+
2	88.5	26.8	-
3	100	84.5	-
4	85.1	60.2	+
5	88.5	64.0	+
6	23.1	77.5	-
7	36.2	63.0	+

[a]- inhibition of HIV-1 replication was determined by syncytia formation (%). The number of syncytia/10^5 cells was 324 for HIV-1_{IIIB} (m.o.i.=0.1)-infected SupT1 control. The mean of duplicate determinations is shown; variance did not exceed 5-10%.

[b]- RT is the percent inhibition of HIV-1 RT. The HIV-1_{IIIB}-infected SupT1 control averaged 4325 dpm.

[c]- Inhibition of HIV-1 reverse transcription was measured by PCR amplification of partial reverse transcripts; + = no amplification by any of the four primer sets used (R/U5, U3/U5, Gag1/Gag2, R/5NC); - = amplification by one or more primer sets.

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