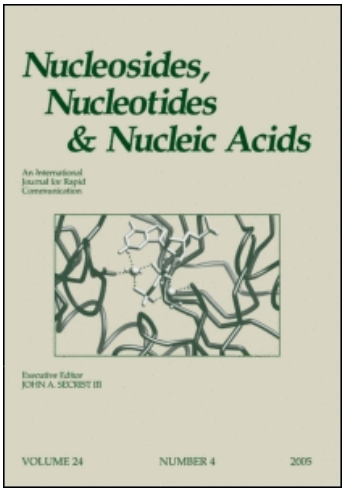

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Synthesis and Activity of Oligonucleotides Containing a Biologically Active Nucleoside at the 2'End

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SYNTHESIS AND ACTIVITY OF OLIGONUCLEOTIDES CONTAINING A BIOLOGICALLY ACTIVE NUCLEOSIDE AT THE 2'END

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The antiviral activity of (E)-5-(2-bromovinyl)-2'-deoxyuridine (BVdUrd), acyclovir and other antiherpetic nucleosides depends on a selective phosphorylation by the herpesvirus-induced thymidine kinase in the infected cells. Viruses not encoding a specific thymidine kinase (TK) activity are resistant to the action of these nucleoside analogues. The nucleoside monophosphates are as such poorly taken up by the cells. In order to circumvent the necessity of intracellular phosphorylation, we synthesized four core oligonucleotides bearing a biological active nucleoside at the 2'end. It was hypothesized that these core oligonucleotides, like core 2-5A itself, would be taken up within the cell and that, following intracellular 2'-5' phosphodiesterase cleavage, the 5'-monophosphate of the active product would be formed. In these circumstances, activity against TK^- strains could be expected.

The oligonucleotides 1-4 were evaluated for their antiviral activity against different herpes viruses. However, no activity was found for the BVdUrd- and acyclovir-oligonucleotide analogues against TK^- herpes simplex virus (HSV) mutants. The antiviral activity of the oligonucleotide analogues against HSV-1, TK^- HSV-1, HSV-2 and vaccinia virus was comparable to the activity of the parent nucleosides BVdUrd, acyclovir and 5-fluoro-2'-deoxyuridine (FdUrd). This indicates that the oligonucleotides were hydrolyzed such that they did directly release the nucleosides BVdUrd, acyclovir and FdUrd but not the 5'-monophosphates thereof. By which enzyme(s) these oligonucleotides are degraded and whether they are degraded intra- or extracellularly remain issues for further study.

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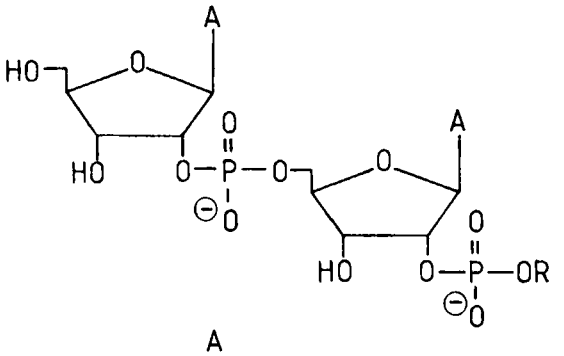

R = BVdUrd 1
Acyclovir 2
FdUrd 3

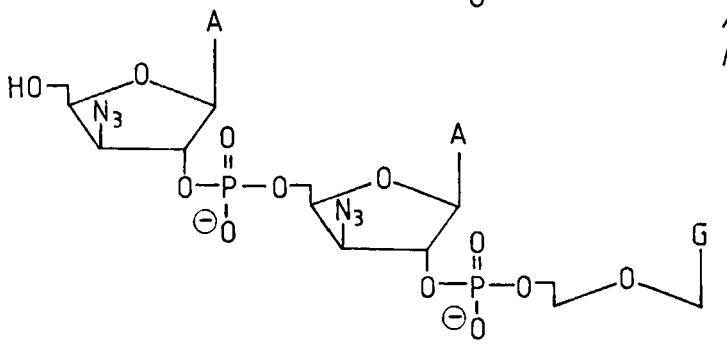

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Table 1. Antiviral activity of oligonucleotides containing a biologically active nucleoside at the 2'end

Compound	Minimum inhibitory concentration[a] (μg/ml)			
	HSV-1	TK⁻ HSV-1	HSV-2	Vaccinia virus
1	0.07	⩾ 100	10	7
2	0.7	100	0.4	> 100
3	40	0.4	70	0.2
4	1	70	1	7
2-5A	> 200	> 200	> 200	> 200
BVdUrd	0.02	⩾ 100	4	10
Acyclovir	0.1	70	0.2	> 100
FdUrd	10	0.07	40	0.07

[a]Required to reduce virus-induced cytopathogenicity by 50 %. Average values for three HSV-1 strains (KOS, F, McIntyre), three HSV-2 strains (G, 196, Lyons) and two TK⁻ HSV-1 mutants (B2006, VMW-1837).