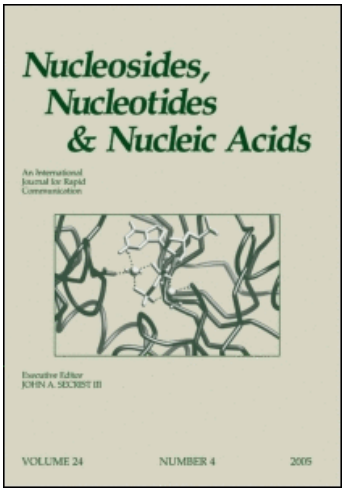

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The Effect of Oligodeoxyribonucleotide Terminal Phosphate and Ribose Modification on the Interactions of Oligonucleotides with Cells and Intracellular Stability

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THE EFFECT OF OLIGODEOXYRIBONUCLEOTIDE TERMINAL PHOSPHATE AND RIBOSE MODIFICATION ON THE INTERACTIONS OF OLIGONUCLEOTIDES WITH CELLS AND INTRACELLULAR STABILITY

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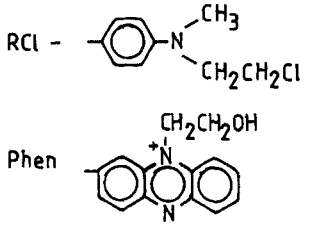
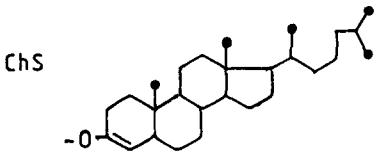
ABSTRACT. Coupling of lipophilic groups to the termini of oligonucleotides facilitates their binding to mammalian cells and protects them against nucleases attack.

In order to improve the ability of oligonucleotides to enter animal cells and to protect oligonucleotides against cellular enzymes degrading nucleic acids, terminal residues of oligodeoxyribonucleotides were chemically modified. The following 5'-[^{32}P]-labeled oligonucleotides were synthesized[1,2]: I - $(pT)_{10}$; II - $RClCH_2N(CH_3)(pT)_{10}$; III - $pTp(Tp)_8Tp(CH_2)_2NHPhen$; IV - $pTpCpCpTpCpTpCpCpTpTpTp(CH_2)_2$-NHPhen; V - $pT(pTp)_8TpChS$; VI - pTpCpCpTpCpTpCpCpTpTpTpChS; VII - $RClCH_2N(CH_3)(pTp)_9TpChS$; and a [^{14}C]-radioactive oligonucleotide derivative: VIII - $ChS(pT)_9rUCHRCl$, where





In experiments with Krebs 2 ascites carcinoma cells (KAC) and mouse fibroblasts L929 it was found that cholesterol groups at the 3'- or 5'-ends of oligonucleotides stimulate (by a factor of 15-30) the binding of the oligonucleotides to cells at 37°C as compared to derivatives of oligonucleotides I-IV, with the derivatives concentration in the

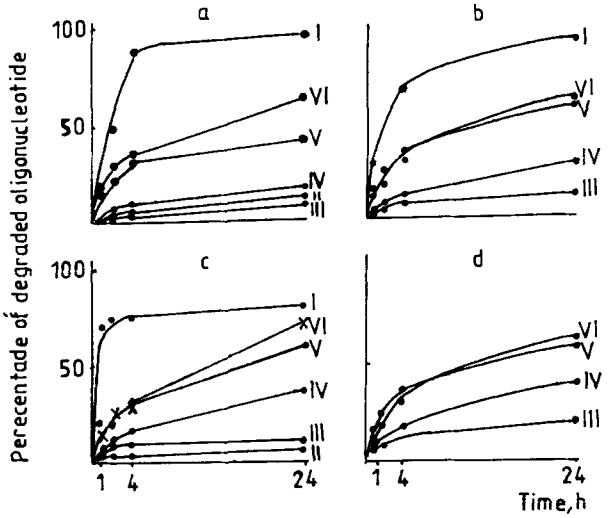


FIGURE 1. Kinetics of oligonucleotide derivatives (I-VI) degradation in culture medium with Krebs 2 ascites carcinoma cells (a), with mouse fibroblasts L929 (b), and inside the cells (c and d, respectively) at 37°C in $DMEM_6$ solution. Concentration of the ascitic cells was $5 \cdot 10^6$ per ml, concentration of oligonucleotide derivatives - 5 μM.

medium being in the range of 0.1-10 μM. The alkylating oligonucleotide derivatives taken up by cells, in particular those bearing a cholesterol group (VII,VIII), efficiently react with cellular biopolymers (RNA, DNA, and proteins).

Electrophoresis proved oligonucleotides and their derivatives (I-VII) to be stable in culture medium without serum during 24 h. In the medium with KAC cells (Fig.1a) or ascitic fluid, the oligonucleotides are rapidly dephosphorylated.

In KAC cells, the labeled phosphate is rapidly reutilized and oligonucleotides are degraded to mononucleotides. Modifications of the oligonucleotides termini considerably increase their stability in the medium with fibroblasts, with KAC cells and inside the cells (Fig.1)

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