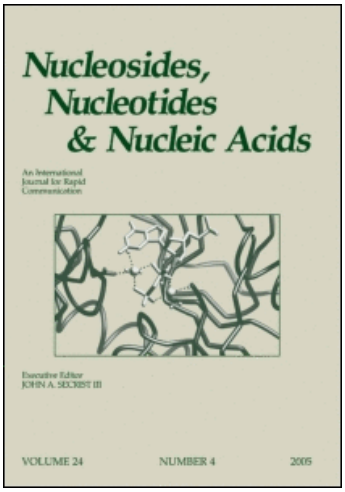

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From Pro-nucleotides to Pro-oligonucleotides

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FROM PRO-NUCLEOTIDES TO PRO-OLIGONUCLEOTIDES

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Abstract. Consequences of masking the phosphate functions of nucleic acid derivatives by enzyme labile bioreversible protecting groups are discussed.

One of the main problems which arise with potential bioactive phosphorylated or phosphonylated compounds concerns their poor uptake by cells. One way to overcome this drawback is to transitorily neutralize their negative charge(s) with enzyme labile bioreversible protective groups, which could be selectively removed inside the cells.

Taking the 5'-mononucleotide structure as a first example, it has been shown that the corresponding SATE (S-acylthioethanol) or DTE (dithiodiethanol) phosphotriester may intracellularly deliver the expected nucleotide, thus by-passing the first activating step of the parent nucleoside.[1-3] When applied to anti-HIV dideoxynucleosides, such a concept leads to numerous biological consequences going from the activation of an inactive nucleoside (i.e., ddU)[1,2] to an increase of the anti-HIV effect, as shown for ddA (due to metabolism modification)[4] or for PMEA (due to an uptake increase).[3]

Extension of this concept to oligonucleotides has also been considered and some interesting preliminary data have been obtained.

The proposed approach for "*in vitro*" intracellular delivery of phosphorylated bioactive nucleoside analogues may be of great interest in the design of new antiviral and antitumor agents.

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