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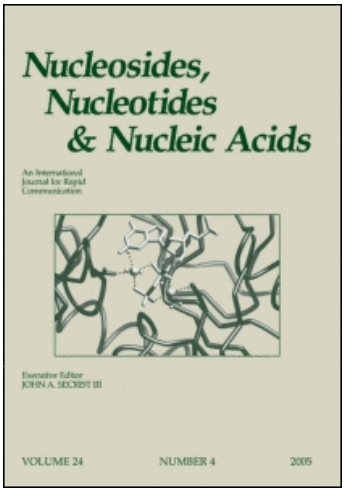

Nucleosides, Nucleotides and Nucleic Acids

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Synthesis of Nucleopeptide-Oligonucleotide Conjugates

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SYNTHESIS OF NUCLEOPEPTIDE-OLIGONUCLEOTIDE CONJUGATES

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ABSTRACT: Two nucleopeptides (NPs) were synthesized on the base of δ-ornithine peptides by modification of the α-amino ornithine functions with pyrimidyl-1- and purinyl-9-acetic acids or with pyrimidyl-1- and purinyl-9-alanines. NPs were prepared on solid polymer bearing photolinker. Conjugates with the 16-mer oligonucleotide complementary to the env AUG codon region of the Friend murine leukemia virus were prepared.

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INTRODUCTION

The field of the synthesis of peptide-oligonucleotide conjugates has been developed widely in the recent years. Hybrid molecules composed of peptides and nucleic acids have found different applications including the field of therapeutic oligonucleotides. Hydrophobic, signal, viral fusion and basic peptides have been coupled to oligonucleotides in order to improve the oligonucleotide penetration inside cells and to increase the oligonucleotide stability against nucleolytic degradation [1,2]. Coupling some cationic peptides to oligonucleotides is shown to enhance binding affinity of conjugates for target nucleic acids [3,4]. As a part of our studies on inhibition of oncogene expression and retrovirus proliferation by antisense oligonucleotides [5] and on preparation of nucleopeptides [6], we report the synthesis of two new nucleopeptides and their conjugates with an oligonucleotide complementary to the env AUG codon region of the Friend murine leukemia virus.

RESULTS AND DISCUSSION

Peptide fragments of nucleopeptide-oligonucleotide conjugates are supposed to have favorable interactions with cell membranes, to provide improved resistance to 3'-exonucleases and to retain binding affinity for target nucleic acids. Both nucleopeptides

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comprise of 5 nucleic bases linked with δ-ornithine peptide backbone [(N)attct(C)]. In the first nucleopeptide (NP I) nucleic bases are linked with α-amino groups of ornithine residues by acylation with pyrimidyl-1- or purinyl-9-acetic acids. In the second nucleopeptide (NP II) δ-ornithine backbone is modified by acylation with nucleoamino acids: 3-(thyminyl-1)alanine, 3-(cytosinyl-1)alanine, 3-(adeninyl-9)alanine). Nucleopeptides were synthesized by solid phase procedure on the hydroxyethyl photolinker Nova Syn TG resin [7]. The use of photolinker allows both base and acid labile protecting groups to be removed during peptide synthesis as well as to keep the protecting groups after the cleavage of peptide from the resin. The synthesis was performed using Boc/Fmoc-strategy for the NP I and Boc-strategy for the NP II. In the NP II trifluoroacetic groups were used to protect α-amino functions of nucleoamino acids. Coupling reaction were carried out using O-(benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate. Cleavage of the peptides from the resin was performed upon irradiation with 365 nm UV light. Purification of NPs was achieved by reversed phase HPLC. The purity of the target compounds was checked by HPLC and amino acid analysis. The 16-mer oligonucleotide [5'-TGAACACGCCATGTCGp-3'] containing 3'-end phosphate was synthesized using automatic routine phosphoramidite scheme. Conjugation with NPs was performed on the deprotected oligonucleotide in solution via phosphoramidate bond as a result of interaction of α-amino groups of NPs and a reactive 3'-end 1-hydroxybenzotriazole phosphodiester of the oligonucleotide [8]. The conjugate formation was confirmed by selective acid hydrolysis of the phosphoramidate bond and digestion with proteinase K.

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