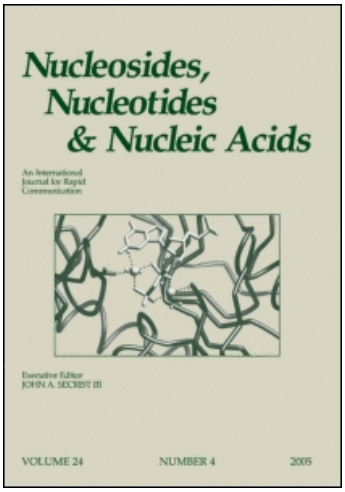

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2-5A-PNA COMPLEXES: A NOVEL CLASS OF ANTISENSE COMPOUNDS

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ABSTRACT: This paper presents the fully automated solid phase synthesis of 2-5A-PNA hybrids. These stable antisense probes cause RNase L mediated hydrolysis of target RNA sequences.

INTRODUCTION

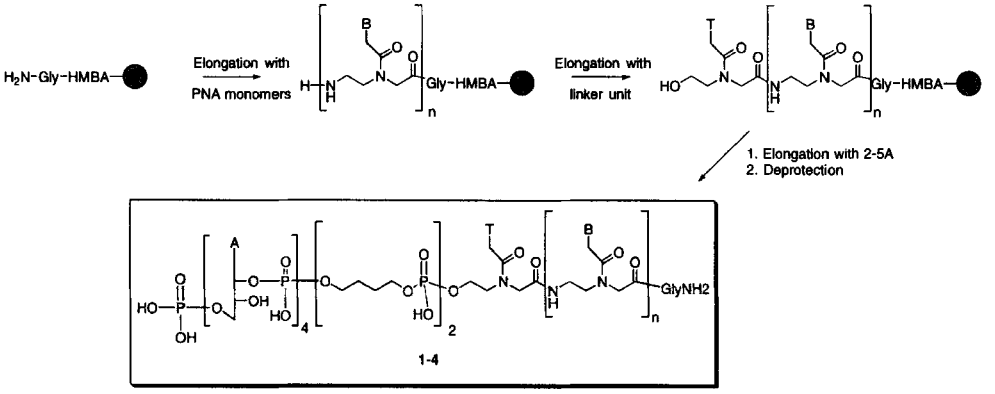
Despite their resistance to enzymatic degradation and favorable hybridization properties, the application of Peptide Nucleic Acids (PNAs)[1] as antisense agents is limited because PNA•RNA duplexes are not recognized by RNase H. Therefore hybridization of PNA to RNA does not result in the hydrolytic breakdown of the target sequence. It occurred to us that this drawback could be overcome by linking $p(5'A2'p)_3A$, so-called 2-5A[2], to the aminoterminus of PNA. This would lead to stable antisense probes with the ability to cleave target RNA *via* activation of RNase L.

We here report the synthesis of 2-5A-PNA complexes (**1-4**, Scheme 1) as well as a preliminary evaluation of their antisense activity.

RESULTS AND DISCUSSION

The 2-5A-PNA complexes were obtained following the solid phase synthesis protocol presented in scheme 1: First, the PNA part was synthesized on a fully automated DNA synthesizer with MMTr/acyl protected PNA building blocks[3] using HATU as the coupling agent. The last cycle of the PNA synthesis was followed by the introduction of the *N*-thymin-1-ylacetyl hydroxyethylglycine linker.[4] Next, the 2-5A part could be appended using standard phosphoramidite chemistry.

SCHEME 1



PNA Sequence: **1** AAA.A **3** AAA.AAA.AAA.AAA
2 AAA.AAA.AA **4** ACT.CCC.TGC.T

Preliminary biological evaluation revealed that the thus obtained 2-5A-PNA hybrids lead to the hydrolysis of complementary mRNA through activation of RNase L with comparable activity as 2-5A-DNAs.

In conclusion, the results presented here show that 2-5A-PNA hybrids form an interesting novel class of antisense agents which may be of great importance for the future development of pharmaceuticals. A full report on the synthesis and biological properties of 2-5A-PNAs will be published in due course.

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