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SYNTHESIS OF DIFFERENT TYPES OF PNAS, CONTAINING CHIRAL PSEUDOPEPTIDE BACKBONE

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ABSTRACT

Peptide nucleic acid (PNA) is a nucleic acid analogues with an achiral polyamide backbone consisting of N-(2-aminoethyl)glycine units. The purine or pyrimidine bases are linked to the each unit via a methylene carbonyl linker to target the complementary nucleic acid. Chiral PNAs were found to form slightly less stable PNA–DNA duplexes than their achiral analogues. By introducing positively charged Lys based monomers, more stable PNA–DNA duplexes were obtained. In this work we presented synthesis for several new PNAs, containing chiral pseudopeptide backbone.

Key words: unnatural amino acids, nucleic acid analogs, arginine, canavanine

INTRODUCTION

In 1991 Nielson, Egholm, Berg and Buchardt (1, 2) reported the synthesis of peptide nucleic acids (PNAs), a new completely artificial DNA/RNA analogues in which the backbone is a pseudopeptide rather than a sugar. First PNAs were based upon an N-(2-aminoethyl)glycine pseudopeptide backbone. The bases (corresponding to A, G, C, T) are attached to the backbone via a methylene carbonyl linker. Their structure completely mimics the structure of DNA or RNA and they are able to form very stable complexes with complementary DNA and RNA. Aminoethylglycyl peptide nucleic acids emerged more than a decade ago as strong and specific DNA/RNA binding agents. Many second-generation PNA-like molecules have been designed, synthesized and evaluated for interesting or improved properties. For example, much work has been devoted to investigate various cyclic backbone-based PNAs, with the goal of increasing the selectivity or strength of interaction with natural nucleic acids. Another class of PNA analogues is based on a diamino acid backbone carrying the nucleobase by means of an amidic bond to one amino group (3-5).

Our purpose is to design totally new PNA with chiral backbone, containing unnatural amino acids based on natural amino acids Arg, Orn and Lys, as shown on **Figure 1**.

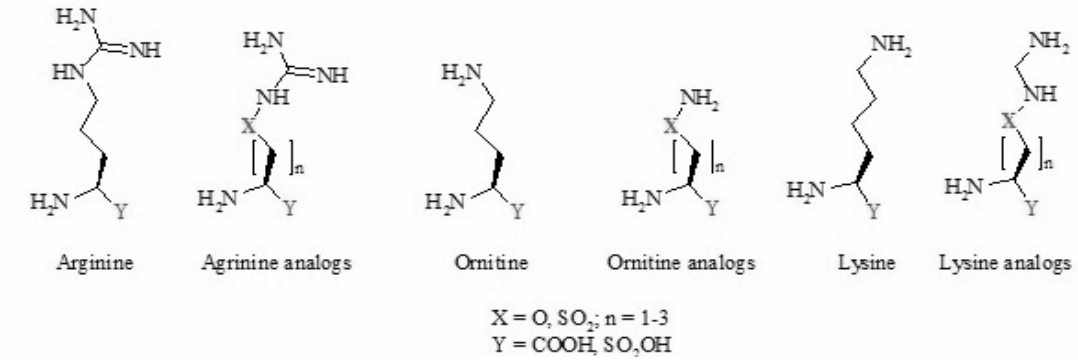

Figure 1. Structures of the amino acid analogues.

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We present here different synthetic schemes and different approaches for obtaining these new PNA monomers and oligomers, using both syntheses in solution and solid-phase synthesis.

RESULTS AND DISCUSSION

For preparation of the new PNA analogues with chiral backbone we applied several synthetic methods and schemes. The building monomers for PNA with N-(2-aminoethyl) glycine pseudopeptide backbone and PNA oligomer were obtained by means of variant methods, such as synthesis in solution, conventional SPPS, SPPS with sonochemical and microwave irradiation, as we previously described (6) **(Figure 2).**

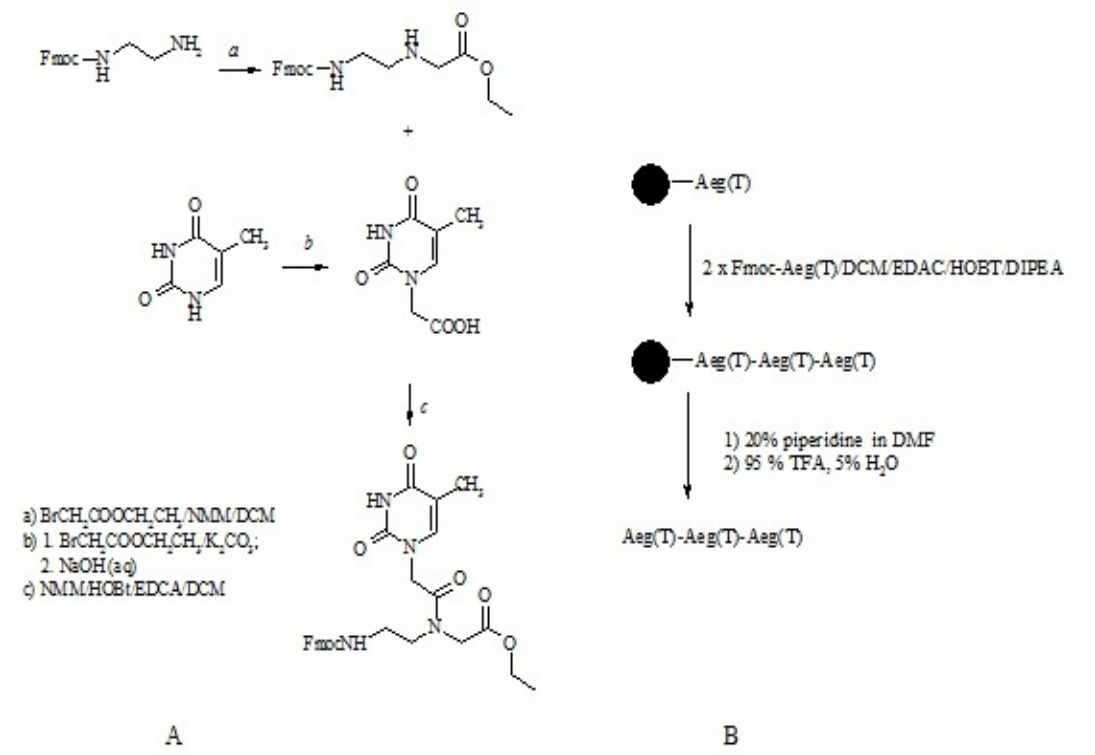

Figure 2. A general strategy for synthesis of aegPNA monomer (A) and PNA oligomer (B).

For the synthesis of PNA with a chiral backbone, we applied two different strategies – preparation of monomers followed by SPPS of PNA, or SPPS of the pseudopeptide chain and consequent coupling with nucleobases **(Figure 3B)**.

Sulfo- and oxo-analogues of Arg used for preparation of monomers were synthesized by original synthetic scheme using common starting mesylated fully protected Ser. Synthetic approach is shown on Figure 3A. PNA oligomers were made by SPPS of the backbone followed by coupling with thymine bases.

Similar approach was used for synthesis of lysPNA and slysPNA. Protected amino acids were involved in SPPS of pseudopeptide backbone. After removal of protecting groups in side chain, acetylated thymine was use for synthesis of this new type of PNAs **(Figure 4)**.

We presented here also, the synthesis of PNAs with pseudopeptide backbone where carboxyl group was replaced by sulfo-group. Synthetic approach on a example of ψ[SO_2NH]lysPNA is shown on **Figure 5.**

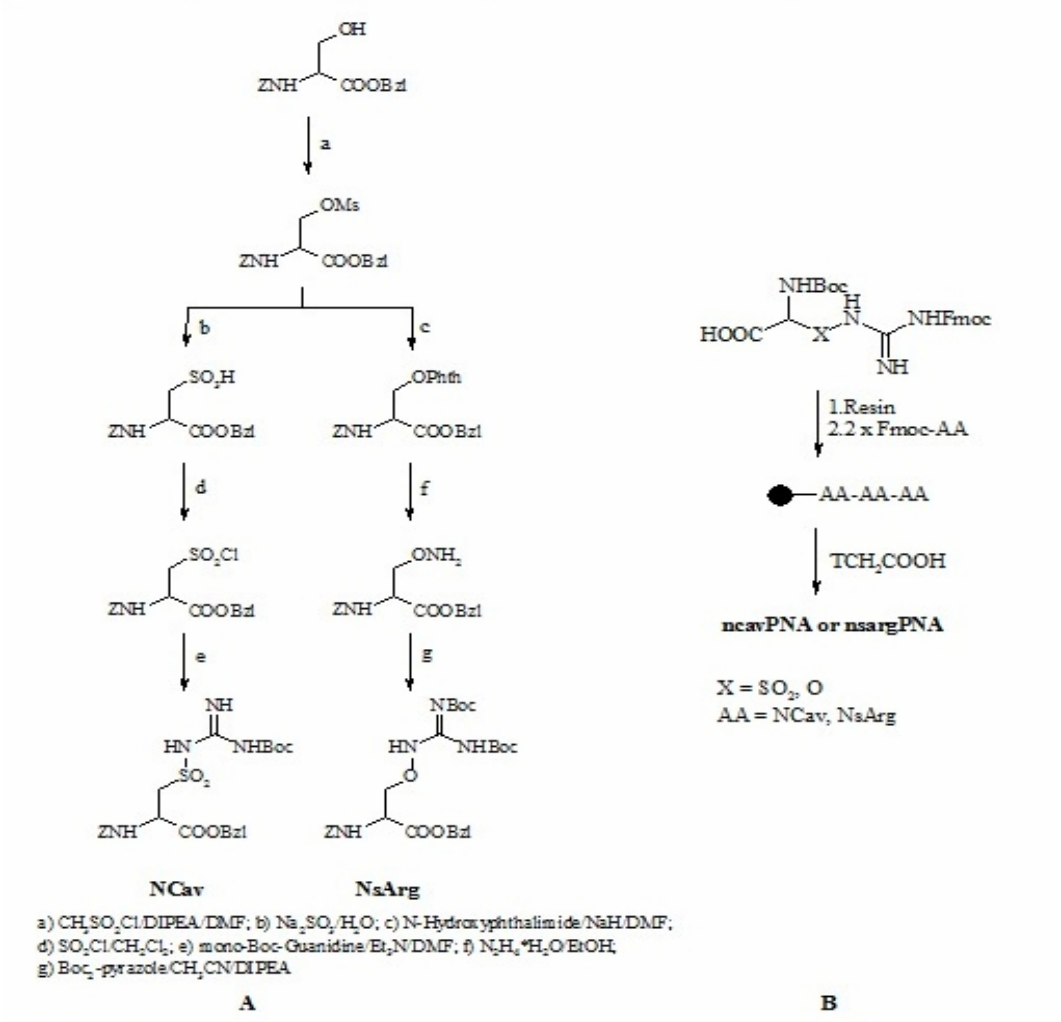

Figure 3. Synthetic schemes for synthesis of PNA, containing unnatural amino acids: A. Synthesis of amino acid analogs. B. Synthesis of PNA.

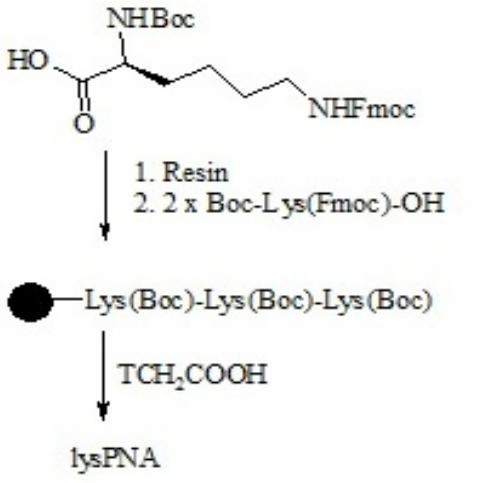

Figure 4. Synthesis of lysPNA

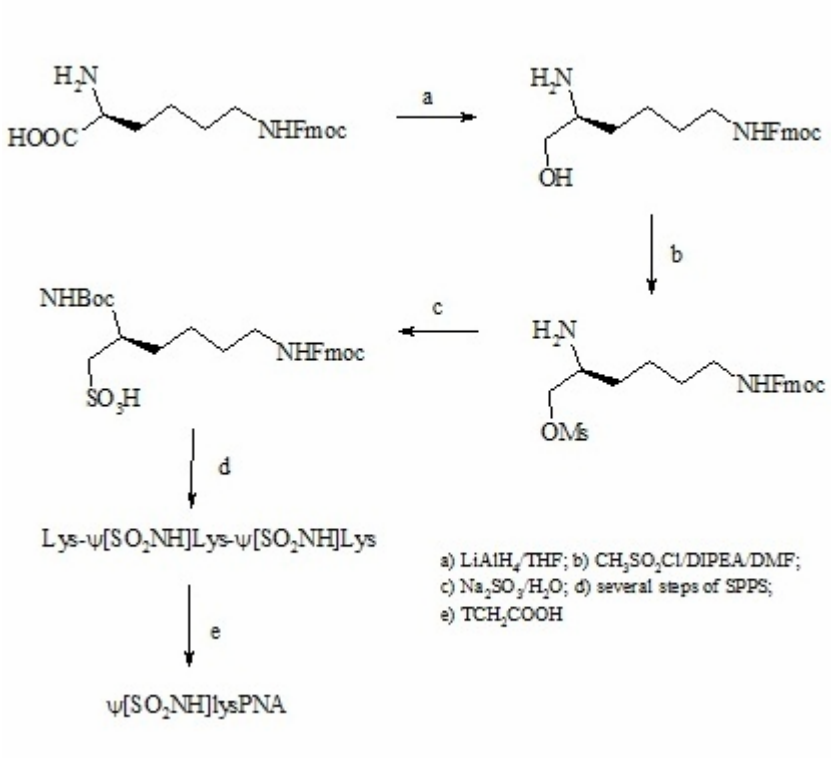

Figure 5. Synthesis of PNAs with sulfonamide pseudopeptide chain.

CONCLUSIONS

As a result of our work we synthesized several new types of PNA with a chiral backbone which could be very useful in different fields of molecular biology. We applied several new methods and strategies for synthesis of these compounds, such as SPPS, synthesis in solution, as well as new methods for preparation of sulfo-analogues of amino acids.

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