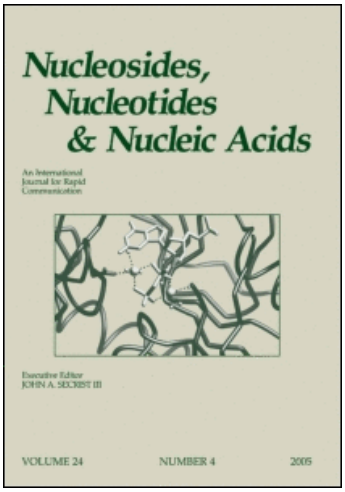

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Pallavi Lonkar[a]; Vaijayanti A. Kumar[a]
[a] Division of Organic Chemistry, National Chemical Laboratory, Pune, India

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Piperidinyl Peptide Nucleic Acids: Synthesis and DNA-Complementation Studies

Pallavi Lonkar and Vaijayanti A. Kumar*

Division of Organic Chemistry, National Chemical Laboratory,
Pune, India

ABSTRACT

Synthesis of a new six membered PNA analogue by introducing a methylene bridge between β carbon atom of ethylene diamine and β′ carbon atom of linker to nucleobase.

INTRODUCTION

Peptide Nucleic Acids have emerged as potential antisense agents.[1] They bind to DNA in both parallel as well as antiparallel orientation. To discriminate between this binding property one can introduce chirality in PNA. In earlier work from our laboratory a built-in chirality was achieved by introducing a methylene bridge[2] between the α-C atom of the glycyl unit and the β-C atom of the ethylene segment of *aeg*PNA(I) which gave *pr*PNA(II). The homooligomers derived from these *aminoprolyl* PNA monomer do not bind to the complementary DNA sequence,

*Correspondence: Vaijayanti A. Kumar, Division of Organic Chemistry, National Chemical Laboratory, Synthesis, Dr. Homi Bhabha Road, Pune 411008, India; Fax: +91 20 5893355; E-mail: vkumar@dna.ncl.res.in.

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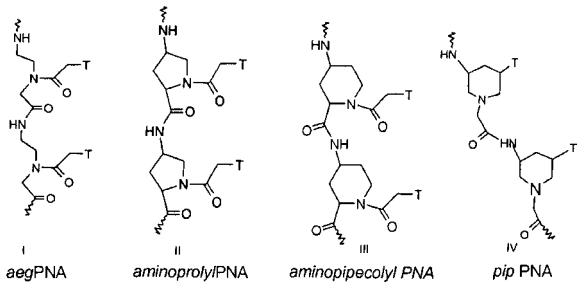
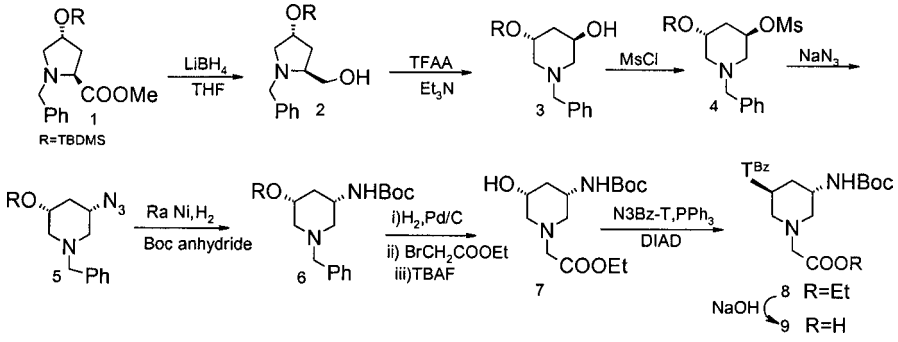
probably due to conformational rigidity in the oligomer. To release this conformational rigidity, aminoethyl backbone in *aminoprolyl* PNA was replaced by aminopropyl backbone still retaining the two chiral centers to obtain *pipecolyl*PNA (III)[3] which too was found to significantly impair the complexation of PNA with complementary DNA.



Herein, we report synthesis of a new six membered PNA analogue by introducing a methylene bridge between β carbon atom of ethylene diamine and β′ carbon atom of linker to nucleobase. (*pip* PNA molecules with a methylene bridge inserted between α carbon atom of ethylenediamine and β′ carbon atom of linker to nucleobase and simultaneously removing rigid carbonyl group. Their DNA/RNA binding preferences may be dictated by the geometry of the backbone as well as the orientation of the nucleobase.

RESULTS AND DISCUSSION

The suitably protected *trans*-4-hydroxy proline **1** was converted to the *trans*-2*S*,4*R* pyrrolidine-2-methanol **2** by reduction of ester function. Treatment with trifluoracetic anhydride followed by triethylamine gives the six membered rearranged product **3** with retension of configuration. Mesylation of the resulting unprotected hydroxy group and reaction with sodium azide gave **5** with inversion at C3. Compound **5** was then selectively hydrogenated using Ra-Ni and Boc-protected to get amino piperidine derivative **6** as shown in Scheme 1. Compound **6** was then



Scheme 1.

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Table 1. UV TM studies of PNA2:DNA complexes.

	Sequences	UV Tm°C
PNA10	H-TTTTTTTT-β-ala-OH	43
PNA11	H-TTTTTTT**t**-β-ala-OH	50.7
PNA12	H-TTT**t**TTT**t**-β-ala-OH	54.4
PNA13	H-TTT**t**TTTT-β-ala-OH	41.4
PNA14	H-**t**TTTTTTT-β-ala-OH	–
DNA	5′-GC$(A)_{10}$CG-3′	

t indicates modified PNA unit.

subjected to hydrogenation, alkylation of ring nitrogen using ethylbromoacetate followed by removal of silyl protection using TBAF to get **7**. *Trans*-5*S*-N3-benzoyl-Thymin-1-yl-3*S*-Bocaminomethyl pyrrolidine derivative **8** was synthesized under Mitsunobu conditions. This was then hydrolyzed using aqueous methanolic sodium hydroxide to get the thymine monomer **9** that could be used for solid phase synthesis of PNA-PyrrolidinePNA oligomer/mixmers. All the new compounds were characterized using suitable spectroscopic analysis.

PNA oligomers containing the *aeg*PNA and piperidine-PNA backbone units were synthesized by SPPS using the BOC- protection strategy. DNA oligomers were synthesized on Pharmacia GA plus synthesizer employing phosphoramidite chemistry.

The PNA10 is the unmodified PNA10 with aminoethylglycyl backbone. PNA11-PNA14 are the modified PNA oligomers with the modified PNA units incorporated at the predefined sites as represented in Table 1. The UV-Tm studies of these monomers indicate that the modified PNA unit at the C-terminus in PNA 11 stabilizes the complex with complementary DNA by about 7°C. The synergistic effect is observed with one more unit in the center of the sequence PNA12 as the PNA_2:DNA complex is further stabilized by about 47°C. Modified unit only in the center of the sequence PNA13 causes 2°C destabilization. These preliminary results are very encouraging and need to be further investigated.

CONCLUSIONS

A high yielding stereospecific ring expansion of protected hydroxy prolinol gives suitably substituted piperidine ring. The ring nitrogen is protonated at physiological pH and oligomers are highly water-soluble. DNA complementation studies by UV-Tm measurements indicate that the six membered monomer is capable of stabilizing the PNA_2:DNA complexes.

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