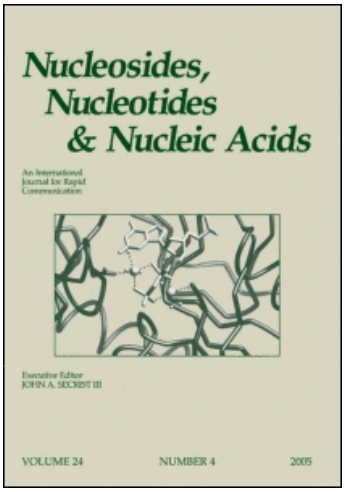

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Oligonucleotides with 2,6-Diaminopurine Base Replacing for Adenine: Synthesis and Properties

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OLIGONUCLEOTIDES WITH 2,6-DIAMINOPURINE BASE REPLACING FOR ADENINE : SYNTHESIS AND PROPERTIES

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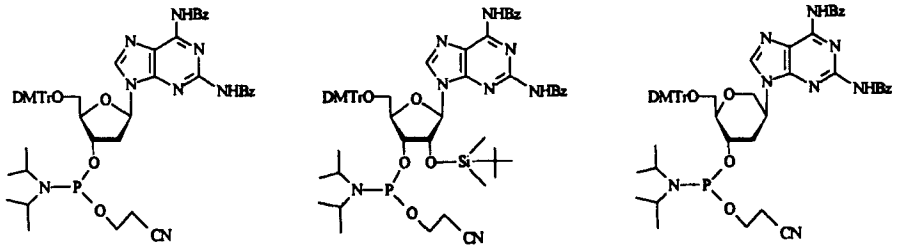
ABSTRACT : Synthesis of three nucleoside building blocks with a benzoyl protected diaminopurine (DAP) base and their incorporation at different positions of DNA, RNA and hexitol oligomers (HNA) have been accomplished. DNA hairpins with a DAP substituted for one (or more) adenine in the loop structure were not found to be more stable. But the stability of RNA-hexitol as well as hexitol-hexitol duplexes improved when the adenine base was replaced with DAP.

The incorporation of modified nucleosides into oligonucleotides may have a profound effect on the structure and stability of the resulting oligomers. The replacement of adenine base by 2,6-diaminopurine (DAP) generally stabilizes nucleic acid duplexes due to the formation of three hydrogen bonds with uracil or thymine bases. However, conformational information on the replacement of adenine by DAP in hairpin structures and in oligonucleotides with modified backbone is rather scarce. We report the preparation of three nucleotide building blocks (**1**, **2** and **3**, FIG. 1) and their incorporation, respectively, in DNA- and RNA-hairpin and in hexitol nucleic acids (HNA) as well as the preliminary results of hybridization studies.

From a synthetic viewpoint, the classical dimethoxytrityl- and tert-butyldimethylsilyl- groups were chosen for protection of the 5'-primary and 2'-secondary alcohol [in the case of ribonucleoside], respectively. Protection of the two exocyclic amino functions was realized by the well established benzoyl group and a mixture of methylamine/ammonia[4] (AMA) [which is more nucleophilic than ammonia] was used for final deprotection.



1 2 3

FIGURE 1

Chemical incorporation of these 3 monomers into oligonucleotides was accomplished without difficulties, following a standard protocol[5] for 1 and 2, while the RNA sequence was assembled and purified by Xeragon (Switzerland). The obtained sequences were deprotected and cleaved from the solid support by treatment with AMA, 45 min at 70°C (90 min for the triple substituted DNA sequence and 60 min at 80°C for the RNA sequence).

All DNA sequences are folding into a hairpin-like structure, however, a slight drop in the stability of the different hairpins is noticed, especially when positioning the diaminopurine at the end of the stem. The sequence 5'-GGAC GTAATD GTCC-3' was selected for studying by NMR the influence of the A *versus* DAP replacement in the base-pair linking the stem and loop structures of the RNA hairpin. For the modified backbone (HNA), the replacement of DAP for A induced a strong stabilisation of RNA / hexitol duplexes and likewise improved the self-pairing potential of hexitol nucleic acids (Δ Tm = 3-5°C/modification).

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REFERENCES :

1. Brown, T; Booth, E.D. and Graig, A.G. *Nucleosides, Nucleotides*, **1989**, 8, 1051.
2. Gaffney, B.L.; Marky, L.A. and Jones, R.A. *Tetrahedron*, **1984**, 40, 3-13.

3. Luyten, I.; Van Aerschot, A.; Rozenski, J.; Busson, R. and Herdewijn, P. *Nucleosides, Nucleotides*, **1997**, 16, 1649-1652 and references cited therein.
4. Reddy, M.P.; Hanna, N.B. and Farooqui, F. *Tetrahedron Lett.*, **1994**, 35, 4311-4314.
5. Ceulemans, G.; Van Aerschot, A.; Wroblowski, B.; Rozenski, J.; Hendrix, C. and Herdewijn, P. *Chem. Eur. J.*, **1997**, 3, 1997-2010.