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xylo-Configured Oligonucleotides (XNA, Xylo Nucleic Acids): Synthesis and Hybridization Studies

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xylo-Configured Oligonucleotides (XNA, Xylo Nucleic Acids): Synthesis and Hybridization Studies

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ABSTRACT

We report synthesis and high-affinity hybridization of fully modified home-thymine 2'-deoxy and 2'-deoxy-2'-fluoro xylo nucleic acids.

Key Words: XNA (xylo nucleic acids); Oligonucleotides; Hybridization.

Oligonucleotides containing 3',4'-threo-configured phosphodiester backbone have attracted only limited attention. [1-4] We here report on novel xylo-configured oligonucleotides (XNA, Xylo Nucleic Acids). 1-(2-Deoxy-2-fluoro-β-D-xylofuranosyl) thymine was obtained starting from methyl 2-deoxy-2-fluoro-3,5-di-O-benzoyl- β -D-xylofuranoside^[5] via Vorbrüggen-type condensation. The xylonucleosides were transformed into phosphoramidite building blocks 1^[1] and 2 (Sch. 1).

ON1 and XNAs ON2-ON5 were synthesized using standard procedures except for modified coupling conditions as described for xylo-LNA synthesis. [4,6]

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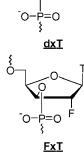
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Scheme 1. i) AcOH, Ac₂O (3.8:1 v/v), conc. H₂SO₄, 75 min, 97%; ii) silylated thymine, TMSTf, 1,2-DCE, reflux, 3 h, 73% (α : β = 1:2); iii) NH₃, MeOH, 20 h; iv) DMTrCl, pyridine, 20 h, 90%; v) NCCH₂CH₂OP(Cl)N(i-Pr)₂, (i-Pr)₂NEt, DCM, 30 min, 81%.

Table 1. Hybridization studies on XNAs **ON2-ON5**.^a

Sequences	Complementary DNA $[d(A_{14})]$ $T_m/^{\circ}C$ $(\Delta T_m \text{ vs. } \mathbf{ON1})$	Complementary RNA $[r(A_{14})]$ $T_m/^{\circ}C$ $(\Delta T_m \text{ vs. } \mathbf{ON1})$
ON1 (T ₁₄)	33 (Reference)	29 (Reference)
ON2 $(5'-T_7 dxTT_6)$	23 (-10)	25 (-4)
ON3 $(5'-T_7\overline{FxT}T_6)$	23 (-10)	25 (-4)
ON4 $(5'-(dxT)_{13}T)$	33 (+/-0)	38 (+9)
ON5 $(5'-(\overline{FxT})_{13}T)$	36 (+3)	36 (+7)

^aMedium salt buffer (10 mM sodium phosphate, 100 mM sodium chloride, 0.1 mM EDTA, pH 7.0).



Hybridization data are shown in the Table. A strong destabilizing effect of single incorporations of both XNA monomers is observed towards a DNA complement. The first data on hybridization of XNAs towards RNA complements are included in the Table. It is revealed that XNA is a class of molecules able to efficiently target RNA, and it is noteworthy that the almost fully modified XNAs (ON4 and ON5) displays significantly increased binding affinity towards RNA compared to the reference (ON1). We are currently studying the structure of XNA-containing hybrids.

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