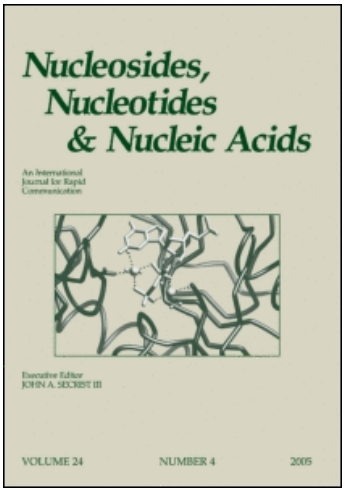

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Synthesis and Binding Properties of a Homopyrimidine 2',5'-Linked Xylose Nucleic Acid (2',5'-XNA)

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Synthesis and Binding Properties of a Homopyrimidine 2′,5′-Linked Xylose Nucleic Acid (2′,5′-XNA)

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ABSTRACT

The synthesis and hybridization properties of pyrimidine 2′,5′-RNA and 2′,5′-Xylose Nucleic Acid (2′,5′-XNA) are described.

Key Words: Xylonucleosides; Xylonucleic acids (XNA); Thermal melting; Antisense.

Oligonucleotides comprised of 2′,5′-phosphodiester linkages (2′,5′-DNA and 2′,5′-RNA)[1] are able to associate with complementary RNA (3′,5′-linkages) and, as such, can potentially be used as antisense inhibitors of gene expression.[2] An interesting property that distinguishes 2′,5′-RNA (and 2′,5′-DNA) from the native RNA is its inability to form duplexes with single stranded DNA (ssDNA). We wondered whether this selective pairing behavior could likewise be manipulated via stereochemical inversion at carbon 3′ of the natural ribose sugar moiety, i.e., we asked ourselves "*what properties, if any, do 2′,5′-linked D-xylose-derived oligonucleotides possess that may distinguish them from other nucleic acids*?" To address this question, we report here the synthesis and hybridization properties of a 2′,5′-linked β-D-xylose

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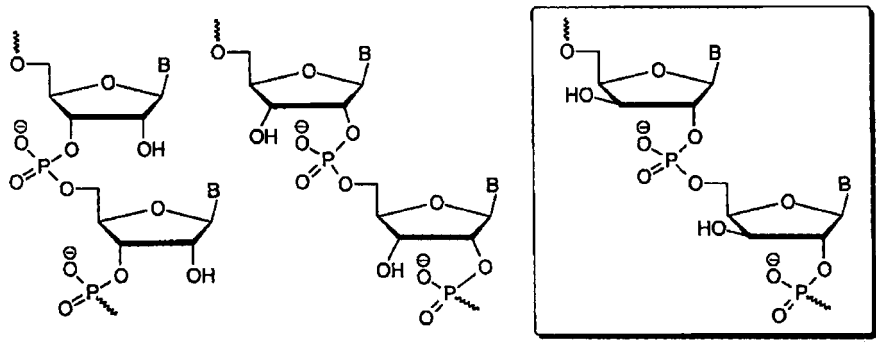

Figure 1. From left to right, primary structures of RNA, 2′,5′-RNA and 2′,5′-XNA.

nucleic acid (2′,5′-XNA; Fig. 1). To the best of our knowledge, previous studies concentrated solely on 2′,5′-x(pApApA) trimers and their potential use for interferon-induced degradation of mRNA by activation of RNase L.[3]

The synthesis of β-D-5-methyl-xylouridine (xU^{5Me}) was performed by Vorbrüggen coupling[4] of the base and sugar, by a procedure analogous to that described by Imbach et al.[5] Full details for the preparation of this and several other xylonucleosides will be published elsewhere. 5′-Dimethoxytrityl-3′-O-acetyl-β-D-5-methyl-xylouridine (xU^{5Me}) 2′-O-phosphoramidite was used as building block for automated synthesis of the octadecanucleotide 2′,5′-xT_{18}. 5-(Ethylthio)tetrazole was used as the coupling reagent. The average coupling monomer efficiency was 85–102%, and the isolated yield of the oligomer was 4% (1 μmol scale synthesis). This compound, along with the 2′,5′-rU_{18} and rU_{18} counterparts, was tested for duplex formation. Contrary to what is found for 2′,5′-rU_{18}, no association was observed between 2′,5′-$xU_{18}^{(5Me)}$ and complementary RNA and DNA (Table 1). Therefore, we conclude that inversion of configuration at C3′ of the ribose is detrimental to duplex formation. This could be explained in terms of steric factors involving the 3′-hydroxyl or, more likely, by an inappropriate structure of 2′,5′-$xU_{18}^{(5Me)}$ to form duplexes. Previous studies indicate that the sugars of 2′,5′-xA_3 adopt a C3′-*endo* conformation,[6] likely the result of two gauche effects along the O3′-C3′-C4′-O4′ and O2′-C2′-C1′-O4′ frameworks. Similarly, a C3′-*endo* conformation in 2′,5′-$xU_{18}^{(5Me)}$ would force the sugar-phosphate backbone to adopt an "*extended*" conformation of almost equivalent length to that found in the native DNA (i.e., C2′-*endo*) conformation.[7] Oligonucleotides that are pre-organized in an "*extended*" (or DNA-like) conformation bind weakly, if at all, to a "*compact*" RNA target. Such conformational incompatibility or spatial "mismatching" of the two strands likely accounts for their inability to maintain stable associations and may also explain why 2′,5′-XNA ("*extended*") binds poorly to RNA ("*compact*"). By contrast, 2′,5′-RNA (C2′-*endo*) and RNA (C3′-*endo*) both adopt a "*compact*" sugar-phosphate backbone[7] that is compatible for binding to "*compact*" RNA targets (i.e., in this cases, a compact/compact "match" can be realized). The synthesis of 2′,5′-XNA of mixed base oligonucleotides and 3′-fluoro-2′,5′-linked XNA are in progress in order to determine whether the properties of 2′,5′-$xU_{18}^{(5Me)}$ are representative of all 2′,5′-xylose nucleic acids.

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