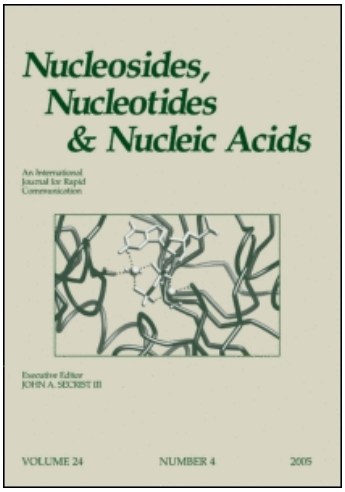

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Methylated Hexitol Nucleic Acids, Towards Congeners with Improved Antisense Potential

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ABSTRACT

In an effort to further improve the hybridisation potential of anhydro-hexitol nucleoside analogues, the 1′-methoxyl and 3′-methoxyl substituents were introduced and evaluated for their antisense potential. In view of the selectivity of pairing with RNA, especially the introduction of a 3′-*O*-alkyl moiety deserves further study.

1,5-Anhydrohexitol nucleic acids (HNA) are oligonucleotide analogues with 6-membered rings substituting for the natural deoxyribose moieties. These backbone modified oligonucleotides are endowed with high affinity for complementary RNA sequences.[1] Efforts to further augment the hybridisation potential and to reduce

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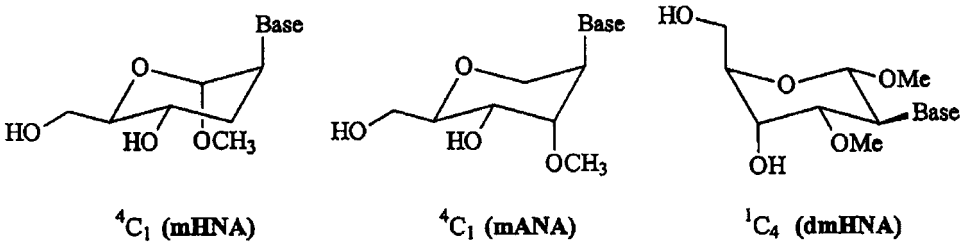

Scheme 1.

the cost of synthesis resulted in some alkylated congeners, and preliminary physicochemical studies in the pyrimidine series were accomplished.[2] To further complete these studies with 1′-methoxyl and 3′-methoxyl HNA,[2] as well the adenine congeners as the bis-methoxylated analogues (see Sch. 1) were synthesized and incorporated into oligonucleotides.

The use of 3′-*O*-methyl altritol nucleoside analogues (mANA) proved marginally advantageous as compared to HNA, but did not seem to augment the effects as obtained by the altritol analogues (ANA). In addition, however, 3′-*O*-alkylation seemed to prohibit the unwanted hT-hT or hU-hU homopolymer pairings. The 1′-methoxyl analogues (mHNA) likewise display increased affinity for RNA as compared to HNA, however, the mhT homopolymer does show increased self-pairing. Introduction of a second methoxyl substi-tuent (dmHNA) as expected changes the overall conformation as of steric clashes of substi-tuents at C1 and C3, resulting unmistakably in a $^1C_4$ conformation for the adenine congener, with the base and both methoxyl substituents oriented equatorially. For the thymine analogue, NMR signals hinted at an unstable distorted chair conformation.

Preliminary incorporation studies yielded a mixed picture with apparent pairing potential for the purines but not so for pyrimidines with the actual conformation within oligomers being uncertain.

A feature very important in obtaining good antisense properties for new constructs is not only to display strong **affinity** for RNA sequences, but at the same time to be endowed with strong **selectivity for** interaction with **the RNA target only**. Hereto, dodecamer sequen-ces containing three modifications were used to compare the effects of 2′-*O*-methylated adenosine, the altritol analogue, the 3′-O-methylated altritol analogue, the 1′-*O*-methylated hexitol analogue, and the adenine LNA congener versus the DNA control sequence.

While all modifications increased the affinity for RNA target sequences, except to our surprise the 2′-*O*-alkyl adenosine, within the hexitol class, the 3′-O-alkyl modification outbeated even the so far best performing altritol modification. Its affinity for RNA was only surpassed by the strongly pairing LNA analogue, but the latter modification displayed increased affinity for all sequences, and therefore has a reduced RNA selectivity.

It is clear therefore that for having strong antisense properties, both affinity and selectivity for RNA need to be envisaged.

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