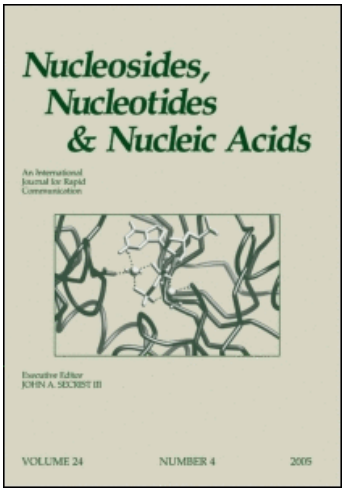

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Synthesis, Hybridization, and Nuclease Resistance Properties of 2'-O-Aminooxyethyl Modified Oligonucleotides

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SYNTHESIS, HYBRIDIZATION, AND NUCLEASE RESISTANCE PROPERTIES OF 2'-O-AMINOOXYETHYL MODIFIED OLIGONUCLEOTIDES

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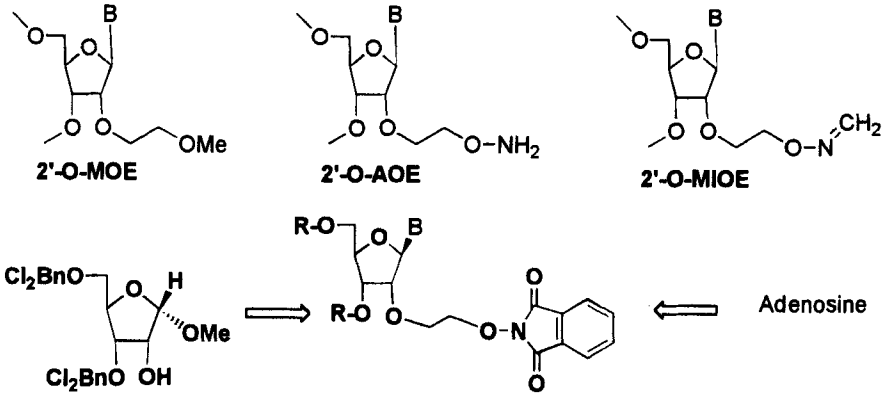
ABSTRACT: We have synthesized the novel 2'-O-AOE- and MIOE-5-methyluridine and –adenosine nucleosides and successfully incorporated them into oligonucleotides. The 2'-O-modifications significantly enhance hybridization against RNA (1.2 deg C/substitution) and furthermore, exhibits specificity for RNA vs. DNA. The nuclease resistance (SVPD) of 2'-O-AOE and MIOE modified oligonucleotides is comparable to that of 2'-O-MOE.

The paradigm of antisense oligonucleotide as drug with clinical applications requires that the oligonucleotide forms a stable duplex with target mRNA, prevents translation of message (most often via RNase H-mediated cleavage), and is resistant to nucleases. Thus far, 2'-O-modified oligonucleotides incorporated with a phosphorothioate backbone have provided the most effective antisense molecules,[1] the 2'-O-substituent providing enhancement of hydridization and the phosphorothioate linkage increasing nuclease resistance. However, with experience we have found that sulfur-containing oligonucleotides can alter the pharmacokinetic profile of the compounds, especially with regard to oligonucleotide-protein binding. Thus, to modulate these parameters we aspire to control, albeit not necessarily eliminate, the sulfur content of the oligonucleotide while maintaining the desired attributes of an antisense drug. To date the 2'-O-methoxyethyl-modified oligonucleotide[2] (2'-O-MOE, Figure 1) used with the «gapmer» technology has emerged as the leading candidate for clinical application. Although the 2'-O-MOE modification has desirable antisense qualities, its nuclease resistance could be further

Figure 1



improved upon. Hence, we were led to investigate the pseudoisostere of MOE, the novel 2'-O-aminooxyethyl modification (2'-O-AOE, Figure 1).

In this work we have successfully prepared the 2'-O-AOE-5-methyluridine and -adenosine and incorporated the modified nucleosides into oligonucleotides. In addition the 2'-O-methyleneiminooxyethyl-5-methyluridine and -adenosine (2'-O-MIOE) nucleosides and modified oligonucleotides were synthesized. The 2'-O-modifications significantly enhance hybridization against RNA (1.2 deg C/substitution) and furthermore, exhibits specificity for RNA vs. DNA. The nuclease resistance (SVPD) of 2'-O-AOE and MIOE modified oligonucleotides is comparable to that of 2'-O-MOE. The primary aminooxy group of 2'-O-AOE nucleosides allows for further derivatization, e.g., into oximes, dialkylaminooxy (see accompanying poster, T. P. Prakash, et al.), etc., and thus we are currently elaborating the function to optimize the desired attributes of antisense molecules.

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