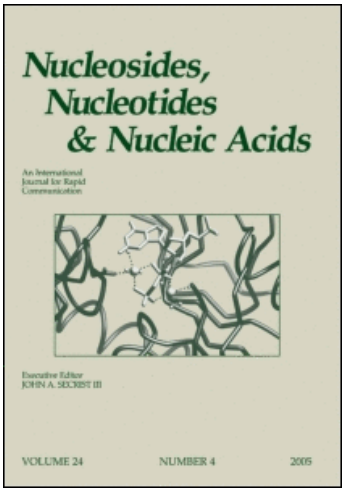

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2'-DMAOE RNA: Emerging Oligonucleotides with Promising Antisense Properties

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2'-DMAOE RNA: EMERGING OLIGONUCLEOTIDES WITH PROMISING ANTISENSE PROPERTIES

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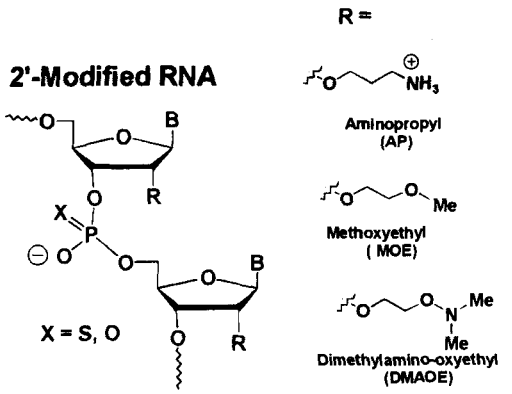
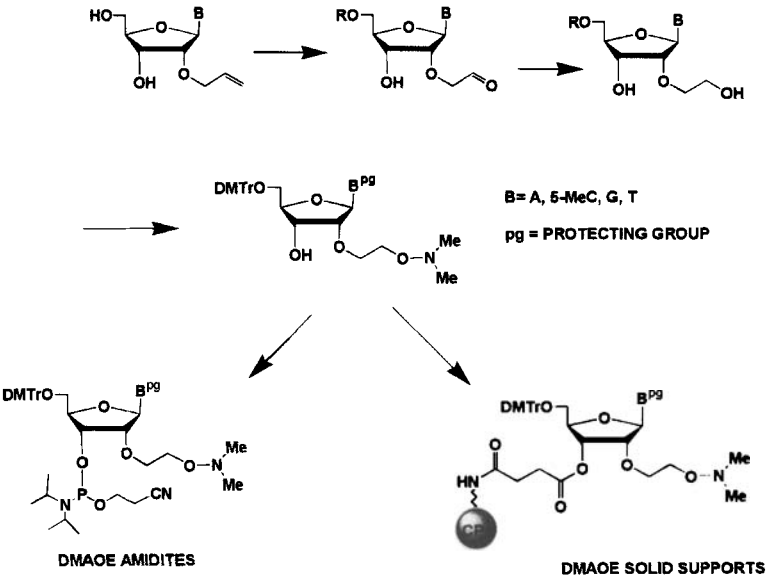
Oligonucleotides with modifications at the carbohydrate 2'-position offer potential second-generation drug candidates[1]. ISIS 13312, a chimeric compound targeting CMV retinitis, has 2'-*O*-methoxyethyl[2] (2'-MOE) modifications at the ends to offer enhanced binding affinity and nuclease resistance is an example of this trend. 2'-MOE modification offers high binding affinity and nuclease resistance presumably due to conformational constraints placed on the linkage by the oxygen-oxygen gauche effect[3]. On the other hand, 2'-*O*-aminopropyl modification (2'-AP) exhibits the highest nuclease resistance[4], due to the presence of a cationic charge at the physiological pH. However, it lacks the binding affinity advantage of MOE due to the lack of oxygen-oxygen gauche effect. To optimize the antisense properties of both 2'-MOE and 2'-AP modifications, we have designed and constructed 2'-*O*-(aminooxyethyl) modification (2'-AOE)[5] and 2'-*O*-(dimethylaminooxy ethyl) modification (2'-DMAOE) and synthesized oligomers having these modifications. 2'-DMAOE oligomers demonstrate higher binding affinity and nuclease resistance than 2'-MOE oligomers and stand out as promising candidates for future antisense oligonucleotide drug development.



Synthesis of DMAOE-RNA phosphoramidites and solid supports.

The 2'-alkylation chemistry developed at Isis over the past years has been employed to generate gram quantities of 2'-DMAOE nucleoside phosphoramidites. Essentially, there are two starting materials involved, one involving 2'-*O*-allyl modified nucleosides and another involving 2'-*O*-CH_2-CH_2-OH modification. The reaction sequences have been established and has been extended easily to all four (A, C, G, and T) nucleosides to generate sufficient quantities of phosphoramidites and solid support needed for automated synthesis of DMAOE-RNA antisense oligonucleotides. Both phosphodiester and phosphorothioate oligonucleotides have been synthesized with 2'-DMAOE modification.



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