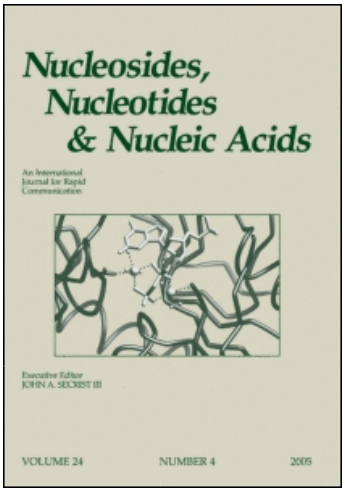


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# 4'-Thio-RNA: Synthesis, Base Pairing Properties and Interaction with Dimerization Initiation Site of HIV-1

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# 4'-THIO-RNA : SYNTHESIS, BASE PAIRING PROPERTIES AND INTERACTION WITH DIMERIZATION INITIATION SITE OF HIV-1

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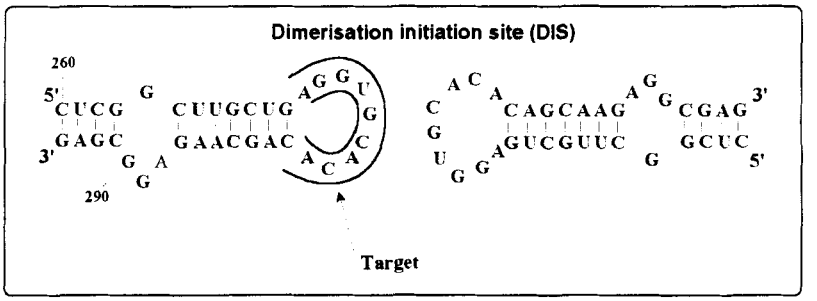
**ABSTRACT**: in the present paper, we describe the synthesis of a modified 9-mer oligonucleotide, **4'-S-r(UGUGCACCU)** containing for the first time 4'-thio-guanosine units. This modified 9-mer was found to inhibit *in vitro* genomic RNA dimerization as well as the wild type RNA.



Antisense oligonucleotides constitute a promising class of antiviral drugs that offer a new and highly selective chemotherapeutic strategy to treat human diseases. To be successful, antisense therapeutics have to fulfill some criteria including nuclease resistance and affinity. We have showed that 4'-thio-β-D-oligoribonucleotides (4'-S-RNA) containing three of the four bases such as U, C and A exhibit very good nuclease resistance in comparison with wild-type RNA and bind more tightly to its complementary RNA strand than to its complementary DNA strand[1].




SCHEME

To explore further the biological applications of 4'-S-RNA series, we report the synthesis of 4'-S-r(UGUGCACCU) complementary to the loop of the HIV-1 Mal Dimerization Initiation Site (DIS) (Scheme). RNA dimerization is an ubiquitous property of retroviruses and is required for recombination. Furthermore, the DIS is involved in encapsidation and proviral DNA synthesis. Thus, the DIS represents a promising target for antiviral agents[2].

We found that 5-O-acetyl-2,3-O-isopropylidene-4-thio-D-ribofuranose is the best candidate for nucleosidic condensations on account of its anomer β orientation. This sugar was obtained in large quantities starting from D-gulono-1,4-lactone. Using Vorbrüggen condensation methods, the four 4'-thio-ribonucleosides (U, N4-bz-C, N6-bz-A, N2-Ac-G) were obtained. Each nucleoside was converted into its phosphoramidite derivatives for solid phase synthesis. Then, the 9-mer 4'-S-r(UGUGCACCU) was automatically synthesized, purified by HPLC and characterized by MALDI-TOF mass spectrometry.



Unlike the unmodified RNA 9-mer, this 4'-thio-RNA oligonucleotide was able to form a stable duplex by a self-association phenomenon (six bases in row), suggesting that Watson-Crick interactions are stabilized by the S→O substitution. We studied the ability of this modified series targeted against the DIS to interfere a pre-formed viral RNA dimer. The 4'-thio-RNA was found to inhibit *in vitro* genomic RNA dimerization as the natural 9-mer, provided that the self-association was disrupted by a treatment involving heating and rapid cooling, before addition to the genomic RNA dimer. All these data indicate that 4'S-RNA can be considered as good candidates in antisens approach.

## REFERENCES

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