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OLIGO-[α]-DEOXYNUCLEOTIDES COVALENTLY LINKED TO INTERCALATING AGENTS. DNA AND RNA BINDING PROPERTIES.

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We previously described the synthesis and the nucleic acid binding properties of oligodeoxynucleotides covalently linked to intercalating agents [1,2]. The oligonucleotide specifically recognizes its complementary nucleic acid sequence both at the DNA and RNA level. The intercalating agent provides an additional binding energy which stabilizes the complexes. Oligonucleotide-intercalator conjugates efficiently block messenger RNA translation in procaryotic [3] as well as eucaryotic systems [4]. Oligodeoxynucleotides synthesized with the natural [β] anomers of nucleoside units are hydrolyzed by nucleases. Their nuclease sensitivity limits their potential utilization *in vivo*. The natural [β] anomers can be replaced by synthetic [α] anomers. Oligo-[α]-deoxynucleotides can be synthesized using the same chemical strategies as those used for oligo-[β]-deoxynucleotides [5,6]. They can be covalently linked to intercalating agents.

Oligo-[α]-deoxynucleotides are much more resistant to nuclease digestion than their [β] analogues [6,7]. They bind to complementary sequences and form more stable complexes with RNA than with DNA [6]. We have covalently attached a photocrosslinking reagent at the end of oligo-[α]-deoxynucleotides to probe the relative orientation of the two strands in [α]-[β] heteroduplexes [8]. The results demonstrate that double helices with parallel strands are formed when an oligo-[α]-deoxynucleotide binds to a complementary DNA single strand [8]. The same conclusion is reached from fluorescence studies [9]. Double helix formation only occurs when the two complementary sequences ([α] DNA and [β] DNA) run in a parallel orientation.

Oligo-[β]-deoxynucleotides are efficient in blocking mRNA translation because their hybrid with mRNAs act as substrates for RNase H [4]. This enzyme recognizes the oligodeoxynucleotide-mRNA duplex and hydrolyzes the mRNA. Oligo-[α]-deoxynucleotides-mRNA hybrids are poor substrates for RNase H and therefore inhibition of mRNA translation is very inefficient *in vitro*. This difficulty can be overcome by attaching reactive groups at one end of the oligo-[α]-deoxynucleotide ([10] and unpublished results). These reactive groups can induce either a cleavage of the target sequence or a photocrosslinking reaction. Irreversible reactions can thus be targeted to specific sequences.

Oligo-[α]-deoxypyrimidines can recognize an oligopurine-oligopyrimidine sequence in a double-stranded DNA [10]. This interaction involves local triple helix formation. The oligo-[α]-deoxypyrimidine binds in the large groove of the double helix.

Oligo-[α]-deoxynucleotides covalently linked to intercalating agents and to active

reagents represent an interesting family of molecules which can be used as tools in molecular and cellular biology and could represent a starting point for the rational design of therapeutic agents.

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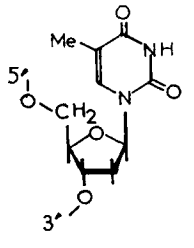
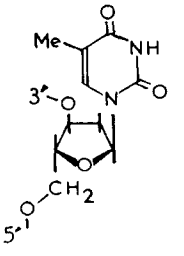


β-nucleoside



α- nucleoside