Synthesis and triplex-forming properties of α-oligonucleotides containing diaminoquinoline and 4N-(2-guanidoethyl)cytosine derivatives

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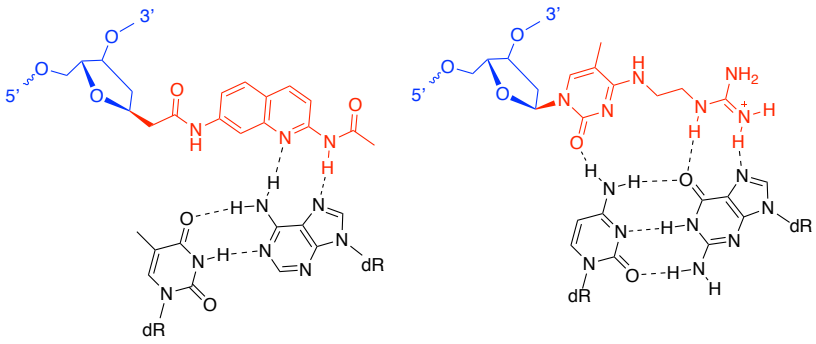
Triplex-forming oligonucleotides (TFOs) can recognize the targeted sequence of genomic DNAs and regulate their expression for gene therapy. However, unmodified TFOs are easily degradated by nuclease. This low nuclease resistance limits their application. Generally, changing the anomeric configuration of the nucleosides from β to α can increase the resistance of oligonucleotides against nuclease.[1] α-Oligonucleotides can bind to their corresponding DNAs in the reverse orientation and with the similar Hoogsteen bonding pattern comparing to β-oligonucleotides, yet the binding affinity of them is slightly lower than β-oligonucleotides.[2] Moreover, unmodified α-oligonucleotides cannot recognize pyrimidine-purine base pairs of the targeted DNA. This sequence dependency also limits the application of α-oligonucleotides.

In this study, we synthesized the α-oligonucleotides containing thymine (α-T), 5-methylcytosine (α-5meC), N-acetyl-2,7-diaminoquinoline (α-$^{7da}Q_{ac}$) and 4N-(2-guanidoethyl)-5-methylcytosine (α-^{g}C) for improvement of nuclease resistance and base-recognition abilities. According to our previous studies, $^{7da}Q_{ac}$ can selectively recognize T-A base pair,[3] while ^{g}C can recognize C-G base pair.[4] Therefore, the triplex-forming abilities of α-oligonucleotides containing such modified bases are evaluated by melting temperature, and their nuclease resistance in serum is also assessed.



α-$^{7da}Q_{ac}$:T-A α-^{g}C:C-G

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