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Antisense oligonucleotides: modifications and clinical trials

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There has been an upsurge in the number of clinical trials involving chemically modified oligonucleotide-based drug candidates after the FDA approval of Vitravene, Macugen, and recently, Kynamro. Over the years, different types of backbone, nucleobase and/or sugar-modified oligonucleotides have been synthesized because natural DNA/RNA based oligonucleotides pose some limitations, such as poor binding affinity, low degree of nuclease resistance, affecting their direct use in antisense therapeutics. In this review article, we discuss in detail different modifications of nucleosides/oligonucleotides along with the related clinical trials, which demonstrated their potential as drug candidates for antisense and related nucleic acid based therapeutics.

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Introduction

Most of the drugs present in the market interact with proteins; moreover, they often bind to non-target proteins or exert an adverse effect through unknown interactions.[1] The dream of modern drug research to develop a therapeutic technology that can act specifically only on the target responsible for the disease has led to the development of drugs that can turn off genes by targeting directly the nucleic acids that code for the proteins. Antisense therapeutics were introduced after Paterson *et al.*[2] in 1977 reported the utility of nucleic acids in modulating gene expression, and shortly after, Zamecnik and Stephenson[3] demonstrated the inhibition of viral replication by modified oligonucleotides (ONs).[4] In the quest of effective antisense candidates, various chemical modifications of the natural ONs have been studied, such as modifications in the phosphodiester backbone, heterocyclic nucleobase and sugar moiety, which confer high affinity and specificity for their target nucleic acid sequences (Fig. 1).[5]

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