ETH zürich

Licensing Opportunity

Building blocks for the synthesis of stereochemically pure oligonucleotides

Summary

The use of chemically-modified oligonucleotides as potential therapeutics has received much attention in recent years. This invention introduces a solid phase synthesis path for stereo designed phosphorothioate oligonucleotides based on 2'-O-methoxy-ethylribose (MOE) nucleoside building blocks.

Background

Oligonucleotides have generally poor pharmacokinetics. They are rapidly cleared from the circulation and are degraded by enzymes. Chemical modifications improve their pharmacokinetics as well as their pharmacodynamic properties. One of the most common modifications is the exchange of oxygen for sulfur at most or all internucleotide linkages. However, as the internucleotide phosphorothioate linkage is chiral, an increasing number of diastereomers is created with each extra phosphor-sulfur (PS) linkage. The pharmacokinetics and -dynamics are significantly affected by the stereochemical configuration. Thus, a synthesis route leading to stereopure oligonucleotides is highly desirable.

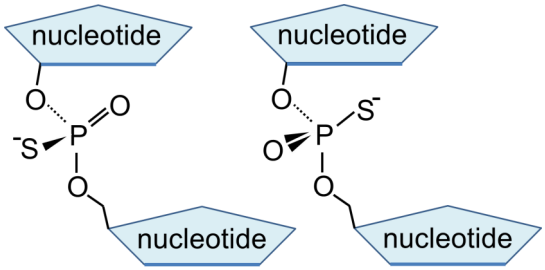

Fig. 1 Diastereomers due to the chiral PS linkage.

Invention

The invention describes the synthesis of 8 new stereopure MOE nucleoside phosphoramidites according to the structures in Fig. 2. With these building blocks stereodefined phosphorothioate MOE oligonucleotide can be produced via solid phase synthesis. The stereo designed phosphorothioate MOE oligonucleotides can comprise 30 building blocks and more.

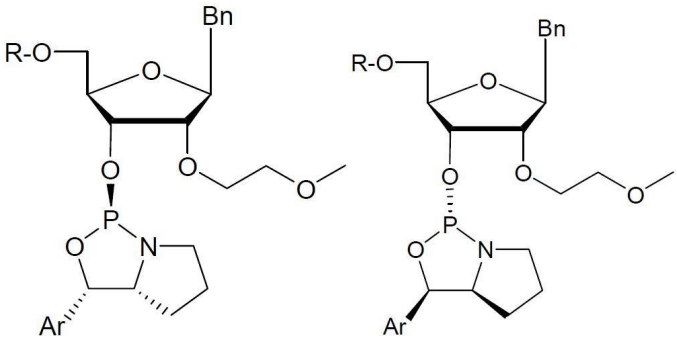

Fig. 2 The chiral phosphoroamidites (left) and (right) represent novel monomers for the synthesis of stereodefined MOE oligonucleotides wherein Ar is preferably phenyl, R is a protective group of the hydroxyl group and Bn is a nucleobase or a derivative thereof.

Features & Benefits

- Novel and clinically-validated oligonucleotide chemistry
- Stereopure MOE drugs

Fields of Application

- Synthesis of PS oligonucleotide drugs

Patent Status

- Patent pending

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ETH transfer
transfer@sl.ethz.ch
www.transfer.ethz.ch
+41 44 632 2382

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Developed by: Institute for Pharmaceutical Sciences
Professor Jonathan Hall, Dr Meiling Li