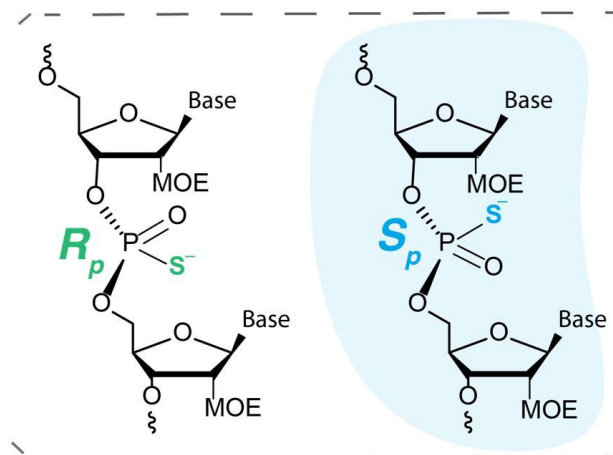
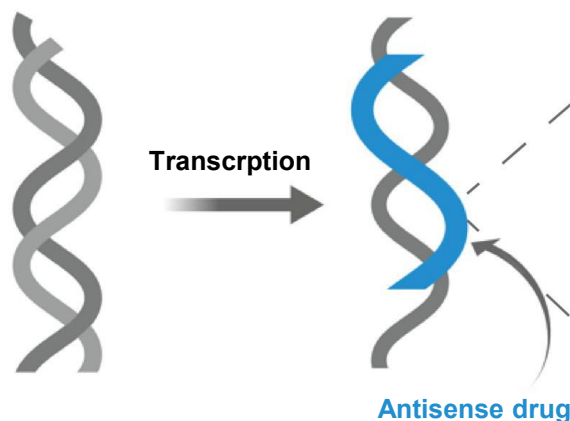


Licensing Opportunity

Building blocks for stereopure antisense oligonucleotide (ASO) therapeutics



Application

The preparation and testing of stereochemically-pure phosphorothioate ASOs identifies those stereocenters that may enhance potency, extend lifetime, and reduce neurotoxicity. Hence, the synthetic path towards improved oligonucleotide therapeutics is optimized. Candidate drugs are among others Nusinersen, Inotersen and Volanesorsen, which are currently distributed as pools of diastereomers.

Features & Benefits

- Full-length stereopure MOE phosphorothioate oligonucleotides with all 4 building blocks
- Next generation MOE ASO therapeutics to address gain-of-function and loss-of-function genetic diseases
- Solid phase synthesis kit with preloaded stereopure nucleotide

Publication

- "Synthesis and cellular activity of stereochemicallypure 2'-O-(2-methoxyethyl)-phosphorothioate", *Chem. Commun.* **53**, 541 (2017), <https://doi.org/10.1039/C6CC08473G>
- Patents [PCT/EP2017/061991](https://patents.google.com/patent/PCT/EP2017/061991), [PCT/EP2023/079206](https://patents.google.com/patent/PCT/EP2023/079206)

Background

ASO are synthetic, linear, single-stranded nucleic acid polymers. They bind to sites on complementary messenger RNA (mRNA, including pre-mRNA) and alter the biosynthesis of disease-related proteins. A prominent example of an ASO is Nusinersen for the treatment of spinal muscular atrophy. Nusinersen contains a chain of 18 chemically-modified nucleotides: 2'-O-2-methoxyethyl (2'-MOE) replacing the 2'-hydroxy groups of the ribo-furanosyl rings and phosphorothioate (PS) linkages between the nucleotides (see figure above). The PS linkage increases drug lifetime. At the same time, it introduces chirality, which complicates drug development. A synthesis route leading to the stereopure oligonucleotides with improved pharmacokinetic and pharmacodynamic properties is desirable.

Invention

The invention introduces two chiral phosphoroamidites as building blocks for the synthesis of stereodefined MOE oligonucleotides.

Complete stereocontrol is possible by selecting one of the two building blocks at each PS linkage. A pre-loaded solid support facilitates large scale production. The support is preloaded with the S_p diastereomere, which forms a protective stereopure cap at the 3' end and renders the MOE oligonucleotide metabolically stable. From there, the chain of nucleosides is grown with either conventional (non-stereopure) methods or with the stereochemically-pure method described in this invention.

The method has been lab-tested. A stereopure diastereomer variant of Nusinersen, a 18-mer oligonucleotide, was synthesized.



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 Reference
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Technology Readiness Level

1 2 3 4 5 **6** 7 8 9