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Synthesis of a Building Block for Oligopeptide-Oligonucleotide Conjugates

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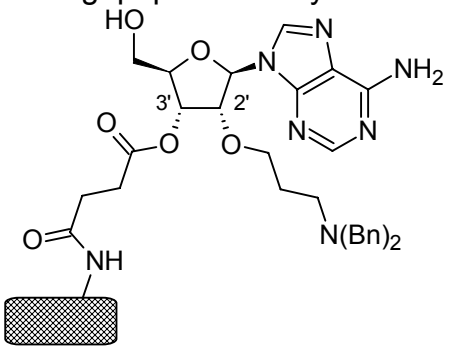
Antisense and siRNA oligonucleotides have been widely used in the past decade as an efficient gene-silencing tool in molecular biological investigations. However, their therapeutic application has hitherto been hampered by their poor pharmacokinetic properties.

Conjugation of oligonucleotides to oligopeptides as a way of uptake enhancement has recently gained considerable attention. The main focus of this work lies on the synthesis of a modified adenosine nucleoside which is aimed to serve as the joining point of oligopeptide moiety at the 2'-position.



Functionalization of the 2'-OH group not only provides a tether for further in-line solid-phase synthesis, but also imparts nuclease stability to the oligonucleotide-oligopeptide conjugate.

Poor reactivity of the 2'-position along with non-selectivity of substitution characterize the alkylation reaction as the limiting step in the synthesis of modified nucleosides.

Our synthetic route started with protection of the 5'-OH group. Subsequent alkylation through Finkelstein reaction afforded the 2'-alkylated compound in 32 % isolated yield. Protection of the exocyclic amino group and subsequent succinylation were the next steps before resin loading.

The oligonucleotide was afterwards synthesized on a DNA-synthesizer. Our ongoing investigations are currently focused on orthogonal deprotection of the aminoalkyl arm and sequential on-resin synthesis of the oligopeptide half as final steps.