

## Novel Methods for the Reversible Incorporation of Functional Groups into RNA and DNA: Synthesis and Uses for 2'-O-aminooxymethyl Nucleoside Derivatives

### Technology Summary

The delivery of DNA/RNA therapeutic drugs is still a major hurdle for the clinical application of DNA/RNA-based drugs. Developments in silencing the expression of specific genes, through RNA interference pathways, have led to an increased demand for synthetic RNA sequences and have created a pressing need for rapid and efficient methods for RNA synthesis.

FDA scientists developed a novel phosphoramidite, 2'-O-aminooxymethyl ribonucleoside (2'-O-protected compounds). The 2'-O-aminooxymethyl ribonucleoside can be modified with any type of functional group using an oximation reaction as long as the functional group contains an aldehyde, ketone, or acetal group. Modification of the 2'-O-aminooxymethyl with an aldehyde results in a conjugated 2'-phosphoramidite that can be easily reverted to the native ribonucleoside and its corresponding by-product. On the other hand, the oximation of 2'-O-aminooxymethyl with a ketone results in an irreversible conjugated form of the phosphoramidite.

The 2'-O-protected compounds of the present technology have several advantages that include, the 2'-O-protected compound is stable during the various reaction steps involved in oligonucleotide synthesis; and the protecting group can be easily removed after the synthesis of the oligonucleotide by reaction with tetrabutylammonium fluoride; and the O-protected groups do not generate DNA/RNA alkylating side products, which have been reported during removal of 2'-O-(2-cyanoethyl)oxymethyl or 2'-O-[2-(4-tolylsulfonyl)ethoxymethyl] groups under similar conditions.

### Potential Commercial Applications

- Preparation of DNA and RNA conjugates
- Labeling DNA / RNA with fluorescent markers or affinity ligands for diagnostic applications
- Attachment of DNA/RNA oligonucleotides to glass, metallic or carbon-based surfaces to create nano and microscale assemblies

### Competitive Advantages

- Ribonucleosides (with aminoxy function) anchor a large array of functional groups like aldehyde, ketone group, acetal group
- Examples of functional groups include, inter alia, fluorescent labels, lipophilic and hydrophobic groups, affinity ligands, carbohydrates, amino acids and metal complexes

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### Publications:

Cieślak J., et. al. Convenient and efficient approach to the permanent or reversible conjugation of RNA and DNA sequences with functional groups. *Curr Protoc Nucleic Acid Chem.* 2012; Chapter 4:Unit 4.52. PMID: [22956458](https://pubmed.ncbi.nlm.nih.gov/22956458/)

### Intellectual Property:

United States Patent No. [9,284,343](https://www.uspto.gov/patents/publications/9284343) issued 03.15.2016

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