Thermolytic Hydroxyl-Protecting Groups for Improved Oligonucleotide Synthesis

Technology Summary

Synthetic oligonucleotides have many uses that include gene therapy, diagnostics, and DNA sequencing microarray technology. Conventional hydroxyl-protecting group technology limits the diversity of oligonucleotide manufacturing to those that are stable under acid/or photochemical deprotection conditions. Hydroxyl-protecting groups that can be removed thermally or under mild conditions would provide considerable advantages over conventional hydroxyl-protecting group technology.

FDA researchers have developed hydroxyl-protecting groups that can be thermally removed, along with methods of using such protecting groups. FDA's patented novel class of 2-pyridyl-substituted hydroxyl-protecting groups can be efficiently cleaved under mild thermolytic conditions at 90°C without the use of harsh chemicals such as, strong acids or bases. Thermal cleavage is also more efficient than photochemical methods used for the removal of protecting groups on arrays, and does not risk reactive radical formation that can damage photosensitive oligonucleotides. Thermal cleavage of protecting groups can permit accurate monitoring of coupling efficiency after each chain elongation step by using fluorescent thermolytic groups for hydroxyl protection of nucleoside phosphoramidite monomers. In addition, thermolytic protecting groups can be used to protect/deprotect drug functional groups under conditions that will not affect other protecting groups on the oligonucleotide.

Potential Commercial Applications

- Improved efficiency in manufacturing oligonucleotides on solid supports or solution
- Monitoring of couple efficiency by fluorescent thermolytic groups

Competitive Advantages

- Thermal cleavage: no harsh chemicals to remove protecting groups
- More efficient than photochemical deprotection

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Publications:

"Solid-phase synthesis of thermolytic DNA oligonucleotides functionalized with a single 4-hydroxy-1-butyl or 4-phosphato-/thiophosphato-1-butyl thiophosphate protecting group." J Org Chem. 2007 Feb 2;72(3):805-15. PMID: 17253799

"Thermolytic release of covalently linked DNA oligonucleotides and their conjugates from controlled-pore glass at near neutral pH." Bioconjug Chem. 2008 Aug;19(8):1696-706. doi: 10.1021/bc800189e. Epub 2008 Jul 23. PMID 18646834

Intellectual Property:

United States Patent: US 7,612,197 B2, issued 11.03.2009

Product Area: oligonucleotide synthesis, drugs

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