Synthesis of modified oligodeoxyribonucleotides containing nitrogen or sulfur atom within internucleotide bonds.

The synthesis of backbone-modified oligonucleotide analogs containing nitrogen or sulfur atom within internucleotide bonds was the subject of the presented thesis.

The first part of my studies was focused on the development of the synthesis of stereodefined oligonucleotide-*(N3'→P5')*thiophosphoramidates (NPS-oligos) – a class of compounds which can act as human telomerase inhibitors.

The main approach to attain this goal was based on the *oxathiaphospholane chemistry.* Due to the fact that this method relies on the usage of P-diastereomerically pure monomers it was appropriate to investigate whether the kind of substituent at position 4 of the oxathiaphospholane ring has affected the chromatographic separation of diastereomers. Appropriate 5'-*O*-DMT-3'-amino-2',3'-dideoxynuceloside-3'-*N*-(2-thio-1,3,2-oxathiaphospholanes) were synthesized by phosphitylation reaction followed by addition of elemental sulfur. 2-Chloro-1,3,2-oxathiaphospholane, 2-chloro-4,4-dimethyl-1,3,2-oxathiaphospholane and 2-chloro-4,4-spiro-pentamethylene-1,3,2-oxathiaphospholane were used as phosphitylating agents. The 3'-*N*-(2-thio-1,3,2-oxathiaphospholane) derivatives were then separated into *"fast"* and *"slow"* isomers by silica gel chromatography. The best result was obtained for 4,4-spiro-pentamethylene-oxathiaphospholane derivative of 3'-amino-2',3'-dideoxyguanosine.

A DBU-promoted reaction of corresponding nucleoside 3'-*N*-oxathiaphospholanes was carried out with addition of tertiary amine. Among the tested amines the best result was achieved by using triethylamine, which gave the average yield of coupling step at the level of 88%. In that way a series of *(N3'→P5')*oligodeoxyribonucleotide thiophosphoramidates was synthesized, including a homothymidine tenmer bearing stereodefined internucleotide bonds.

Moreover, it has been demonstrated that the size of substituent at position 4 of the oxathiaphospholane ring has a considerable impact on the yield of condensation reaction performed on solid phase support. The yield decreases in the following order: 3'-*N*-(2-thio-1,3,2-oxathiaphospholane) > 3'-*N*-(2-thio-4,4-dimethyloxathiaphospholane) > 3'-*N*-(2-thio-4,4-spiro-pentamethylene-1,3,2-oxathiaphospholane).

Additionally, an alternative approach to the *oxathiaphospholane method* of synthesis of stereodefined NPS-oligos was studied. This method was based on utilization of the 1-oxido-2-picolyl moiety as an intramolecular nucleophilic catalytic group.

Therefore, the reaction of 5'-picolyl derivatives with support-bounded 3'-amino-nucleoside in the presence of TPSCl as condensing agent lead to the desired dinucleoside-*(N3'→P5')*thiophosphoramidates. Unfortunately attempts to elongate the oligonucleotides chain were not successful.

However, an "in solution" reaction between 5'-picolyl monomer and 5'-*O*-DMT-3'-amino-2',3'-dideoxynucleosides allowed to obtain a corresponding dinucleotide which could easily be separated into individual P-isomers by a single chromatographic process using silica gel column. This kind of compounds, after the necessary selective removal of dimethoxytrityl group in the presence of trityl group, could be used as building blocks for the introduction of chiral internucleotide linkage into the specific site of the oligonucleotide.

In the last part of dissertation the synthesis of chimeric phosphate/phosphorothioate oligodeoxyribonucleotides (PO/PS-oligo) was presented.

It was demonstrated that the application of *t*BuOOSiMe$_3$ in a place of the standard oxidizing agents (e.g. $I_2/H_2O/Py$) allows to obtain phosphate/phosphorothioate chimeric oligonucleotides using mixed oxathiaphospholane and phosphoramidite chemistry. By this methodology a series of chimeric PO/PS-oligo containing terminal PS bonds (1 to 6) was synthesized on solid phase support.