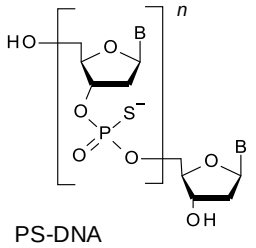
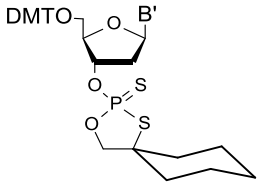
The potential of synthetic oligonucleotides to modulate the biological functions of DNA or RNA has been recognized for more than thirty years. DNA is targeted in an antigene strategy, where inhibition of the transcription should be achieved by the recognition of the double-stranded DNA by an oligonucleotide probe, followed by the triplex formation employing the Hoogsteen interactions. In the antisense strategy, the inhibition of translation is expected by the use of synthetic oligonucleotide, resulting in the formation of an oligonucleotide-mRNA duplex and activation of RNase H to destroy the messenger RNA. New expectations arose from recent developments of oligonucleotides with alternative modes of action, like ribozymes or oligomers obeying the *RNA interference* (RNAi) mechanism. Unfortunately, non-modified oligonucleotides are very quickly degraded by nucleases, thus more stable analogs were tested with phosphorothioate oligonucleotides (PS-DNA), being the most extensively studied. Phosphorus atoms in PS-DNA are stereogenic, so each PS-oligomer, if synthesized by a "stereorandom" method, consists of hundreds of P-diastereomers, while each diastereomer may interact with other biomolecules (usually existing in a single stereochemical form) in a different manner. The first method for stereocontrolled synthesis of PS-DNA was an oxathiaphospholane approach (developed in our laboratory) employing the OTP monomers. Another important factor is thermal stability of the complexes to be formed by the probes. Unfortunately, usually the complexes of PS-DNA with DNA or RNA are much less stable. However, several years ago we discovered an exception to that rule, as we documented high thermodynamic stability of parallel triplexes RNA/[All-R_P-PS]-DNA/RNA (**I**) containing a homopurine phosphorothioate central DNA strand with all phosphorus atoms of R_P configuration ([All-R_P-PS]-DNA).



PS-DNA

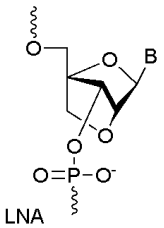


Monomer OTP

RNA (H)	5'-r(CUCCUUUUUCUC)-3'	*so called Hoogsteen strand*
[All-R_p-PS]	5'-d(GAGGAAAAAGAG)-3'	*central PS-DNA strand*
RNA (WC)	3'-r(CUCCUUUUUCUC)-5'	*Watson-Crick strand*

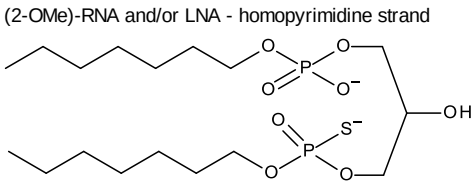
I

We have also found that the complexes **I** are much more stable when RNA(H) possesses (2'-OMe)-RNA or LNA units.



LNA

We tried to use the RNA(H)/[All-R_P-PS]-(DNA) system to "arrest" mRNA, but the inhibition of reverse transcription slightly exceeded 90%. In this project we want to challenge this weakness using a few additional structural factors. First, we will link the strands interacting according to the Hoogsteen scheme (with a glycerol molecule) to form a **double stranded probe** (DSP), as there will be a significant favorable gain in the entropy factor. Secondly, we assume that, similarly to the above described stabilizing effect of the LNA units in the Hoogsteen strand, PS-LNA units or PS-(2'-OMe)-RNA units (the latter to be developed) present in the [All-R_P-PS]-DNA strand should push the overall conformation of that strand towards the A conformation. If so, the energetic toll of the B→A conformational transition during hybridization of the "parallel" part should be smaller and the thermodynamic stability of complexes consisted of the conformationally better matched strands should increase.



Double stranded probe - **DSP**

Both structural factors, when combined in DSP, are expected to provide a very potent tool able to "arrest" Watson-Crick paired RNA molecules quantitatively. But we also seek for another tempting opportunity, as it seems plausible that a parallel duplex with the overall A conformation such intensely imposed**/**fixed will be able to "catch" and "arrest" a Watson-Crick paired **DNA** oligomer. If so, the list of tools available for molecular biologists will be extended with a new useful and precise item.