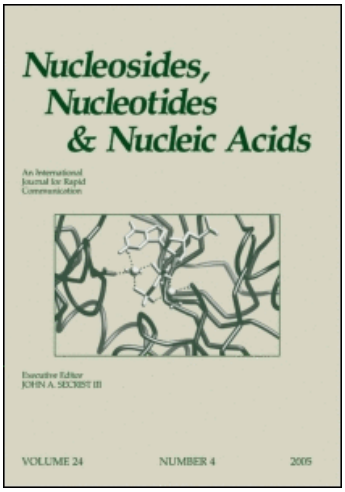

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Design of Functional Diversity in Oligonucleotides via Zwitter-Ionic Derivatives of Deprotected Oligonucleotides

V. Zarytova[a]; E. Ivanova[a]; A. Venyaminova[a]
[a] Novosibirsk Institute of Bioorganic Chemistry, Siberian Division of RAS, Novosibirsk, Russia

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REVIEW

DESIGN OF FUNCTIONAL DIVERSITY IN OLIGONUCLEOTIDES *via* ZWITTER-IONIC DERIVATIVES OF DEPROTECTED OLIGONUCLEOTIDES

V.Zarytova*, E.Ivanova, A.Venyaminova

Novosibirsk Institute of Bioorganic Chemistry, Siberian Division of RAS,
Novosibirsk 630090, Russia

ABSTRACT: In this work a number of new designed mono- and bifunctional derivatives of oligonucleotides (deoxyribo-, ribo-series, and their 2'-O-methyl-, P-ethyl, methylphosphonate, and thiophosphate analogs) is described including those bearing reactive, stabilizing, and hydrophobic groups. New approach based on the use of cooperative tandems of short oligonucleotide derivatives is suggested to enhance the selective recognition of nucleic acids.

The synthetic oligonucleotides and their chemically reactive derivatives are widely used for the artificial regulation of gene expression. The directed site-specific influence of oligonucleotides on functions of nucleic acids is based on the principle of complementarity and underlies the design of antivirus and antitumor therapeutic drugs of a new generation.

The most common approaches used for the preparation of oligonucleotide derivatives are based on the introduction of modifying groups during oligonucleotide synthesis [1-3]. We have developed the convenient approach for attachment of various functional groups to the terminal phosphates of deprotected oligonucleotides [4]. Their conjugates with reactive, stabilizing, and hydrophobic groups were prepared by the approach. Alky-

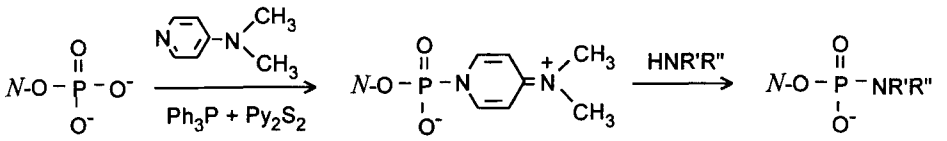
*FAX: 007 3832 35 16 65; e-mail: zarytova@niboch.nsc.ru

Dedicated to the memory of Prof. Tsujiki Hata, the world famous scientist in the field of nucleic acid chemistry

lating, photoreactive groups, or groups capable to cleave nucleic acids were used as the reactive groups.

The review of our previous works dealt with design and synthesis of a number of new mono- and bifunctional derivatives of oligonucleotides (deoxyribo-, ribo- series, and their 2'-O-methyl-, P- ethyl,methylphosphonate, and thiophosphate analogs) is presented below.

General method of design of oligonucleotide derivatives. The method is based on the use of deprotected oligonucleotides containing the terminal phosphate and the couple of the reagents Ph_3P and Py_2S_2 which was proposed and used in the works of Mukaiyama [5] and Hata [6] as condensing reagent. In our approach the activation of the terminal phosphate of oligonucleotide by these reagents was carried out in the presence of nucleophilic catalyst such as DMAP, MeIm or DMAP→O. Using physico-chemical methods the intermediates of this process were identified. The final product was shown to be an oligonucleotide bearing the terminal zwitter-ionic phosphate group, which reacts fast with various molecules containing nucleophilic groups without any by-products.



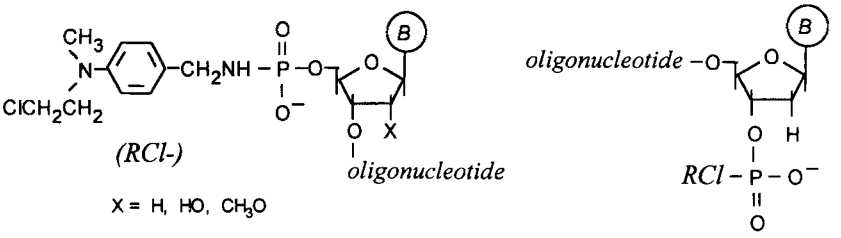
N – oligonucleotide or its derivatives

The internucleotide bonds and deblocked heterocyclic bases were intact during the process that makes this method very useful and important for the practical purposes. It can be used for both oligoribo- and oligodeoxyribonucleotides and their analogs containing native or modified internucleotide bonds. Using this approach, many oligonucleotide derivatives were synthesized in preparative scale that was enough for the structural physico-chemical investigations as well as for the biological trials with the cells and animals.

The oligonucleotide derivatives containing modified groups at the terminal phosphate. A range of various groups (alkylating, photoactive, cleaving of DNA and RNA chains, stabilizing complementary complexes, facilitating the penetration through the cell membranes and others) were incorporated into oligonucleotides by the proposed method.

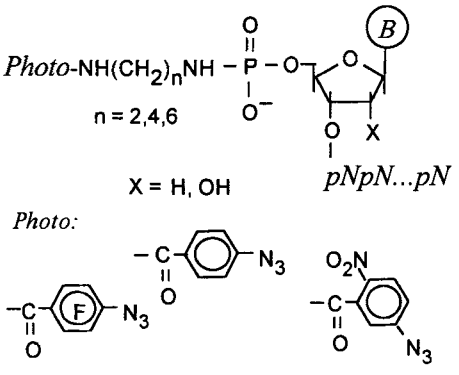
Alkylating derivatives of oligonucleotides and their analogs. The synthesis of alkylating derivatives of oligodeoxyribonucleotides [4] and their individual methylphos-

phonate diastereomers [7], phosphorothioate [8], and phosphoethyl [9] analogs of oligodeoxyribonucleotides as well as ribo- and (2'-O-methylribo)oligonucleotides [10] was carried out.

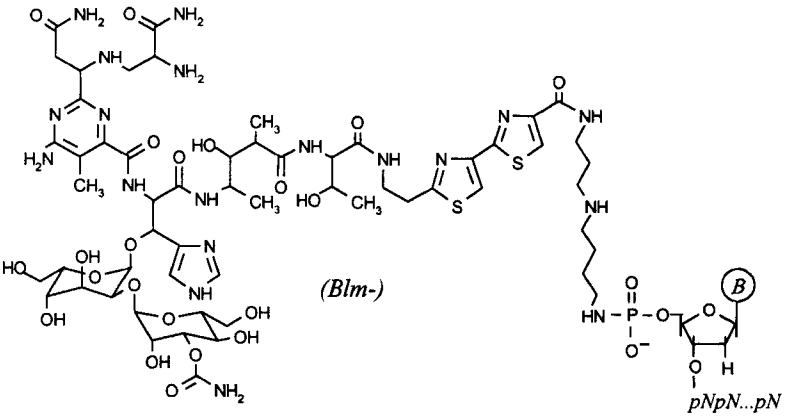


The properties of oligonucleotide derivatives containing the residue of 4(N-2-chloroethyl,N-methylamino)benzylamine (*RCl*) were studied [11]. It is important to mention, that the general features of complementary addressed modification of DNA ("antisense" strategy) were obtained using the alkylating derivatives of oligonucleotides [11].

Photoreactive derivatives of oligonucleotides. Oligonucleotides conjugated with photoactive groups are known to be promising reagents for the site-specific modification of nucleic acids and for the affinity labeling of biopolymers. The photoreagents based on aromatic azides are of interest because they have a high quantum yield of photomodification (φ=0.3-0.5). They are highly reactive and the rate of biopolymer modification by arylazides is more than 10 times greater then comparable reactions using other photoreagents. The presence of fluorine atoms at the aromatic ring appeared to stabilize intermediate singlet nitrene which is much more reactive than the species obtained under irradiation of other arylazide derivatives. Such oligonucleotides modify single-stranded or double-stranded DNA fragments as well as RNA fragments with a high yield [12-17]. They can be used for the affinity modification of different biopolymers.

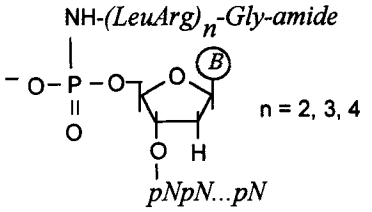


The reagents generating the active oxygen species. Among the reactive compounds the special attention should be paid on the structures helating the transition metals that generate an active form of oxygen and catalytically damage a NA target. For this purpose using our approach we incorporated into oligonucleotides antitumor antibiotic bleomycin A5 (*Blm*), which was covalently attached to the terminal phosphate of oligonucleotide *via* the terminal amino group of the spermidine residue of bleomycin A5 [18-21].



It was shown that bleomycin-oligonucleotide conjugates form duplexes and ternary complexes and site-specifically cleave single-stranded and double-stranded DNA targets [18-20, 22]. The bleomycin covalently bound to the oligonucleotide preserves its ability to catalyze the damage of DNA target [23]. Catalytic activity of oligonucleotide-bleomycin conjugates is realized both by repeated cleavage of one molecule of DNA target and several DNA target molecules by one molecule of the reagent from duplexes. Moreover the highest activity of bleomycin-oligonucleotide conjugates is observed at the temperature close to the melting temperature of the *reagent·target* complex [23].

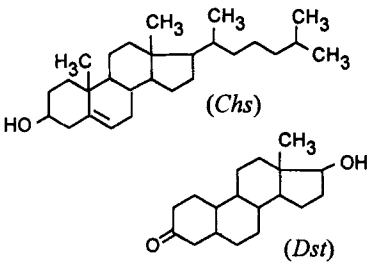
Peptidyl oligonucleotides. Our approach for functionalization of the terminal phosphate gave the opportunity for the simple preparation of peptidyl oligodeoxyribonucleotides. The peptide residues can be easily attached to the terminal phosphate of a deblocked oligonucleotide either *via* own terminal amino group of a peptide or through amino spacer introduced into peptides [24]. The new peptidyl oligonucleotides containing alternated hydrophobic and basic amino acids were synthesized with the high yields [25].

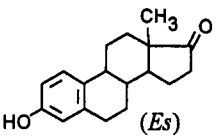


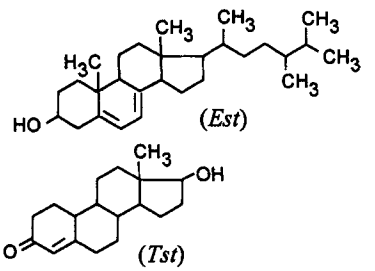
The hybridization properties of the peptidyl oligonucleotides were investigated on estimation of the melting points of their duplexes with complementary oligodeoxyribonucleotide. The slight increase of T_m values of the complementary complexes was found to depend on the length of the peptide residues. These peptidyl oligodeoxyribonucleotides were found to hydrolyze site-specifically the phosphodiester bonds of RNA target. The level of cleavage of the model oligoribonucleotide target amounted to 80% for n=4 (48 h, 20°C, pH 7.5) [25].

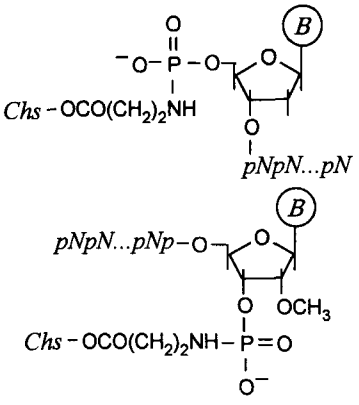
Oligonucleotide derivatives linked to the steroid residues. As far as interaction of oligonucleotides and their derivatives with intracellular nucleic acids is concerned, the key problem is their ability to penetrate through the cell membranes. The native oligonucleotides and their reactive derivatives permeate insufficiently into the cells because of the immanent negative charges of the phosphate groups. The blocking of the internucleotide phosphates of oligonucleotides is the widely used approach to enhance the permeability of oligonucleotides through the cell membranes.

We have proposed and worked out another method to intensify such ability of oligonucleotides by the introduction of the steroid residues in their structure [26, 27]. The same approach was simultaneously suggested by Letsinger [28]. Cholesterol (*Chs*), estrone (*Es*), ergosterine (*Est*), deuterotestosterone (*Dst*), and testosterone (*Tst*) were used as steroids [27, 29-32]. Several methods were developed to attach the steroid residue to an oligonucleotide.



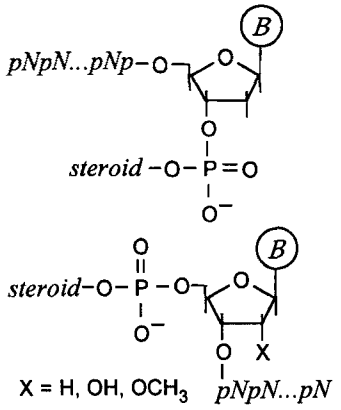






β-Alanine ester of cholesterol was attached to the 5'- or 3'- terminal phosphate of oligodeoxyribo- or oligo(2'-O-methylribo)- nucleotides by the general method *via* the active zwitter-ionic intermediates. In this case the phosphoroamide bond is formed [30].

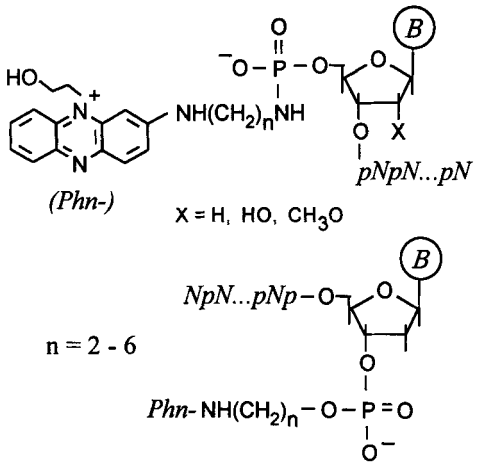
Furthermore steroids containing hydroxyl group can be linked to the 5'- or 3'-terminal phosphate during the oligonucleotide synthesis by the triester method in solution forming the phosphoester bond [27, 29]. This approach allows the preparative amounts of steroid-oligodeoxyribonucleotide conjugates to be obtained (up to 1000 OU).



Another approach was the use of steroid-H-phosphonates which were linked at the 5'-end of oligonucleotide on the last stage of the solid phase synthesis by the H-phosphonate method. This technique was used for the preparation of the 5'-steroid derivatives of ribo-, 2'-O-methylribo-, and deoxyribo- oligonucleotides [31, 32].

It was shown that the attachment of the bulky hydrophobic residues (cholesterol, estrone, etc.) to the terminal phosphate of oligonucleotides did not prevent their ability to form complementary complexes [27, 29, 32] and significantly increased the permeability of such conjugates into the cells [33].

Oligonucleotide derivatives containing the polycyclic dye residues. The attachment of aromatic dyes to oligonucleotides enhances the efficiency of their binding with nucleic acids. For this purpose we propose to use the N-(2-hydroxyethyl)phenazinium (*Phn*) which can be easily attached to the amino spacer at the terminal phosphate. A number of the derivatives of deoxyribo-, ribo- oligonucleotides and their analogs (methylphosphonate, phosphorothioate, 2'-O-methylribo) containing the phenazinium residue at the 3'-or 5'-ends of an oligonucleotide chain was synthesized [8, 32, 34]. The phenazinium residue was



shown to increase significantly the stability of the corresponding complementary duplexes. The structure of the duplexes formed by 5'-phenazinium derivatives of oligodeoxyribonucleotides with DNA or RNA targets was studied using NMR spectroscopy of high resolution [35, 36].

Furthermore benzocoumarine [37], ethidium [38-39], azidoethidium [39], and daunomycin [40] were attached to oligonucleotides using 2,2'-dipyridyl disulfide and triphenylphosphine procedure.

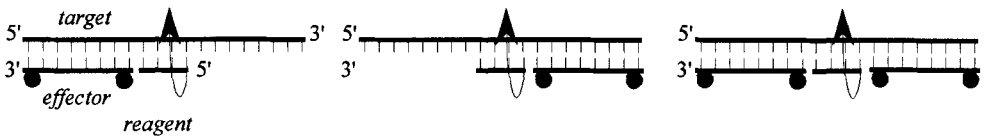
3',5'-Disubstituted derivatives of oligonucleotides. The methods described above allow the mono- as well as disubstituted derivatives of oligonucleotides or their analogs to be synthesized. We have synthesized a number of such derivatives containing simultaneously reactive (alkylating, cleaving (bleomycin A5, peptides), or photoactive) and stabilizing (phenazinium) groups [25, 33, 41-43]; reactive and steroid groups [27, 33, 42-45]; stabilizing and steroid groups [30]; two stabilizing groups [34].

Disubstituted derivatives of oligonucleotides acquire the package of the new properties. It was shown that the efficiency of nucleic acid modification by the oligonucleotide derivatives bearing the alkylating group at one end and the phenazinium residue on the other end increased significantly due to the stabilizing effect of the latter [41, 42]. The introduction of the steroid group into the reactive oligonucleotide derivatives results in the enhancement of their ability to penetrate into the cells that increases the extent of modification of the intracellular biopolymers as compared with the initial reagent [33, 43-45]. The study of the properties of diphenazinium oligonucleotides showed the additive influence of both residues on the stability of the corresponding complementary complexes [34]. This fact is the distinguish feature of the phenazinium residue. The attachment of the phenazinium residue to the oligonucleotides containing steroid leads to the same positive effect on their ability to form duplexes [30]. It is important to note that oli-

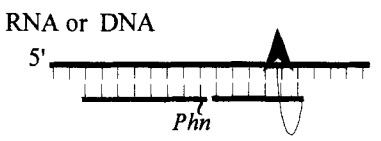
gonucleotides bearing any groups at the 3'- and 5'-ends are much more stable in cell systems than nonmodified analogs [44, 45].

The unique properties of new mono- and disubstituted derivatives of oligonucleotides give opportunities of their particular application. Thus, the ability of the phenazinium derivatives of short oligonucleotides to form stable complementary complexes with nucleic acids and to stabilize the complexes of adjacent short oligonucleotides allow us to develop the new approach for DNA recognition by short oligonucleotides.

The new approach to enhance the selectivity of DNA recognition by oligonucleotides. For the enhancement of the site-specificity of DNA recognition long oligonucleotides (more than 20-mer) are commonly used. However, such oligomers are able to form not only perfect but also imperfect (with a mismatched base pair or with a bulge) complexes which are sufficiently stable at the physiological conditions. We propose the special method to increase the selectivity of complementary interaction of oligonucleotides which is based on the usage of a reactive derivative of short oligonucleotide in the presence of effector(s) [46-56]. The effectors were auxiliary oligonucleotides or their derivatives containing phenazinium or steroid groups.



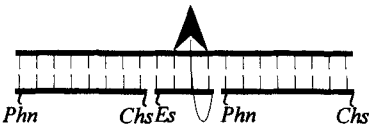
The main function of the effector(s) which flank the reactive derivative of short oligonucleotide (tetra-, hexamer) is stabilization of the complex formed by target and reagent. The diphenazinium effectors stabilize the binding of a short oligonucleotide with the DNA target stronger than the native oligonucleotides [53]. This difference is due to the higher hybridization properties of the diphenazinium derivatives of oligonucleotides [34] and to the higher cooperative interaction between tandem components if one of them contains phenazinium residue at the junction site [57]. The effector pair flanking the reagent and fixing it on the target results in the maximum effect on the interaction of the short oligonucleotide reagent with nucleic acid [48, 53]. It is registered that the effective and site-specific modification of target DNA may be carried out by tetranucleotide conjugated with alkylating [46-48], photoreactive [56] groups or bleomycin residue [51, 52] when the diphenazinium derivatives of oligonucleotides are used as effectors.



d-, r-, m - oligonucleotides

The modification of deoxyribo- and ribo- eicosanucleotides by alkylating derivatives of 2'-O-methylribo- (m), ribo-, and deoxyhexanucleotides in the presence of the monophenazinium effectors of the same oligonucleotide series was comparatively studied. The maximum extent of the modification of DNA target by all three types of the reagents in the absence of the effectors was very small and did not exceed 20% at 20°C. According to efficacy of modification the reagents can be arrange in the order d > r > m. In the presence of the effectors the order remains the same however in this case the substantial increase of the extent of modification for all three types of reagents was observed (80-85% at 20°C). According to efficacy of RNA modification the reagents can be arranged in the order m > r > d. The increase of the extent of RNA modification occurs in the presence of effectors. The maximum extent of modification is achieved using the derivatives of oligo(2'-O-methylribonucleotides) as reagent and effector (95% at 40°C).

The new type of effectors was designed for the 5'- alkylating, photoactive and cleaving (bleomycin) oligonucleotide reagents bearing a steroid residue at the 3'-end. They were oligonucleotides containing

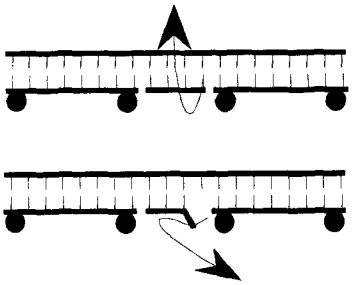


Es - estrone

phenazinium at the 3'-end and a steroid residue at the 5'-end of the chain, which intensified the effect of the reagent due to hydrophobic interactions [49-51, 56]. Some quantitative characteristics were obtained for the modification of nucleic acids by the alkylating oligonucleotide derivatives in the presence of oligonucleotide effectors [58].

Unlike extended oligonucleotide, tandem of short oligonucleotides can provide the more accurate recognition of DNA due to the higher selectivity of the interaction. The ability of the tandem of short oligonucleotide derivatives to discriminate the «right» DNA target from the target containing a single nucleotide discrepancy has been demonstrated by the alkylation of DNA target with oligodeoxyribonucleotide reagents in the perfect and mismatched complexes.

The proposed approach was shown to allow the modification of the DNA target to be occurred exclusively from the perfect complex [54, 55]. It is possible to detect any nucleotide changes in the sites of the target binding with the short oligonucleotide reagent. In the presence of flanking diphenazinium effectors the tetranucleotide alkylating reagent



modifies DNA target efficiently and site-specifically only from the perfect complex and does not modify it from the mismatched complex. On the contrary the level of modification of DNA target by dodecanucleotide reagent is equal for both incorrect and mismatched duplexes [54]. These data testify that extended oligonucleotide reagents can modify DNA site-specifically but not selectively, shorter octanucleotide reagents show a high selectivity without site-specificity, and only very small tetranucleotide reagent in the presence of effectors can modify ssDNA selectively and site-specifically.

The site-specificity of recognition of DNA by the tetramer is provided by flanking effectors because tetranucleotide can bind with DNA only when the complete complex *effector-tetramer-effector* with DNA is formed, so that the binding site of this tandem is equal to the binding site of extended oligonucleotide of the sum total length [48]. The suggested approach may be used for enhancement of selective recognition of the definite sequence of DNA, for detection of point mutation in DNA, for design of gene-directed therapeutic drugs, ets.

Therefore the functional diversity of designed oligonucleotide derivatives and their unique properties offer great promise for using them as the precise research tools for investigation of complex biochemical pathways and as the magic arrows against genetic, cancerous, and infectious diseases.

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