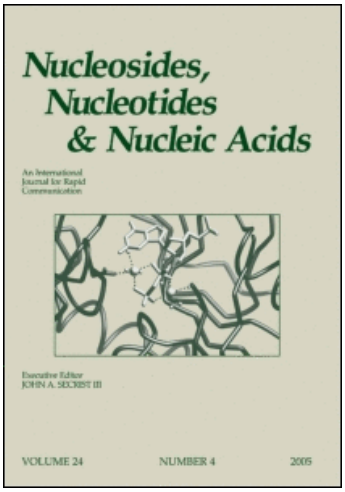

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Synthesis and Properties of Daunomycin Mono- and Oligonucleotide Derivatives

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SYNTHESIS AND PROPERTIES OF DAUNOMYCIN MONO- AND OLIGONUCLEOTIDE DERIVATIVES

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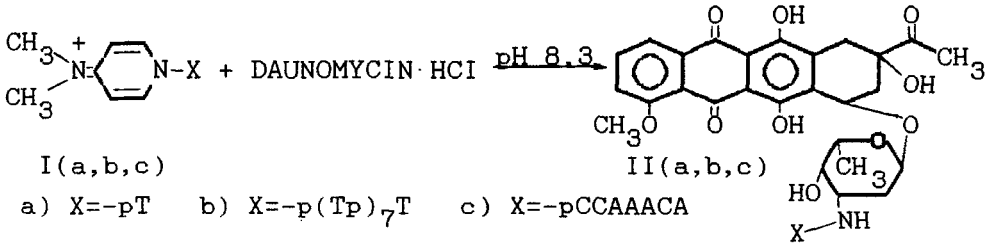
Abstract. Daunomycin mono- and oligonucleotide derivatives were synthesized and their structure and some properties were investigated.

Searching for antisense agents efficiently affecting multiplication of cell genetic material, we have synthesized oligonucleotide derivatives bearing antitumor antibiotic residues. To preserve the ability of oligonucleotides to form complementary complexes and to save biological activity of daunomycin[1], NH_2-group of daunomycin sugar was coupled with a terminal phosphate group of oligonucleotide. This was done after the terminal phosphate (^{31}P-NMR δ=+3.6ppm for pT) had been converted into a reactive zwitterionic group (^{31}P-NMR δ=-5.9 ppm for Ia) by treating mono- and oligonucleotides with a mixture of triphenylphosphine and 2,2′-dipyridyldisulfide in the presence of 4-dimethylaminopyridine[2].



I(a,b,c) II(a,b,c)

a) X=-pT b) X=-p$(Tp)_7$T c) X=-pCCAAACA

The obtained derivatives I(a,b,c) reacted with daunomycin (6 h, 0.2 M $NaHCO_3$,pH 8.3) to form the corresponding phosphoroamidates II(a,b,c) (^{31}P-NMR δ=+6.4 ppm for IIa) with the yield of 70-80%. Electron spectra of II(a,b,c) are

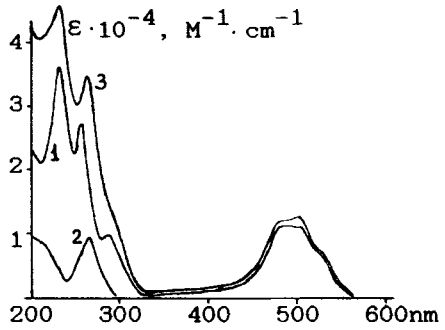


Fig.1. The electronic absorption spectra of daunomycin (1), thymidine-5′-phosphate (2) and its daunomycin derivative IIa (3).

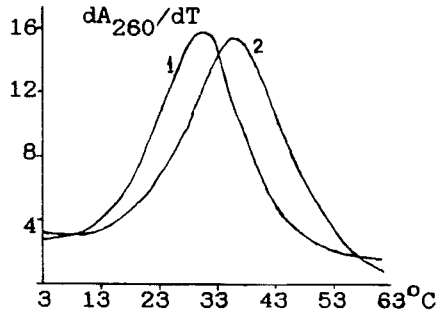


Fig.2. The differential curves of thermal denaturation of complementary complexes of pTGTTTGGC with pCCAAACA (1) and with IIc (2).

actually a sum of the spectra of daunomycin and respective mono- or oligonucleotide (FIG.1).According to anion-exchange chromatography data the daunomycin oligonucleotide derivatives IIb are converted back to the initial oligonucleotides under conditions of hydrolysis of the phosphoroamidate bond (0.1 HCl, 37°C, 2.5 h).

Daunomycin oligonucleotide derivatives formed more stable complexes than the corresponding unmodified oligonucleotides (FIG.2). Both one- and two-dimensional (2D NOESY

and 2D COSY) NMR spectra of IIa were recorded and proton signals assigned. The detected cross-relaxation between H-6 of thymidine and H1, H2 of the carbohydrate residue of daunomycin favoured stable conformation of the Ia molecule in DMSO which is most likely to be due to the stacking interaction between the mononucleotide and daunomycin residue.

REFERENCES

1. E.M.Acton, G.L.Tong, C.W.Mosher (1984) J.Med.Chem.,27,638.
2. V.F.Zarytova, T.S.Godovikova, I.V.Kutyavin and L.M.Khalimskaya (1987) Biophosphates and Their Analogues, Synthesis, Structure, Metabolism and Activity, (Eds. Bruzik and Stec W.J. Elsevier) Amsterdam.