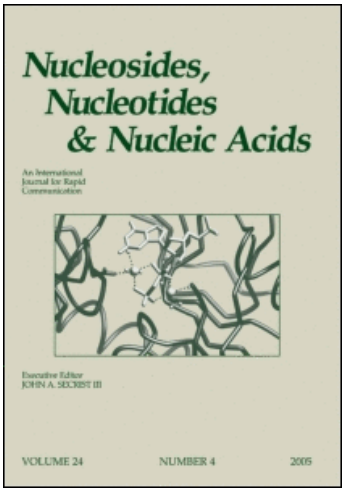

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Synthesis of Sugar Modified Nucleosides Containing Nicotinic, Quinaldic, Indol-3-ylpropionic or 1-Nitroanthraquinone-2-carboxylic Acid Residue

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SYNTHESIS OF SUGAR MODIFIED NUCLEOSIDES CONTAINING NICOTINIC, QUINALDIC, INDOL-3-YLPROPIONIC OR 1-NITROANTHRAQUINONE-2-CARBOXYLIC ACID RESIDUE

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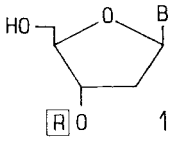
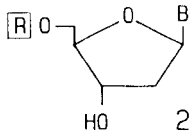
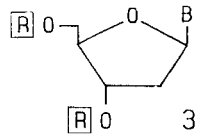
Abstract. The nucleoside derivatives were synthesized with arylcarbonic acid residue as an anchor group at the sugar moiety coupled by an ester or an amide bond. Their cytotoxic properties and effects on DNA structure were studied.

Approaches to the synthesis of nucleoside derivatives with anchor group in the sugar residue which may provide a non-covalent interaction with nucleic acids (by intercalation, ion-binding, etc.) have been studied. Nicotinic, quinaldic indol-3-ylpropionic or 1-nitroanthraquinone-2-carboxylic acid residue served as an anchor coupled to the nucleoside moiety through an ester or an amide bond. Nucleosides interacted with nicotinic acid chloride *in situ* (nicotinic acid-$POCl_3$-pyridine) or with quinaldic acid chloride in CH_2Cl_2 in the presence of 4-dimethylaminopyridine to give di-O-acylated analogs. Under similar conditions the suitably protected nucleosides (3'-O-acetyl, 5'-O-trityl, 2',3'-O-ethoxymethylidene) were used for the preparation of 3'- or 5'-mono-O-acyl derivatives. Nucleoside **2c** was synthesized also from thymidine and quinaldic acid by the Mitsunobu reaction (Ph_3P-diethylazodicarboxylate). 5'-Amino-5'-deoxynucleosides, as well as 3'-amino-3'-deoxy-2',3'-secoadenosine synthesized by standard procedures, reacted with nicotinic, indol-3-ylpropionic and 1-nitroanthraquinone-2-carboxylic acid in the presence of 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline or with the active ester (N-hydroxysuccinimide, pentafluorophenyl) of quinaldic, nicotinic and indol-3-ylpropionic acid. As a result, the corresponding amide derivative was formed. For the preparation of the 5'-modified 2',3'-secoadenosine analogs 5'-deoxy-5'-nicotinamido-, 5'-deoxy-5'-(quinoline-2-carboxamido)- and 5'-deoxy-5'-(indol-3-ylpropionylamido)adenosine were subjected to H_5IO_6 oxidation - $NaBH_4$ reduction procedure.

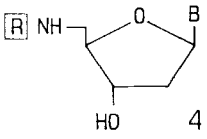
The structure of synthesized compounds was confirmed by UV, IR and ^{1}H-NMR data.

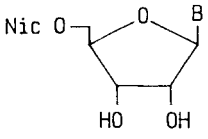


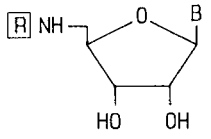




B=Ura, R=Nic (a), Qn (b), B=Thy, R=Qn (c); B=$SiMe_3$Ura, R=Qn (d)

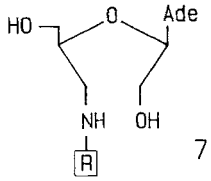


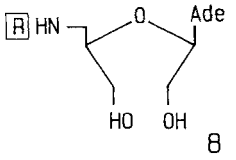


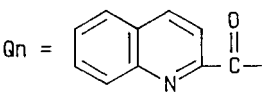


B=Ura: R=Ind (a), Ant (b);
B=Thy: R=Qn (c),
QnNH$(CH_2)_3CO$ (d)

B=6-azaUra: R=Nic (a), Qn (b),
QnNH$(CH_2)_3CO$ (c), Ind (d);
B=Ade: R=Nic (e), Qn (f),
Ind (g)

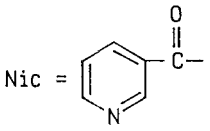


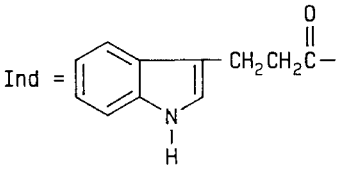


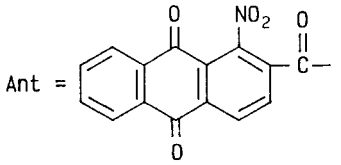


R=Nic (a), Qn (b),
Ant (c)

R=Nic (a), Qn (b),
Ind (c)







Compounds **1b,c**, **2c**, **3a-d**, **4b,c**, **6a**, **7b**, **8c** showed cytotoxic properties for CaOv cells *in vitro* (50% inhibitory concentration : ~ 10^{-5} M). Antitumor activity *in vivo* was found for **1b**: at a dose of 100-150 mg/kg it inhibited Lewis lung carcinoma (LLC) growth by 70-87% and adenocarcinoma 755 (Ca755) by 50-68%. Binding of **1c**, **2c** and **3c** with DNA from chicken red cells was studied by fluorescent probes method. Hst and EtdBr were used as fluorophores which distinguish one from the other by the type of DNA binding. It was shown that **1c** and **2c** prevented Hst fluorescence quenching when EtdBr was added at the concentration of 2-20 mcg/ml: relative intensity of fluorescence decreased by 10-12%, as compared to 40% for **3c** and 80-90% for the control. The bathochromic shift of fluorescence maximum and the change of half-width of fluorescence peak (data not given) showed that a mobility of Hst in the presence of nucleosides was increased. The measurements of fluorescence polarization in the titration of DNA-nucleoside-Hst complex with EtdBr revealed that **1c** and **2c** decreased Hst polarization coefficient but did not affect EtdBr polarization (Fig. 1A and B). These data indicated that **1c**

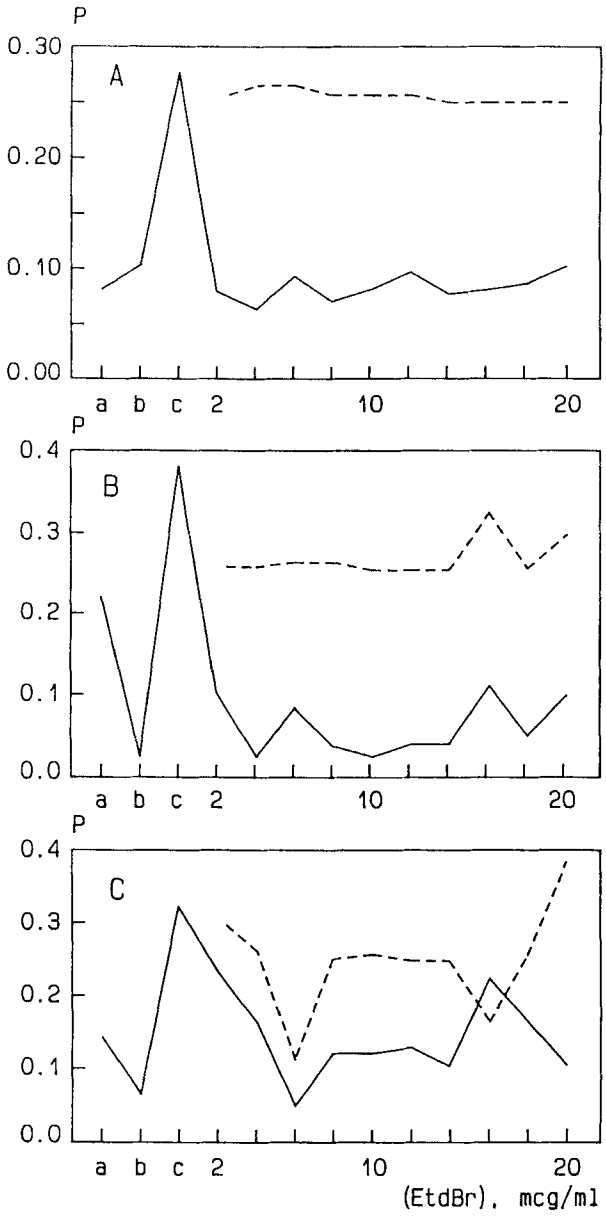


FIG. 1. Effects of nucleosides on fluorescence polarization of Hoechst 33258 (Hst) (——) and ethidium bromide (EtdBr) (---) in the titration of DNA-nucleoside-Hst complex with EtdBr: a - DNA; b - DNA + 5'-O-quinaldinoylthymidine (A), DNA + 3'-O-quinaldinoylthymidine (B), DNA + 3',5'-di-O-quinaldinoylthymidine (C); c - DNA + nucleoside + Hst; concentrations: DNA - 1 mcg/ml, nucleoside - 10^{-5} M, Hst - 10^{-6} M, EtdBr - 2-20 mcg/ml.

and **2c** varied Hst mobility, while they did not compete for binding sites with EtdBr. Thus it can be concluded that **1c** and **2c** are not intercalators and that observed increased of Hst mobility was a result of a competition of the nucleoside with Hst for binding sites in the region of DNA minor groove. Contrary to mono-derivatives, the interaction of **3c** with DNA caused synchronous polarization changes of both Hst and EtdBr. This indicates that synchronous changes of space characteristics of binding sites took place for the external fluorophore - Hst and for the intercalator - EtdBr. It seems likely that **3c** binds both externally and internally to DNA.