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Doctoral dissertation abstract:

„New nucleosides and cholesterol derivatives modified with boron clusters – synthesis methods elaboration and physicochemical and biological research"

Carboranes ($C_2B_{10}H_{12}$) provide a wide family of boron clusters characterized by a spherical shape and high lipophilicity. Metallocarboranes $[M(C_2B_9H_{11})_2]^{-1}$, complexes of metals and carboranes in ionic form, represent in turn a vast class of a sandwich-type coordination compounds which can consist ions of different metals. Generally, metallocarboranes are characterized by amphiphilic properties and varied electrochemical features. Due to low cytotoxicity, carboranes and often metallocarboranes are frequently used as components of biologically active compounds. Conjugates of nucleosides and carboranes are tested among others as boron carriers in the Boron Neutron Capture Therapy (BNCT), modified monomers in the synthesis of therapeutic nucleic acids and potential antivirus or anticancer compounds.

The main purpose of my dissertation entitled „New nucleosides and cholesterol derivatives modified with boron clusters – synthesis methods elaboration and physicochemical and biological research" was to elaborate methods of synthesis and to obtain new nucleosides and cholesterol derivatives modified with boron clusters as well as to examine certain properties of the newly obtained chemical entities.

As a result of these works I obtained uridine and 2'-deoxyuridine derivatives containing a carboranyl constituent in a pyrimidine part of the nucleoside with different kinds of linkers using the Sonogashira reaction or the Huisgen-Meldal-Sharpless 1,3- dipolar cycloaddition ("click reaction"). The structures of the obtained products was -confirmed using the following methods: ^{1}H NMR, ^{13}C NMR, ^{11}B NMR, FT-IR, UV spectroscopy and mass spectrometry.

In the second part of the studies described in the PhD thesis the obtained nucleosides derivatives were tested in the presence of thymidyl kinases TK1 and TK2 and deoxycytidine kinase dCK to determine the susceptibility to enzymatic phosphorylation. Subsequently, the influence of boron cluster modification of the nucleosides on cytotoxic and antivirus activity

was studied. In order to determine cytotoxicity of the obtained compounds MTT colorimetric method was applied on A549, Vero, L929, MRC-5 and LLC-MK2 cell lines. The antivirus activity of tested compounds was determined using HSV-1, HCMV and EMCV as examples of DNA containing virus strains and HPIV-3, VSV as RNA viruses.

In the next part of PhD thesis relying on a dioxane ring opening reaction I obtained cholesterol derivatives modified with metallocarboranes containing cobalt, iron or chromium ion or with carborane cluster only in open cage form: 7,8-dicarba-*nido*-undecaborate ion. The structure of the obtained compounds was confirmed by ^{1}H NMR, ^{13}C NMR, ^{11}B NMR, FT-IR spectroscopy and mass spectrometry. The selected cholesterol/metallacarborane conjugate containing cobalt ion was used to prepare liposome series with various final boron concentration in the liposomal membrane. Boronated liposomes were obtained by the reverse-phase evaporation (REV) method and afterwards they were subject to extrusion. The final boron concentration, boron to phosphorus ratios, diameters and zeta potentials of boronated liposomes were measured. The boron and phosphorus concentrations were measured by applying inductively coupled plasma atomic emission spectroscopy (ICP-AES). The particle size distribution of the boronated liposomes was measured by electrophoretic light scattering spectroscopy.

The boron accumulation studies were conducted in Colon 26 cells after incubation with boronated liposomes. The final boron concentration was measured by ICP-AES. Next *in vivo* study on liposomes incrusted with metallocarborane cholesterol biodistribution in tumor-bearing mice were performed. The final boron concentrations were measured after 24 and 36 hours following the injection.

In summary, as ~~a~~ results of the presented works~~,~~ methods for the synthesis of novel nucleoside or cholesterol boron cluster conjugates were developed or optimized, 19 new nucleosides derivatives and 4 novel cholesterol derivatives were synthesized and fully characterized. The influence of boron cluster modification on susceptibility to enzymatic phosphorylation, cytotoxic and antivirus activity was studied. In the case of cholesterol derivatives, an effect on cellular uptake in Colon 26 cells and in tumor-bearing mice was examined in the light of their potential applications as boron carries for BNCT.

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