SYNTHESIS OF NOVEL CONJUGATES OF *CLOSO*-DODECABORATE DERIVATIVES WITH CHOLESTEROL

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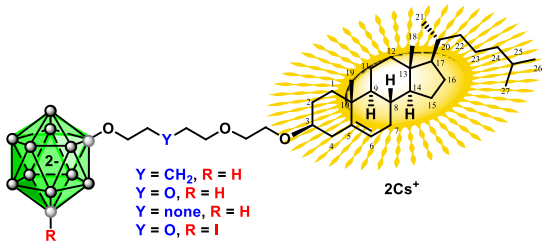
Abstract

New *closo*-dodecaborate-containing cholesterols are synthesized by the ring-opening reactions of the cyclic oxonium derivatives of $[B_{12}H_{12}]^{2-}$ with modified cholesterol. The compounds obtained are of potential interest for the delivery of liposomal drugs in boron neutron capture therapy of cancer.



Key words: polyhedral boron hydrides, *closo*-dodecaborate, cholesterol, liposomes, boron neutron capture therapy (BNCT).

Introduction

Boron neutron capture therapy (BNCT) is a promising binary method for the treatment of cancer, which is based on the selective accumulation of the non-radioactive isotope ^{10}B in tumor cells and their subsequent treatment with low-energy thermal neutrons [1–4]. The most important requirements to novel boron compounds for BNCT are the minimum tumor concentrations in the range of 20–35 μg ^{10}B per gram of tumor tissue and the selective delivery to tumor cells [5]. At present, there are two boron compounds that have been extensively studied in clinical BNCT trials: L-*p*-dihydroxy-borylphenylalanine (BPA) [6] and disodium mercaptoundecahydro-*closo*-dodecaborate (BSH) (Fig. 1) [7–11]. In some cases, the treatment efficiency can be improved by a combination of BPA and BSH. However, both of the boron carriers are not ideal for the targeted delivery of the therapeutic amount of ^{10}B toward the tumor. The results of clinical studies with these compounds are not very attractive because of their low selectivities and long retention times in tumors [12, 13].

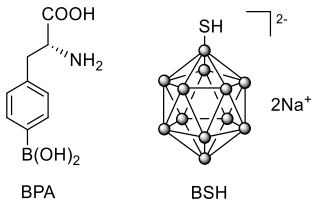


Figure 1. L-*p*-Dihydroxy-borylphenylalanine (BPA) and disodium mercaptoundecahydro-*closo*-dodecaborate (BSH).

Among a broad range of boron compounds, of particular interest as promising agents for BNCT are the functional derivatives of *closo*-dodecaborate dianion $[B_{12}H_{12}]^{2-}$ [1, 14]. It was shown that the oxonium derivatives of the *closo*-dodecaborate dianion are useful synthons for the preparation of various derivatives with biologically active molecules for medical application [15–18] through ring-opening reactions with different nucleophiles [19–25].

The use of liposomes is a high-tech method for the targeted delivery of drugs to cancer cells [26, 27]. Due to the high permeability of blood vessel walls inside a tumor, liposomes are capable of passive targeting and penetrating into the tumor [28, 29]. In addition, the introduction of vector molecules into the composition of the liposome membrane surface can improve the targeting properties for tumors [30, 31]. The liposomal transport can also be used to deliver different types of boron polyhedral hydrides to the tumor, which on their own are not able to penetrate through cell membranes [32, 33]. The reported examples of liposomes based on polyhedral hydrides, such as the derivatives of boranes and carboranes [34–37], were produced both by the encapsulation of boron compounds in an aqueous core of liposomes and by the incorporation of boron-containing lipids in a liposome bilayer [38–40].

One of the observed differences between tumor and normal cells is the rate of metabolism of low-density lipoproteins. This difference stems from the increased need of tumor cells for cholesterol for the formation of new cell membranes. Therefore, the synthesis of boron-containing derivatives of cholesterol can become an efficient approach for the boron delivery to cancer cells using liposomes. Herein, we report on the synthesis of novel conjugates of the *closo*-dodecaborate dianion ($[B_{12}H_{12}]^{2-}$) with cholesterol by the nucleophilic opening of the cyclic oxonium derivatives of $[B_{12}H_{12}]^{2-}$.

Results and discussion

Recently, we have synthesized a series of cholesterols conjugated with cobalt bis(1,2-dicarbollide)(-1) [41] and *closo*-dodecaborate [42] *via* a click-reaction. Poly(ethylene glycol) units are widely used as covalent modifiers of biological macromolecules and particulates as well as linkers for

bioconjugates with various biologically relevant molecules. The oxonium derivatives of *closo*-dodecaborate react with alcohols to give the corresponding substituted derivatives of *closo*-dodecaborate [18, 43]. The syntheses of the *closo*-dodecaborate-containing cholesterols by the ring-opening reactions of the cyclic oxonium derivatives with cholesterol alcoholate were described only in a conference abstract [44], which did not include any experimental procedure. Our attempts to obtain the related conjugates with a flexible poly(ethylene glycol) spacer by the ring-opening reaction of $[B_{12}H_{12}]^{2-}$ with cholesterol using NaH were not successful.

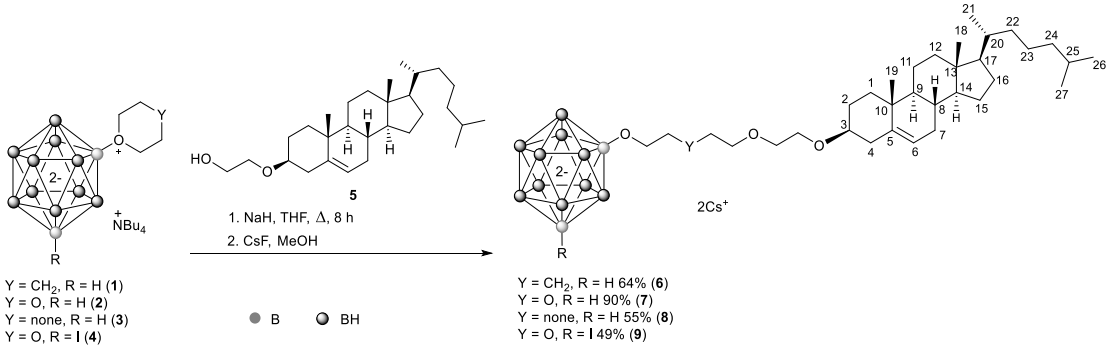
In this work, we used *closo*-dodecaborate derivatives with different oxonium cycles **1**–**4** and the cholesterol derivative modified with the hydroxy group, namely, 3β-(2-hydroxyethoxy)cholest-5-ene **5**, which was synthesized according to the published procedure by the nucleophilic substitution of cholesterol tosylate with ethylene glycol [45]. The cholesterol–*closo*-dodecaborate conjugates were obtained in a simple one-step procedure based on the nucleophilic ring-opening reactions of the oxonium derivatives of boron clusters **1**–**4** with modified cholesterol **5**. It was found that compounds **1**–**4** react with modified cholesterol **5** in the presence of two-fold molar excess of NaH used as a strong base for the generation of an alcoholate ion, resulting in new cholesterol derivatives of the *closo*-dodecaborate dianion. In all cases, the reaction course was monitored by thin-layer chromatography using CH_2Cl_2–CH_3OH (10:1) mixture as an eluent. Dianionic derivatives **6**–**9** were isolated as Cs salts and purified by precipitation from a methanol solution in good yields (Scheme 1). This afforded the cholesterol derivatives of $[B_{12}H_{12}]^{2-}$ featuring different spacers between the boron cage and the biological macromolecule. The ring-opening of 1,4-dioxane-substituted $[B_{12}H_{12}]^{2-}$ under the action of the modified cholesterol afforded compounds **7** and **9** bearing hydrophilic $–(CH_2CH_2O)_2–$ spacers, whereas the tetrahydrofuran and tetrahydropyran analogs gave rise to compounds **6** and **8** bearing lipophilic $–(CH_2)_{4–5}–$ spacers between the boron cage and the bioactive part of the molecule. These spacers can be considered as long units featuring high flexibility degrees and biocompatibility, which can be introduced using a simple synthetic procedure.

The structures of all novel conjugates **6**–**9** were unambiguously confirmed by the NMR and IR spectroscopic as well as HRMS (ESI) data (see Experimental). The ^{11}B NMR spectra of compounds **6**–**9** display four signals in 1:5:5:1 ratio, which is characteristic of monosubstituted boron clusters with the B–O bond. The signal of B(1)–O substituted boron atom at δ ~6.0–6.5 ppm appeared to be shifted by ~3 ppm compared to that of starting compounds **1**–**4** (δ ~ 9.2–9.6 ppm), which is typical for a transition from the BO^+R_2 system to the B(1)–OR [18] system and unequivocally proves the opening of the oxonium ring. The ^1H NMR spectra of compounds **6**–**9** display the characteristic signals of Cst(6)H alkene protons of the cholesterol unit at δ = 5.31, 5.32, 5.32, and 5.31 ppm, respectively. The positions and number of the signals of the cholesterol moiety in the ^1H and $^{13}C\{^1H\}$ NMR spectra of the resulting compounds are in good agreement with the previously reported data [46]. The IR spectra of compounds **6**–**9** show characteristic absorption bands of the BH groups (see Experimental). Compounds **6**–**9** will be used to obtain boronated liposomes in order to study the delivery of new boron clusters to cancer cells for a BNCT experiment.

Experimental

General remarks

Oxonium derivatives of *closo*-dodecaborate **1**–**4** [33] and 3β-(2-hydroxyethoxy)cholest-5-ene **5** [45] were synthesized according to the published procedures. Sodium hydride (60% dispersion in mineral oil) and cesium fluoride were purchased from Sigma-Aldrich and used without further purification. Tetrahydrofuran was distilled *via* a standard technique. Cholesterol, methanol, and CH_2Cl_2 were commercial reagents of analytical grade. The reaction course was monitored by thin-layer chromatography (Merck F245 silica gel on aluminum plates) and visualized using 0.5% $PdCl_2$ in 1% HCl in aq. MeOH (1:10). The NMR spectra at 400.1 MHz (^1H), 128.4 MHz (^{11}B), and 100.0 MHz (^{13}C) were measured in $(CD_3)_2SO$ on a Bruker Avance 400 spectrometer. The residual signals of the NMR solvent relative to Me_4Si were used as the internal references for the ^1H and ^{13}C NMR spectra. The ^{11}B NMR spectra were referenced using $BF_3{\cdot}Et_2O$ as an external standard. The IR spectra were recorded on a SHIMADZU IR Prestige-21 spectrometer. The high-resolution mass spectra (HRMS) were measured on a Brukermict OTOF II instrument using electrospray ionization (ESI). The measurements were carried out in a negative ion mode (interface capillary voltage 3200 V); mass range from m/z 50 to m/z 3000; external or internal calibration was performed with ESI Tuning Mix, Agilent. A syringe injection was used for solutions in $MeCN/H_2O$ (1:1) (flow rate 3 μL/min). Nitrogen was applied as a dry gas; the interface temperature was set at 180 °C. The electron ionization mass spectra were obtained with a Kratos MS 890 instrument operating in the mass range of 50–800.



Scheme 1. Synthesis of *closo*-dodecaborate derivatives of cholesterol **6**–**9**.

Syntheses

General procedure for the synthesis of *closo*-dodecaborate conjugates with cholesterol (6–9). Sodium hydride (60% dispersion in mineral oil, 2.0 eq.) was added to a solution of 3β-(2-hydroxyethoxy)cholest-5-ene **5** (1.2 eq.) in THF (30 mL) under an argon atmosphere. The resulting mixture was stirred for 1 h. Then, the corresponding oxonium derivative (1.0 eq.) was added. The reaction mixture was refluxed for 8 h. After cooling to room temperature, methanol (3–4 drops) was added to remove the excess of sodium hydride. The solvent was evaporated *in vacuo*. The resulting residue was dissolved in MeOH (5 mL). Then, a solution of CsF (1.5 eq.) in MeOH (5 mL) was added. The resulting precipitate was collected by filtration and dried *in vacuo* to give the target products as white solids.

[3β-Chol-(O(CH$_2$)$_2$)$_2$(CH$_2$)$_3$O-(B$_{12}$H$_{11}$)]Cs$_2$ (6). The compound was prepared according to the general procedure from tetrahydropyran derivative of *closo*-dodecaborate **1** (0.32 g), 3β-(2-hydroxyethoxy)cholest-5-ene **5** (0.35 g), and sodium hydride (60% dispersion in mineral oil, 0.07 g). Yield: 0.40 g (64%). ^{1}H NMR ((CD$_3$)$_2$SO, δ, ppm, *J*/Hz): 5.31 (s, 1H, Cst(6)H), 3.50 (m, 2H, CH$_2$O), 3.42 (m, 2H, CH$_2$O), 3.22 (m, 2H, CH$_2$O), 3.17 (m, 2H, CH$_2$O), 3.10 (m, 1H, Cst(3)H), 2.31 (m, 1H), 2.10 (m, 2H), 1.94 (m, 4H), 1.79 (m, 6H), 1.43 (m, 12H), 1.32 (m, 12H), 1.14 (m, 14H), 0.94 (s, 3H, Cst(19)H$_3$), 0.89 (d, 3H, *J* = 6.6, Cst(21)H$_3$), 0.85 (s, 3H, Cst(26)H$_3$), 0.83 (s, 3H, Cst(27)H$_3$), 0.64 (s, 3H, Cst(18)H$_3$). ^{13}C NMR ((CD$_3$)$_2$SO, δ, ppm): 141.0 (Cst(5)), 121.5 (Cst(6)), 78.9 (Cst(3)), 71.0 (O-CH$_2$), 70.2 (O-CH$_2$), 68.5 (O-CH$_2$), 67.1 (O-CH$_2$), 56.6 (Cst(14)), 56.0 (Cst(17)), 50.1 (Cst(9)), 42.3 (Cst(4)), 39.4 (Cst(12)), 39.2 (Cst(13)), 37.2 (Cst(24)), 36.8 (Cst(1)), 36.1 (Cst(10)), 35.7 (Cst(22)), 32.2 (CH$_2$), 31.9 (Cst(20)), 31.8 (Cst(8)), 29.9 (Cst(2)), 28.5 (CH$_2$), 28.3 (Cst(7)), 27.9 (Cst(16)), 24.3 (Cst(25)), 23.7 (Cst(15)), 23.1 (Cst(23)), 22.9 (Cst(26), Cst(27)), 21.1 (Cst(11)), 19.5 (Cst(19)), 19.0 (Cst(21)), 12.2 (Cst(18)). ^{11}B NMR ((CD$_3$)$_2$SO, δ, ppm, *J*/Hz): 6.4 (s, 1B, B-O), –16.8 (d, 5B, *J* = 132), –18.3 (d, 5B, *J* = 142), –23.0 (d, 1B, *J* = 110). HRMS (ESI) *m/z*: found 328.3266 $[C_{34}H_{70}B_{12}O_3]^{2-}$; calcd 328.3273. IR (solid, $\tilde{\nu}$, cm^{-1}): 2478 (BH).

[3β-Chol-(O(CH$_2$)$_2$)$_3$O-(B$_{12}$H$_{11}$)]Cs$_2$ (7). The compound was prepared according to the general procedure from 1,4-dioxane derivative of *closo*-dodecaborate **2** (0.20 g), 3β-(2-hydroxyethoxy)cholest-5-ene **5** (0.22 g), and sodium hydride (60% dispersion in mineral oil, 0.04 g). Yield: 0.35 g (90%). ^{1}H NMR ((CD$_3$)$_2$SO, δ, ppm, *J*/Hz): 5.32 (s, 1H, Cst(6)H), 3.62 (m, 2H, CH$_2$O), 3.37 (m, 10H, CH$_2$O), 3.13 (m, 1H, Cst(3)H), 2.35 (m, 1H), 2.10 (m, 2H), 1.87 (m, 7H), 1.49 (m, 7H), 1.34 (m, 9H), 1.10 (m, 14H), 0.94 (s, 3H, Cst(19)H$_3$), 0.89 (d, 3H, *J* = 6.3, Cst(21)H$_3$), 0.85 (s, 3 H, Cst(26)H$_3$), 0.83 (s, 3 H, Cst(27)H$_3$), 0.64 (s, 3 H, Cst(18)H$_3$). ^{13}C NMR ((CD$_3$)$_2$SO, δ, ppm): 141.0 (Cst(5)), 121.6 (Cst(6)), 79.0 (Cst(3)), 72.6 (O-CH$_2$), 70.4 (O-CH$_2$), 70.2 (O-CH$_2$), 69.6 (O-CH$_2$), 67.5 (O-CH$_2$), 66.9 (O-CH$_2$), 56.7 (Cst(14)), 56.0 (Cst(17)), 50.1 (Cst(9)), 42.3 (Cst(4)), 39.4 (Cst(12)), 39.0 (Cst(13)), 37.2 (Cst(24)), 36.8 (Cst(1)), 36.1 (Cst(10)), 35.7 (Cst(22)), 31.9 (Cst(20)), 31.9 (Cst(8)), 31.2 (Cst(2)), 28.4 (Cst(7)), 27.9 (Cst(16)), 24.3 (Cst(25)), 23.7 (Cst(15)), 23.1 (Cst(23)), 22.9 (Cst(26), Cst(27)), 21.1 (Cst(11)), 19.6 (Cst(19)), 19.0 (Cst(21)), 12.2 (Cst(18)). ^{11}B NMR ((CD$_3$)$_2$SO, δ, ppm, *J*/Hz): 6.0 (s, 1B, B-O), –16.8 (d, 5B, *J* = 137), –18.1 (d, 5B, *J* = 146), –22.7 (d, 1B, *J* = 117). HRMS (ESI) *m/z*: found 321.3200 $[C_{33}H_{68}B_{12}O_3]^{2-}$; calcd 321.3194. IR (solid, $\tilde{\nu}$, cm^{-1}): 2476 (BH).

[3β-Chol-(O(CH$_2$)$_2$)$_2$(CH$_2$)$_2$O-(B$_{12}$H$_{11}$)]Cs$_2$ (8). The compound was prepared according to the general procedure from tetrahydrofuran derivative of *closo*-dodecaborate **3** (0.32 g), 3β-(2-hydroxyethoxy)cholest-5-ene **5** (0.36 g), and sodium hydride (60% dispersion in mineral oil, 0.07 g). Yield: 0.35 g (55%). ^{1}H NMR ((CD$_3$)$_2$SO, δ, ppm, *J*/Hz): 5.32 (s, 1H, Cst(6)H), 3.51 (m, 2H, CH$_2$O), 3.43 (m, 4H, CH$_2$O), 3.22 (m, 2H, CH$_2$O), 3.11 (m, 1H, Cst(3)H), 2.32 (m, 1H), 2.08 (m, 1H), 1.95 (m, 2H), 1.82 (m, 4H), 1.50 (m, 6H), 1.35 (m, 16H), 1.11 (m, 10H), 0.95 (s, 3H, Cst(19)H$_3$), 0.90 (d, 3H, Cst(21)H$_3$, *J*=6.4,), 0.85 (s, 3H, Cst(26)H$_3$), 0.84 (s, 3H, Cst(27)H$_3$), 0.65 (s, 3H, Cst(18)H$_3$).^{13}C NMR ((CD$_3$)$_2$SO, δ, ppm): 141.0 (Cst(5)), 121.5 (Cst(6)), 78.9 (Cst(3)), 71.2 (O-CH$_2$), 70.2 (O-CH$_2$), 68.2 (O-CH$_2$), 67.1 (O-CH$_2$), 56.6 (Cst(14)), 56.0 (Cst(17)), 50.1 (Cst(9)), 42.3 (Cst(4)), 39.4 (Cst(12)), 39.2 (Cst(13)), 37.2 (Cst(24)), 36.8 (Cst(1)), 36.1 (Cst(10)), 35.7 (Cst(22)), 31.9 (Cst(20)), 31.8 (Cst(8)), 28.8 (CH$_2$), 28.5 (Cst(2)), 28.3 (Cst(7)), 27.9 (Cst(16)), 24.3 (Cst(25)), 23.7 (Cst(15)), 23.1 (Cst(23)), 22.9 (Cst(26),Cst(27)), 21.1 (Cst(11)), 19.5 (Cst(19)), 19.0 (Cst(21)), 12.2 (Cst(18)). ^{11}B NMR ((CD$_3$)$_2$SO, δ, ppm, *J*/Hz): 6.5 (s, 1B, B-O), –16.8 (d, 5B, *J* = 126), –18.3 (d, 5B, *J* = 134), –23.0 (d, 1B, *J* = 132). HRMS (ESI) *m/z*: found 972.7805 $[C_{33}H_{68}B_{12}O_4]^{2-}$; calcd 972.7814. IR (solid, $\tilde{\nu}$, cm^{-1}): 2480 (BH).

[3β-Chol-(O(CH$_2$)$_2$)$_3$O-(B$_{12}$H$_{10}$I)]Cs$_2$ (9). The compound was prepared according to the general procedure from 1-iodine-7-(1,4-dioxane) derivative of *closo*-dodecaborate **4** (0.30 g), 3β-(2-hydroxyethoxy)cholest-5-ene **5** (0.52 g), and sodium hydride (60% dispersion in mineral oil, 0.10 g). Yield: 0.26 g (49%). ^{1}H NMR ((CD$_3$)$_2$SO, δ, ppm): 5.31 (br. s, 1H, Cst(6)H), 3.49 (m, 10H, CH$_2$O), 3.14 (m, 3H, CH$_2$O, Cst(3)H), 2.10 (m, 2H), 1.87 (m, 8H), 1.41 (m, 17H), 1.36 (m, 9H), 1.10 (m, 14H), 0.95 (br. s, 3H, Cst(19)H$_3$), 0.84 (br. s, 9H, Cst(21)H$_3$, Cst(26)H$_3$, Cst(27)H$_3$), 0.65 (s, 3H, Cst(18)H$_3$). ^{13}C NMR ((CD$_3$)$_2$SO, δ, ppm): 141.0 (Cst(5)), 121.5 (Cst(6)), 79.0 (Cst(3)), 72.5 (O-CH$_2$), 70.4 (O-CH$_2$), 70.2 (O-CH$_2$), 69.7 (O-CH$_2$), 67.6 (O-CH$_2$), 66.9 (O-CH$_2$), 56.7 (Cst(14)), 56.0 (Cst(17)), 50.1 (Cst(9)), 42.3 (Cst(4)), 39.4 (Cst(12)), 39.1 (Cst(13)), 37.2 (Cst(24)), 36.8 (Cst(1)), 36.1 (Cst(10)), 35.7 (Cst(22)), 31.9 (Cst(20)), 31.9 (Cst(8)), 28.4 (Cst(2)), 28.3 (Cst(7)), 27.9 (Cst(16)), 24.3 (Cst(25)), 23.7 (Cst(15)), 23.2 (Cst(23)), 22.9 (Cst(26), Cst(27)), 21.1 (Cst(11)), 19.6 (Cst(19)), 19.0 (Cst(21)), 12.2 (Cst(18)). ^{11}B NMR ((CD$_3$)$_2$SO, δ, ppm, *J*/Hz): 6.1 (s, 1B), –15.5 (d, 1B, *J* = 142), –16.6 (d, 4B, *J* = 151), –18.1 (d, 4B, *J* = 149), –21.4 (m, 2B). HRMS (ESI) *m/z*: found 392.2658 $[C_{33}H_{67}B_{12}IO_4]^{2-}$; calcd 392.2652. IR (solid, $\tilde{\nu}$, cm^{-1}): 2486 (BH).

Conclusions

A series of *closo*-dodecaborate-containing cholesterols were synthesized by the nucleophilic cleavage of the cyclic oxonium derivatives of these boron clusters under the action of the hydroxy-modified cholesterol. The resulting boronated cholesterols can be used for liposomal drug delivery in boron neutron capture therapy of cancer. The structures of all the novel

compounds were unequivocally confirmed using IR and NMR spectroscopy as well as high-resolution mass spectrometry.

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Electronic supplementary information

Electronic supplementary information (ESI) available online: ^{1}H, ^{11}B, ^{11}B{^{1}H}, and ^{13}C NMR, IR and ESI-HRMS spectra of compounds **6**–**9**. For ESI, see DOI: 10.32931/io2008a

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