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‘Click’ synthesis of cobalt bis(dicarbollide)–cholesterol conjugates

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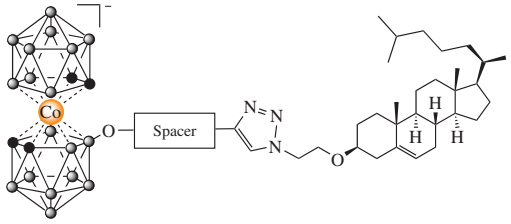
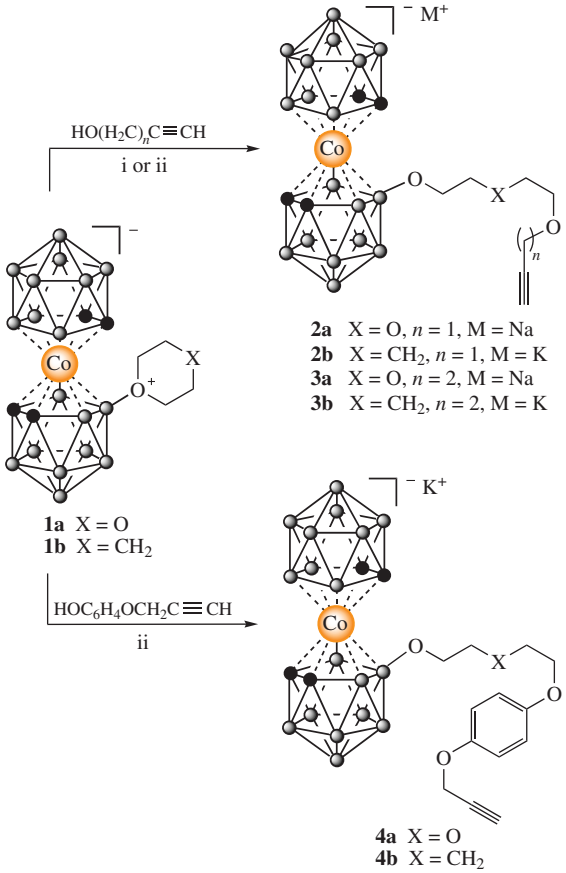
New conjugates of cholesterol and cobalt bis(dicarbollide) were synthesized using ‘click’ cycloaddition of 3β-(2-azidoethyl)cholest-5-ene and acetylene-equipped cobalt bis(dicarbollides). The synthesized boronated cholesterols can be of interest for liposomal drug delivery for boron neutron capture therapy of cancer.



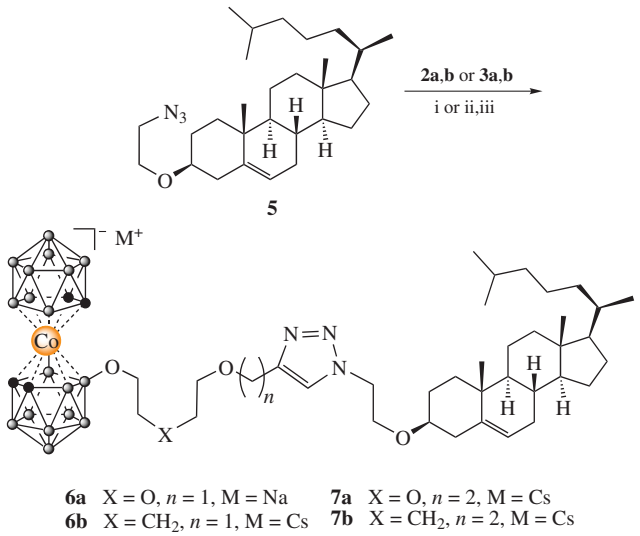
Boron neutron capture therapy (BNCT) is a binary method for the cancer treatment based on the local nuclear reaction of two essentially nontoxic species, low-energy thermal neutrons and non-radioactive ^{10}B isotope. The neutron-capture reaction by ^{10}B nucleus produces high-linear-energy transfer particles ($^{4}He^{2+}$ and $^{7}Li^{3+}$) that dissipate their energy traveling on a distance close to one cell diameter (5–9 μm), ensuring precise tumor cell killing. Ideally, only tumor cells will be destroyed without damage to healthy tissues. Therefore, selective delivery and high accumulation of boron into the tumor tissue (20–35 μg ^{10}B per gram) are the most important requirements to achieve efficient neutron-capture therapy of cancer.[1,2]

Liposomes represent one of the most efficient drug delivery vehicles since they can deliver their contents to various tumors in a manner that is essentially independent of their contents and at the same time protect their contents from the action of external medium. They have tendency to accumulate in tumor tissue much more than they do in normal tissues due to higher endocytic activity of some tumor cells combined with augmented local permeability of capillaries providing the passage of small liposomes, a phenomenon described as ‘the enhanced permeability and retention effect’. Therefore, passive targeting of liposomes to tumor tissues may be useful for delivering cancer chemotherapeutic agents to the target tumors.[3–5] Besides, liposomes are well suited for improving their targetable properties because of the ease of modifying their surface when compared to other drug carriers. Currently, many approaches have been developed to achieve targetable properties of liposomes *via* their attachment to various tumor-targeting vectors.[6–8] Therefore, liposomal boron delivery systems are of great interest for BNCT due to their capability of carrying a large amount of boron compounds into a tumor.[9,10]

Recently, we synthesized[11] a series of boron-containing derivatives of cholesterol using nucleophilic ring-opening reactions of cyclic oxonium derivatives of cobalt bis(dicarbollide) with amino and carboxy cholesterols. These compounds were found to be capable of forming stable and non-toxic liposomes of 120–160 nm in diameter with excellent (up to 97%) boron entrapment efficiency.

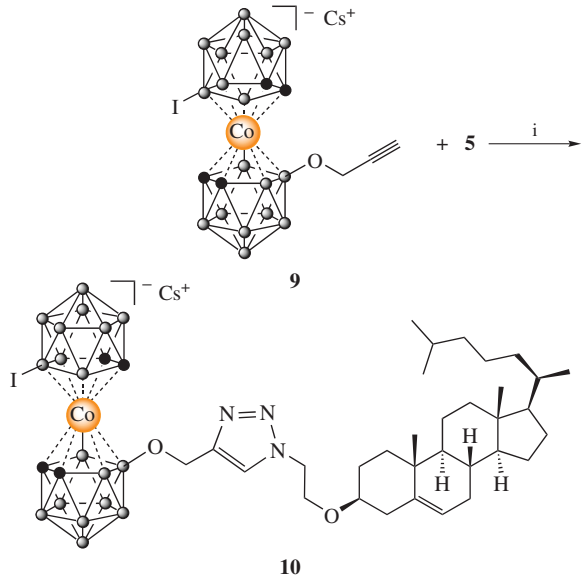


Scheme 1 *Reagents and conditions*: i, Na, THF, reflux, 3 h; ii, K_2CO_3, MeCN, reflux, 5 h.



6a X = O, *n* = 1, M = Na **7a** X = O, *n* = 2, M = Cs
6b X = CH_2, *n* = 1, M = Cs **7b** X = CH_2, *n* = 2, M = Cs

Scheme 2 *Reagents and conditions*: i, CuI, Et_3N, MeCN, reflux, 18 h; ii, CuI, DIPEA, EtOH, reflux, 7 h; iii, CsCl, acetone–water.

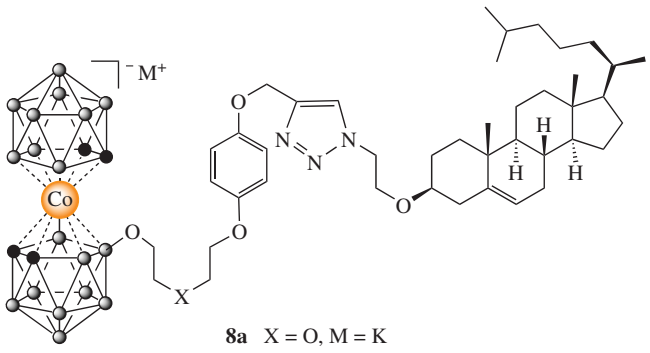


Scheme 3 *Reagents and conditions*: i, CuI, DIPEA, EtOH, reflux, 7 h.

In this work we have synthesized new cobalt bis(dicarbollide) conjugates with cholesterol by azide–alkyne 'click' reactions. The choice of cobalt bis(dicarbollide) as a boron component of lipids, along with high boron content, low toxicity,[12] and high stability combined with the presence of well-developed methods for its functionalization,[13] was also due to the fact that, unlike the *closo*-dodecaborate anion and carboranes, it has absorption in the UV region,[14] which facilitates control of its entrapment efficiency by liposomes.

The Cu^I-catalyzed 1,3-dipolar cycloaddition of alkyne and azide to form a triazole, termed 'click chemistry', has been established as a promising tool for chemical modification of biomolecules.[15] In this work we used only one cholesterol derivative, 3β-(2-azidoethoxy)cholest-5-ene, which was synthesized by two different ways, namely, by alkylation of 2-azidoethanol with cholesterol tosylate[16] and by alkylation of cholesterol with 2-azidoethyl triflate (Scheme S1, see Online Supplementary Materials). Cobalt bis(dicarbollide) derivatives contained different spacers between the boron cage and the terminal acetylene group. These compounds were prepared by the nucleophilic ring-opening reactions of 1,4-dioxane or tetrahydropyran onium derivatives **1a**,**b** of cobalt bis(dicarbollide) with the corresponding alcoholates and phenolates[17–19] (Scheme 1).

The reactions of acetylenes **2**,**3** with 3β-(2-azidoethoxy)cholest-5-ene **5** in boiling acetonitrile or ethanol in the presence of CuI catalyst and Et_3N or Pr^i_2EtN as the base produce the corresponding boronated cholesterols **6a**,**b** and **7a**,**b** (Scheme 2). In a similar way, the reactions of acetylenes **4a**,**b** containing arylene group in the spacer with azide **5** result in cholesterols **8a**,**b**.



8a X = O, M = K
8b X = CH_2, M = Cs

The reaction of azide **5** with compound **9**[20] having shorter spacer between the metallaborane cage and the alkyne group in the presence of catalytic amount of CuI in refluxing ethanol gives the corresponding conjugate **10** (Scheme 3).

Preparation and study of liposomal formulations based on the prepared boronated cholesterols are in a progress and will be published elsewhere.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2019.11.007.

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