SYNTHESIS OF A CONJUGATE OF CURCUMIN WITH A *NIDO*-CARBORANE CLUSTER AND ITS CYTOTOXICITY

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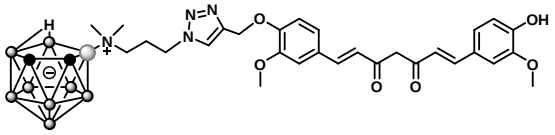
Abstract

A conjugate of curcumin with *nido*-carborane was synthesized by the Cu-catalyzed 1,3-dipolar [3+2]-cycloaddition between a zwitter-ionic B-substituted *nido*-carborane bearing a functional azido group 9-$N_3(CH_2)_3Me_2N$-*nido*-7,8-$C_2B_9H_{11}$ with alkynyl-tagged curcumin. The compound obtained was tested for cytotoxicity against human ovarian adenocarcinoma A2780. The resulting conjugate is potentially suitable for further biological research for boron neutron capture therapy of cancer (BNCT).



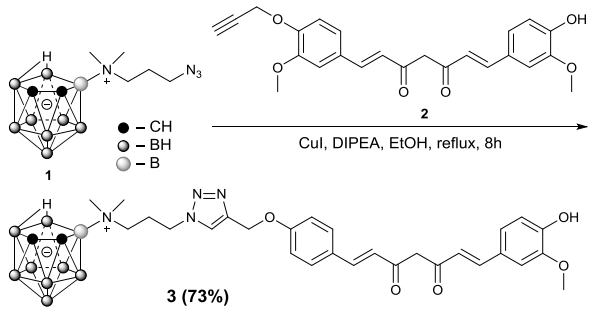
Key words: *nido*-carborane, click reaction, curcumin, cytotoxicity, boron neutron capture therapy (BNCT).

Introduction

Nowadays, carborane derivatives attract particular attention owing to their unusual properties and the possibility of application in various fields, ranging from the creation of new materials (carborane-containing polymers, ionic liquids) to medicinal chemistry (boron neutron capture therapy of cancer) [1]. Boron neutron capture therapy (BNCT) of cancer is one of the most important areas of potential use of carborane derivatives in medicine. This method implies binary cancer treatment based on the interaction of two relatively harmless particles, the ^{10}B nucleus and a thermal neutron, which leads to the formation of high-energy particles ^4He and ^7Li. Selective accumulation of ^{10}B nuclei in tumor tissue with subsequent capture of thermal neutrons leads to localized destruction of malignant cells without affecting neighboring healthy cells. The high potential of this method is proven by its clinical use for the treatment of cancer patients, as well as numerous preclinical trials. It is no coincidence that recently there has been significant development of the methods for obtaining new boron-containing derivatives for BNCT. In this case, it is necessary that boron compounds selectively accumulate in tumor tissue in the required therapeutic concentration for its subsequent irradiation with thermal neutrons. One of the effective directions aimed at achieving the necessary therapeutic concentration of boron in tumor cells is the use of *nido*-carborane derivatives containing a large number of boron atoms in the molecule. Biologically active molecules, such as amino acids [2], porphyrins [3], nucleosides [4], are often used as boron delivery agents. It should be noted that the choice of natural biomolecules linked to polyhedral boron hydrides has proven to be an important strategy in the synthesis of potential BNCT drugs based on boron clusters. Natural compounds or their derivatives have attracted much attention as promising drugs for the treatment of human malignancies. Among such agents, the derivatives and analogs of curcumin play an important role, since this class of compounds has a wide range of biological activity. Furthermore, the literature data indicate that they are capable of accumulating in tumor cells. In this respect, boron-containing derivatives of curcumin seem to be very promising. To date several examples of *nido*-carborane-based curcumin derivatives have been reported [5, 6]. In this work, we used the click methodology for the synthesis of a novel zwitter-ionic *nido*-carboranyl-curcumin conjugate which can be used as a potential drug for BNCT.

Results and discussion

The Cu(I)-catalyzed 1,3-dipolar [3+2]-cycloaddition of azides with alkynes has found widespread use for the bioconjugation of molecules [7]. Earlier the click reaction was successfully used to obtain a wide range of conjugates of polyhedral boron hydrides with nucleosides [8], chlorin e_6 [9], as well as the derivatives of curcumin based on cobalt bis(dicarbollide) [10]. In this work, we used modified curcumin, namely, alkynyl-tagged curcumin and a B-substituted *nido*-carboranyl derivative containing an azido group. It is known that the penetration of biomolecules through cell membranes, their accumulation and retention in cells largely depend on their charge. In particular, the positively charged particles have better penetration through biological membranes than negatively changed ones [11]. Thus, at the first step, using the described procedures we prepared the alkynyl derivative of curcumin [12] and the azido derivative based on *nido*-carborane **1** [13], which application in the synthesis of a carborane-curcumin conjugate leads to zwitter-ionic character of the product structure. Further it was found that boronated azide **1** readily undergoes click reaction with alkynyl curcumin **2** in the presence of CuI used as a catalyst and DIPEA used as a base in ethanol upon reflux for 8 h to give the novel conjugate of curcumin with *nido*-carborane **3** in good yield (73%) (Scheme 1).



Scheme 1. Synthesis of *nido*-carborane derivative of curcumin **3**.

The synthesized conjugate of curcumin and *nido*-carborane was characterized by ^{1}H, ^{11}B, ^{11}B{^{1}H} and ^{13}C{^{1}H} NMR spectroscopy, IR spectroscopy, as well as high-resolution mass spectrometry (see the Electronic supplementary information (ESI)). In the ^{1}H NMR spectrum of **3**, the signal of the proton of the triazole C*H* group appeared at 8.18 ppm. The signals of the aromatic groups appeared as a singlet at 7.36 ppm and two multiples at 7.22 and 6.76 ppm. The ^{1}H NMR spectrum of product **3**, along with the signals of the aromatic moieties, contained the characteristic signals of the heteroaliphatic chain of **3**. The signals of the methylene groups adjacent to the triazole ring were observed at 3.56, 4.67, and 5.27 ppm; the characteristic signals of the Me_2N group appeared at 3.06 and 3.08 ppm; the signals of the methyl groups O*C*H_3 appeared as singlets at 3.90 and 3.94 ppm. The ^{1}H NMR spectrum of **3**, in addition to the signals of the methyl and methylene groups of the compound, contained the signal of the C*H* group, which appeared in the form of a singlet at 6.01 ppm. In addition, the signals of the C*H*carb groups in the ^{1}H NMR spectra of **3** appeared as broad singlets at 2.65 and 1.87 ppm; the signal of the *extra*-hydrogen, as expected, was observed at *ca*. –3.43 ppm. The ^{11}B NMR spectrum of **3** contained a pattern of eight signals (one singlet at 5.5 ppm and seven doublets at –5.5, –17.2, –19.5, –25.0, –26.7, –32.1, and –38.7 ppm), which demonstrates the absence of a plane of symmetry and unambiguously confirms the *nido* form. The ^{13}C NMR spectrum of the conjugate of curcumin with *nido*-carborane **3** showed the characteristic signals of the carbon nuclei of *C*=O groups of allyl curcumin **3** at 183.4 and 183.2 ppm and the signals of the carbon nuclei of the O*C*H_3 groups at 55.4 and 55.3 ppm. For 1,2,3-triazole **3**, the ^{13}C NMR spectrum showed the signals of two carbon nuclei of the triazole unit at 149.2 ppm (the quaternary nucleus) and 121.4 ppm, while he signals of *C*H_{carb} groups appeared at 33.9 and 46.4 ppm. The ^{13}C NMR spectra of compound **3** demonstrated the characteristic signal of CO-*C*H-COH carbon of the curcumin skeleton at 100.9 ppm, the signals of O-*C*H_3 carbon nuclei appeared at 55.4 and 55.3 ppm, and the signals of N-*C*H_3 carbon nuclei were observed at 52.8 and 51.1 ppm, respectively.

The cytotoxicity of the resulting conjugate of curcumin with *nido*-carborane **3** was tested against human cancer cell line A2780 (ovarian adenocarcinoma) using the conventional MTT colorimetric assay. Cisplatin was used as a control in the study. Due to the low solubility of compound **3**, the highest concentration used was 50 μM. For A2780 cell line, it was possible to estimate the cytotoxicity, with the IC_{50} value of 34.0 ± 4.0 μM.

Conclusions

In summary, the zwitter-ionic B-substituted *nido*-carboranyl curcumin was synthesized by the click reaction. The resulting conjugate was tested for cytotoxicity against human ovarian adenocarcinoma A2780 and showed moderate cytotoxic activity, suggesting that the resulting conjugate is suitable for further biological studies for boron neutron capture therapy of cancer.

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Electronic supplementary information

Electronic supplementary information (ESI) available online: the experimental section and spectra for compound **3**. For ESI, see DOI: 10.32931/ioXXXXx.

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