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Review

Glycoconjugates of polyhedral boron clusters

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ABSTRACT

The potential medicinal applications of boron-based compounds have been well established. Among the medicinal applications of boron, its use for the treatment of cancer via boron neutron capture therapy (BNCT) is the most promising. Although a variety of approaches have been evaluated for adequate boron delivery to the cancer tissues for successful cancer therapy, this review focuses on the synthesis of carbohydrate-based boron delivery platforms. Recent advances in the synthesis and utilization of glycoconjugates for boron delivery has been reported.

1. Introduction

Glycochemicals have attracted significant interest for development of therapeutic agents and vaccines because of the functional and structural diversity of carbohydrates. Glycoconjugates and oligosaccharides have significant role in several biological processes such as cell growth, viral and bacterial infection, cell–cell communication and intercellular recognition processes [1,2]. Glycoconjugates have been used as targeted drug delivery systems in immunoactivation, enzyme replacement, antiviral, gene and cancer therapies. Such glycotargeting of drugs relies on the presence of carbohydrate-specific receptor proteins on the cell surface and over expression of lectins on tumor tissues [3–5]. Thus glycoconjugates of polyhedral boron clusters have been synthesized for tumor targeted delivery of boron for successful treatment of cancer via boron neutron capture therapy (BNCT) [6].

The medicinal chemistry of boron drugs for cancer treatment relies on the boron neutron capture reaction that involves a ^{10}B atom capturing a thermal neutron giving an excited ^{11}B. The excited ^{11}B undergoes a rapid fission reaction producing high energy $^{4}He^{2+}$ (α-particle) and $^{7}Li^{3+}$ ions that kills the cancer cells [7]. The therapeutic dose of ^{10}B required to kill a cancer cell is ~10^{9} atoms per cell or about 30 μg/g of tumor. Therefore, an important requirement for an effective BNCT depends on selectively directing the requisite concentrations of ^{10}B to the cancerous tissues and sparing the surrounding healthy tissues. The high linear energy transfer of the emitted α-particle and the recoil lithium particle in biological tissues is ~ 4–9 μm which is approximately the diameter of a cell. Therefore, these high energy particles dissipate their kinetic energy before traveling one cell diameter so that the destructive effect is highly localized only to the boron-loaded tissue [8]. Although BNCT has been primarily used for the treatment of fatal malignant brain cancers such as glioblastoma multiforme [9], it is now being extended to the treatment of other types of cancers such as melanoma [10], and head and neck cancer [11]. Based on the same principle treatment of rheumatoid arthritis could be possible via boron neutron capture synovectomy (BNCS) [12].

In recent years, the applications of polyhedral boron compounds specifically icosahedral boron clusters [13] (Fig. 1) in medicinal chemistry receives increasing attention. Other than BNCT for cancer

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therapy, these compounds have been used as stable hydrophobic pharmacophores, retinoid receptor ligands, steroid analogs, human blood platelet function inhibitors and HIV protease inhibitors [7–12]. All four clusters shown in Fig. 1 possess high chemical and biological stability, rigid geometry and low toxicity. The presence of 10–12 boron atoms in these compounds would make the task of achieving necessary therapeutic concentration of boron atoms in the tumor tissues easier. Dicarba-closo-dodecacarboranes ($C_2B_{10}H_{12}$) (**1**–**3**) are characterized by an exceptional hydrophobic character whereas, *closo*-dodecaborate **4** possesses ionic and hydrophilic characteristics. However, the functionalization of hydrophobic *ortho*, *meta* and *para* carboranes (**1**–**3**) are much easier than the hydrophilic dodecaborate ion which prevents its wider application in synthetic and medicinal chemistry [14]. Polyhedral boron compounds have been conjugated with several tumor targeting moieties such as nucleic acid precursors, amino acids, peptides, lipids, carbohydrates, nanoparticles, lipoproteins, liposomes, porphyrins, DNA binders, polyamines, antigen binders, amines, hydantoins and barbiturates etc. for targeted boron delivery to tumor tissues [15]. There are a number of reviews available on the synthesis of conjugates of carboranes as boron delivery platforms and their various medicinal applications [7,8,14,15]. In addition to their medicinal applications, carboranes have also been utilized in various other applications such as in organometallic chemistry, catalysis and materials science those are described elsewhere [16]. In this paper, we have only reviewed recent advances in the synthesis and medical applications of glycoconjugates of polyhedral boron compounds.

2. Glycoconjugates of carboranes

Glycoconjugates of carboranes were first synthesized a couple of decades ago by Hawthorne's group. It was initially thought that the hydrophilic characteristics of carbohydrates could compensate the hydrophobicity of carboranes [17]. Typically two general synthetic approaches are followed for synthesis of C-substituted *o*-carboranes. One is the reaction of substituted alkynes with decaborane $B_{10}H_{14}$ under appropriate conditions and the other is the reaction of lithiated *o*-carborane with an electrophilic moiety [15]. The first approach was followed for the synthesis of the reported compound 3′-*O*-(*o*-carboran-1-ylmethyl)-D-glucose (**5**). It was obtained as an anomeric mixture and water-insoluble. It has been reported that a minimum of eight hydroxyl groups per carborane cage is required to impart water solubility. Compound **5** contains only five hydroxyl groups, three less than the required number to make it water soluble [15b]. However, it showed remarkable biological properties. The cellular uptake studies of **5** was carried out using rat glioma cells F98 and compared with clinically used BNCT drug sodium mercaptoundecahydro-*closo*- dodecaborate (BSH) **6** (Fig. 2). One example of higher cellular uptake of carbohydrate based boron delivery platform is in the case of compound **13** (Scheme 1). Cellular boron uptake up to 65 μg/g cells was achieved by using

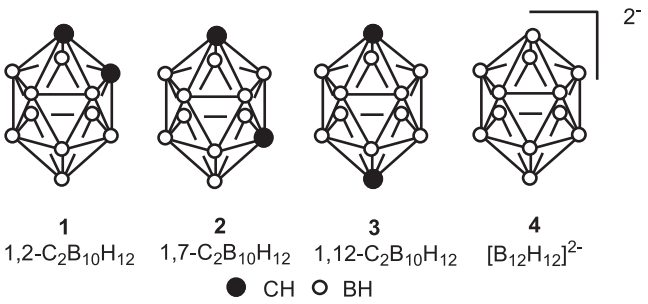

Fig. 1. Icosahedral boron compounds.

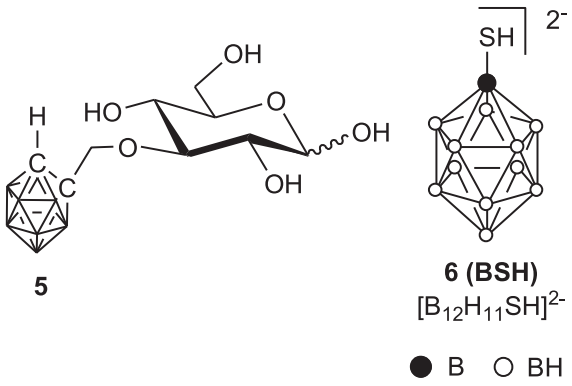

Fig. 2. Carboranyl derivative of D-glucose **5** and clinically used BNCT drug sodium mercaptoundecahydro-*closo*- dodecaborate (BSH) **6**.

compound **13** whereas only 2 μg/g cells boron uptake was observed for BSH (Fig. 2) [18]. The higher cellular uptake via the glycosylated carborane derivatives made such compounds promising candidates for tumor targeted boron delivery and thus synthesis and biological evaluation of several such derivatives followed.

The synthesis of water-soluble glycoconjugates of carboranes for targeted boron delivery to tumor tissues was reported by Tietze and Bothe [19]. They synthesized glycoconjugates of *O*-carborane with both monosaccharides (glucose and mannose) and disaccharides (lactose and maltose). These conjugates were synthesized from their respective trichloroimidates. The reaction of glucose trichloroimidate (**7**) with either 3-butyn-1-ol or 5-hexyn-1-ol in the presence of $BF_3 \cdot Et_2O$ afforded butyl β-glucoside (**8a**) and hexynyl β-glucoside (**8b**) respectively. *O*-carborane moieties were then appended to the alkynyl glucosides via reaction with decaborane in acetonitrile under reflux condition (Scheme 1). The deprotection of the peracetylated glucosides **9a** and **9b** with sodium methoxide/methanol resulted in the desired carboranyl glucosides **10a** and **10b**. Carboranyl mannoside (**11**), carboranyl lactoside (**12**) and carboranyl maltoside (**13**) were synthesized following similar synthetic procedures. Carboranyl monosaccharides **10** and **11** were not sufficiently water-soluble as compared to the disaccharides **12** and **13**.

The toxicity evaluation of water-soluble compounds **12** and **13** were carried out using human bronchial carcinoma cell line A549 and found that they showed no toxicity up to 0.40 mM concentration. The boron uptakes of carboranyl monosaccharide **10a**, and carboranyl disaccharide **12** and **13** were evaluated using B16 melanoma cells and the results were compared with clinically used boron drug **14** (BPA). Carboranyl maltoside **13** exhibited highest uptake among the carboranyl glycosides **10a**, **12** and **13** used for the study. For compound **13** boron accumulation at 3 h after administration was 6.1 ppm and it was increased up to 20.0 ppm after 24 h. In the case of lactoside **12**, the boron concentration was 11.7 ppm at 3 h and reached 13.2 ppm at 12 h and remained almost constant until 24 h. Whereas for carboranyl monosaccharide **10a** the boron accumulation the cells reached the maximum value 11.2 ppm at 3 h and then gradually decreased. These values were significantly higher than that observed for BPA **14** which was only 3.1 ppm after 24 h. The in vitro survival of C6 glioma cells after thermal neutron irradiation indicated that maltoside **13** to be more effective than ^{10}B enriched BSH [20].

Compound **17** which is similar to **9a** was synthesized via trimethyl silyl triflate glycosidation of pentaacetyl-D-glucose **15** with 2-propyn-1-ol. The alkenyl derivative **16** obtained during the reaction was further treated with decaborane and deprotected with sodium methoxide/methanol solution to produce the desired carboranyl glycoside **18**. Compound **12** containing a lactose moiety