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Review

Sweet Boron: Boron-Containing Sugar Derivatives as Potential Agents for Boron Neutron Capture Therapy

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Abstract: Boron neutron capture therapy (BNCT) is a binary type of radiotherapy for the treatment of cancer. Due to recent developments of neutron accelerators and their installation in some hospitals, BNCT is on the rise worldwide and is expected to have a significant impact on patient treatments. Therefore, there is an increasing need for improved boron delivery agents. Among the many small molecules and delivery systems developed, a significant amount of recent research focused on the synthesis of boron-containing sugar and amino acid derivatives to exploit specific transport proteins, as D-glucose transporter 1 (GLUT1) and large neutral amino acid transporter (LAT1), overexpressed by tumor cells. This review will discuss the last year's achievements in the synthesis and some biological evaluation of boronated sugars derivatives. The compounds described in this review are intrinsically asymmetric due to the presence of chiral sugar moieties, often joined to boron clusters, which are structural elements with high symmetry.

Keywords: BNCT; boronated sugars; synthesis; biological evaluation

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1. Introduction

Boron neutron capture therapy (BCNT) is a binary radiotherapeutic approach based on the nuclear capture of low-energy neutrons (thermal) by a boron-10 (^{10}B) nucleus. ^{10}B has a cross-section for neutron capture of 3840 barns (1 barn = 10^{-24} m^2, the size of the uranium nucleus Mughabghab, S.F. (2003), 'Thermal neutron capture cross-sections: Resonance integrals and g- factors', IAEA Nuclear Data Section, Wagramer Strasse 5, A-1400, Vienna), by far greater than that of the elements (among others, nitrogen, hydrogen, and oxygen) commonly present in tissues.

When ^{10}B captures a neutron, the formed ^{11}B isotope is in an excited state which rapidly decays through a fission reaction producing an α particle and recoiling a lithium-7 (^{7}Li) ion. These high-linear-energy transfer (LET) particles dissipate their energy by traveling a distance corresponding to a cell diameter. If a ^{10}B-containing compound is preferentially accumulated within a cancer cell, the irradiation of the tumor area with a neutron flux gives rise to a lethal fission reaction confined within the boron-containing cells, providing selective destruction of the malignant cells saving the surrounding healthy tissues, provided that some requirements are fulfilled, as later discussed (Figure 1).

The principle of the possible therapeutic use of BNCT was first introduced by Locher in 1936 [1], and initially attempted at the Brookhaven National Laboratory [2] and at the Massachusetts General Hospital with irradiation at MIT nuclear reactor in Boston [3]. At the same time Soloway, again at the Massachusetts General Hospital, began studies for finding suitable non-toxic boron-containing compounds. These experiments failed essentially for a lack of selectivity of boron compounds used, together with the low penetration of thermal neutrons. For these reasons, the use of epithermal neutrons that are thermalized by water in the patient's tissues when they arrive proximal to the tumor site was introduced.

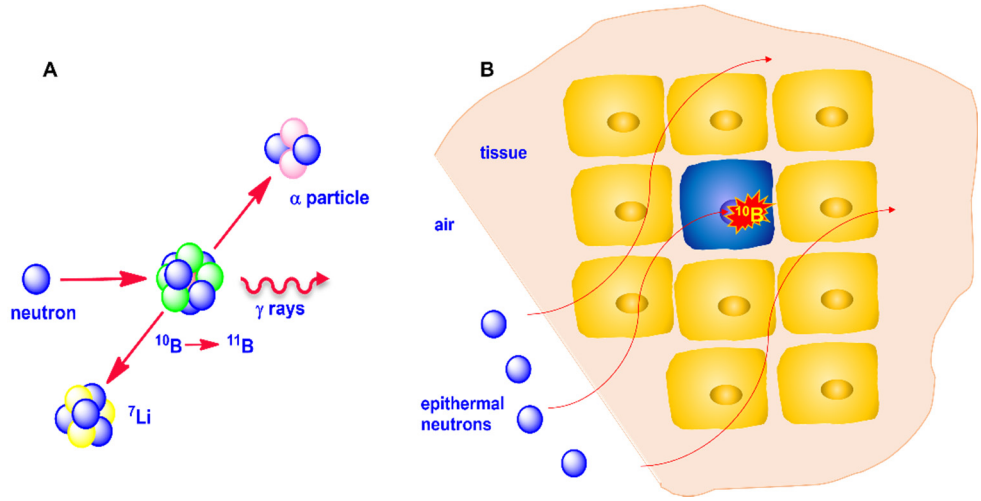


Figure 1. (**A**): Neutron capture by ^{10}B and fission reaction of ^{11}B; (**B**): thermalization of neutron and selective cancer cells destruction.

The results obtained by Hatanaka using BSH (sodium mercapto-undecahydro-*closo*-dodecaborate) at the end of the 1960s [4] gave rise to renewed interest in BNCT both in Europe and in the United States, alongside the development of boron chemistry [5,6].

Since then, BNCT has been applied primarily to selected tumor types, mainly to high-grade gliomas and, more recently, to recurrent head and neck cancer [7], although other kinds of tumors have been occasionally treated [8].

Two basic requirements must be fulfilled to have a chance for effective therapy: first, neutron sources with a sufficient neutron flux are required. Until the second half of the last decade, the only neutron sources with an adequate flux for therapeutic use were nuclear reactors, which hampered the wide development of BNCT due to limitations intrinsic to the use of nuclear reactors. Nowadays some accelerators are already available in Japan, China, and Finland, and others are under installation [8].

The availability of in-hospital neutron sources is expected to give a boost to clinical trials and patient treatment using BNCT. Therefore, the demand for new, more efficient boron delivery agents is rising and will increase in the future.

To have the possibility of successful therapy, the compounds must have some important and commonly accepted requirements: (a) low toxicity; (b) high and selective tumor uptake which means a concentration of at least 20 μg of boron for g of tumor tissue, a tumor/normal tissue ratio and a tumor/blood concentration higher than 3:1; (c) sufficiently fast clearance from normal tissues and blood and adequate persistence (several hours) in the tumor to allow neutron irradiation; (d) adequate water solubility [9].

After the failure of the initial trials during the 1950s–1960s in which boric acid and its derivatives were used, the need for more selective boron carriers immediately became clear. Starting from the pioneering work of Soloway [10] in Boston, a huge number of boronated compounds have been synthesized [9,11]. Three molecules have been approved for clinical use, namely sodium mercapto-undecahydro-*closo*-dodecaborate (or sodium borocaptate, $Na_2B_{12}H_{11}SH$, BSH), L-boronophenylalanine (BPA) and decahydrodecaborate (GB-10). Currently, only two compounds are used for clinical trials, namely BSH, and BPA (Figure 2) which were shown to be safe in humans.

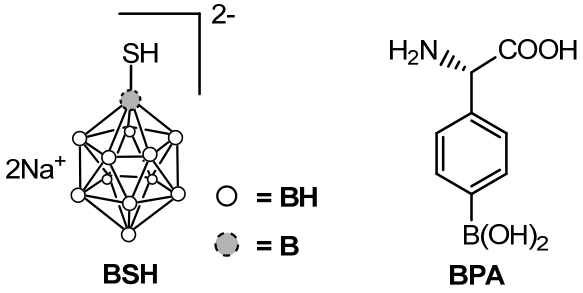


Figure 2. Structures of BSH and BPA.

BPA, administered as a fructose complex (BPA–F) to significantly increase its water solubility, entered into clinical use for the treatment of patients with high-grade gliomas, first in the United States and subsequently in Finland, Sweden, Holland, and Japan, and it subsequently became the drug of choice for clinical BNCT of patients with recurrent tumors of the head and neck region [12].

However, clinical results from the two compounds are not completely satisfactory, mainly because of their rapid clearance from blood and the significant variability in tumor uptake, especially in brain tumors. Both of them show low selectivity for cancer cells and short retention time, BPA being slightly better than BSH.

Therefore, combining all different conditions required for an efficient boron delivery agent for BNCT in a single compound has proven to be a difficult task. It should be noted that the development of efficient BNCT agents has significant differences with respect to a traditional chemotherapy drug or a tumor radiodiagnostic compound, the main problems being the significant amount of boron to be delivered to the tumor tissue which requires a large amount of compound to be administered, and the boron compound persistence within the tumor for a time sufficient to allow the treatment with contemporary clearance from normal tissues and blood.

For these reasons, despite the large number of compounds synthesized after BSH and BPA, only a part of them has been submitted to biological evaluation and none of them were promising enough to be considered for entering into the long and expensive route towards clinical approval. It should be useful to recall here that a reason which hampered the development of new BNCT agents was the lack of neutron sources other than nuclear reactors.

As stated before, the scenario is expected to change with the introduction of accelerators as neutron sources. However, the expected development of new agents for BNCT would require a high-throughput screening of the synthesized compounds to allow a quick selection of the most promising molecules at the beginning of their biological evaluation. Only compounds with established properties (e.g., non-toxic and with good cellular uptake) would pass to in vivo evaluation. Moreover, the translation of data obtained in an animal model to clinical biodistribution studies implies a series of conditions that are not easy to attain, particularly the huge investments required for Phase I clinical studies [9].

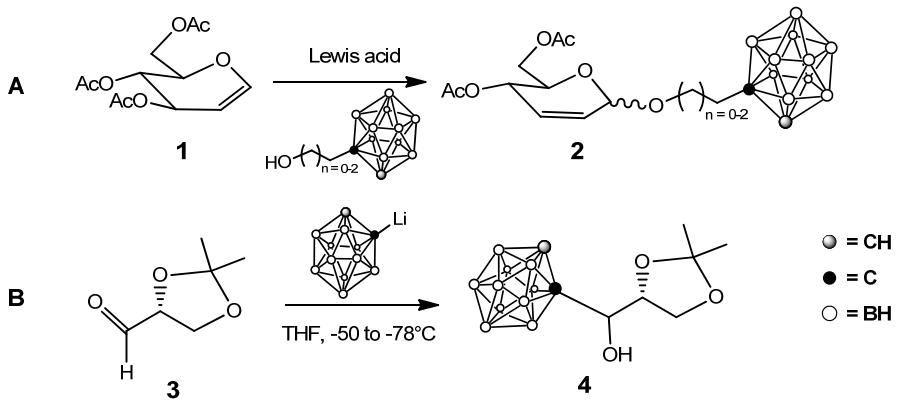
2. Boron-Containing Carbohydrate Derivatives: An Overview

Since their discovery, boron clusters have attracted great interest, forcing chemists to change the classical way to consider covalent bonds, although practical applications were not immediately perceived. The introduction of polyhedral borane anions [13], and their carborane analogs [14] contributed to reestablishing the interest in BNCT. The development of new compounds for BNCT mainly focused on carboranes and, to a lesser extent, on dodecaborate, essentially due to the high number of boron atoms delivered by each cluster-containing molecule. Three positional isomers of carboranes are possible, namely *ortho*-, *meta*- and *para*-carboranes (see e.g., [6] and ref cited therein). All these compounds are characterized by high hydrophobicity which increases in the order *o*-carborane > *m*-carborane > *p*-carborane. This feature, together with relatively easy access to *o*-carboranes,

explains why many studies on polyhedral boron-cluster-containing compounds for BNCT applications have been oriented towards *o*-carborane derivatives.

On the other hand, icosahedral dodecaborates are doubly charged and therefore they are water soluble, although the boron cage maintains a surprisingly high affinity for hydrophobic surfaces, attributed to the chaotropic effect [15]. The use of dodecaborates in the preparation of derivatives for BNCT emerged more recently with respect to carboranes, when an efficient strategy for their functionalization was introduced by the group of Bregadze [16].

A commonly employed strategy to improve the water solubility of *o*-carboranes is their conjugation with a highly water-soluble moiety. Among different classes of natural and synthetic compounds, carbohydrates attracted attention—although their use increased only in recent years, probably because classical carbohydrate chemistry and boron chemistry were traditionally two distinct "chemical worlds". The first examples of sugar-carborane conjugates exploited the so-called Ferrier rearrangement of glycals [17] and the reaction of lithiated carborane with protected aldehydo sugars (Scheme 1) [18], together with a few other approaches [19,20].



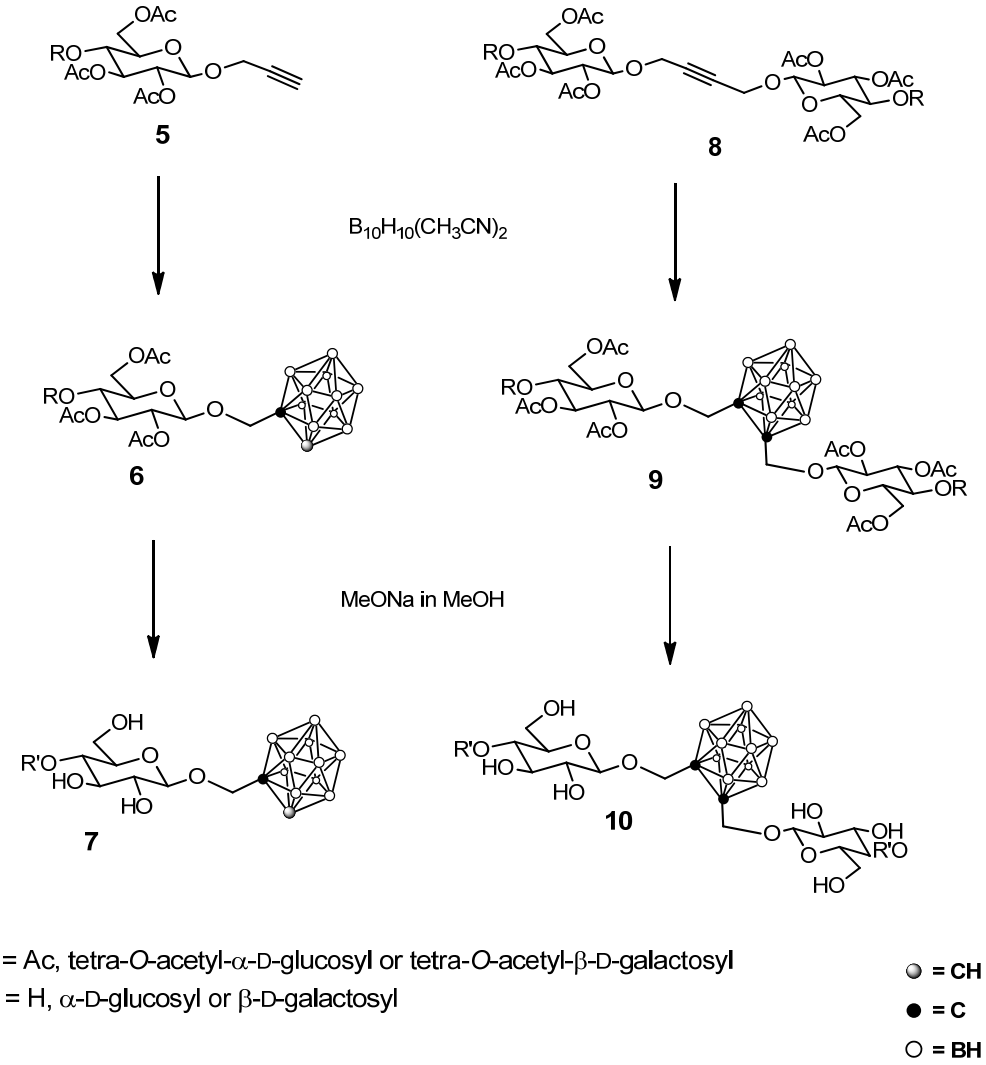
Scheme 1. First examples of sugar-carborane conjugates: (**A**): from glycals; (**B**): from aldehydo sugars.

At the end of the last century, mono- and bisglycosyl carboranes **7** and **10** were obtained [21,22] from the reaction of a decaborane–acetonitrile complex (6,9-bis-(acetonitrile) decaborane) with alkynyl glycosides **5** and **8**, which gave a stimulus towards the synthesis of boron-containing sugars (Scheme 2).

After these seminal studies, several sugar-containing boron clusters were described and some of them were submitted to physicochemical and biological characterization. Among them, glycosides of sugars other than D-glucose or lactose, C-glycosyl carboranes, carbohydrate-containing thioderivatives of carboranes, and conjugates through an amide bond were described (Figure 3) [23–29].

From these studies some preliminary general information was accessible, and this area expanded in the following years [30,31].

As previously stated, carboranes are highly hydrophobic and conjugation to sugars improves their solubility. It has been proven that at least two monosaccharidic units are required to allow water solubility of the compound [21]. It should be noted that when speaking about solubility, the nature of the obtained solution should be taken into account. Carboranes conjugated with a disaccharide have the propensity to act as a surfactant and to form micelles in solution, as demonstrated by their easy incorporation in liposomes [27], which could have negative effects on cell membranes. Moreover, the highly polar sugar part may hamper the compound to cross the blood–brain barrier; on the other hand, a proper choice of the sugar may exploit transport proteins such as GLUT1 to reach different body compartments.



Scheme 2. Some examples of glycosyl carborane synthesis.

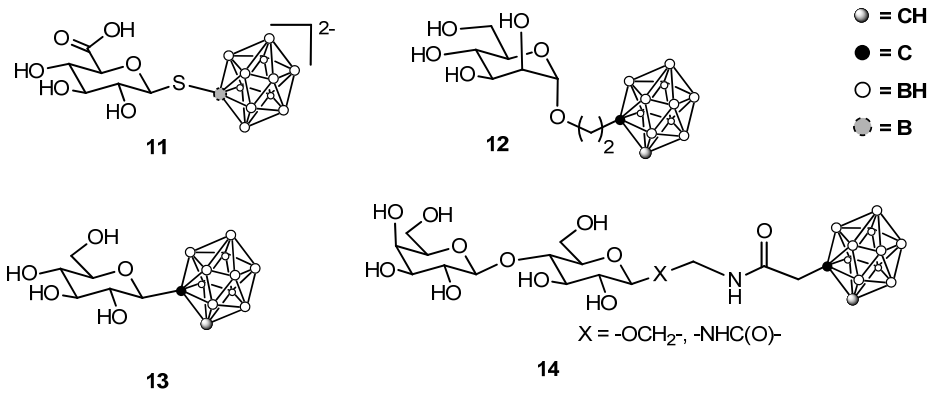


Figure 3. Some representative sugar-containing boron clusters.

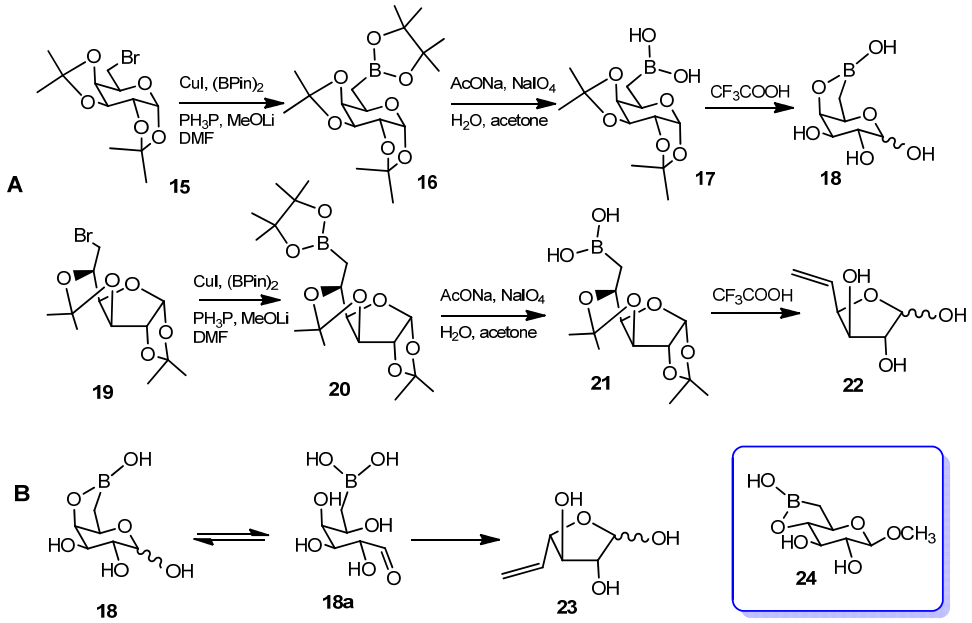
We will focus this review on the more recent advances in the synthesis of boron-containing sugars, as previous achievements have already been reviewed [30–32]. We will exclude nucleoside derivatives from the review as they have been recently reviewed [33].

3. Sugars and Boronic acids

3.1. Sugar-Containing Boronic Acids

As BPA is considered an analog of tyrosine by substitution of the hydroxyl group by a boronic acid, it could be conceivable to apply the same concept to sugars. Some recent publications have addressed this kind of compound and show that these compounds may present stability problems. In general, boronic acids can give degradation in some ways, the most relevant being oxidation, protodeboronation, or elimination reactions [34]. The stability of boronic acids seems to be highly dependent on the structural features of the whole molecule and a detailed description of the compatibility of boronic acids/esters with other functional groups has been reported [35].

In a first report, the boronic acid was introduced by substituting the hydroxyl group at position 6 of D-glucose and D-galactose with a boronic acid. 6-Bromo-6-deoxy sugars **15** and **19**, protected as isopropylidene acetals, were submitted to a copper(I)-catalyzed coupling reaction with bis(pinacolato)diboron, followed by a deprotection reaction (Scheme 3A).



Scheme 3. (**A**): Boronic acid analogs of D-galactose and D-glucose; (**B**): ring-opening and elimination reaction.

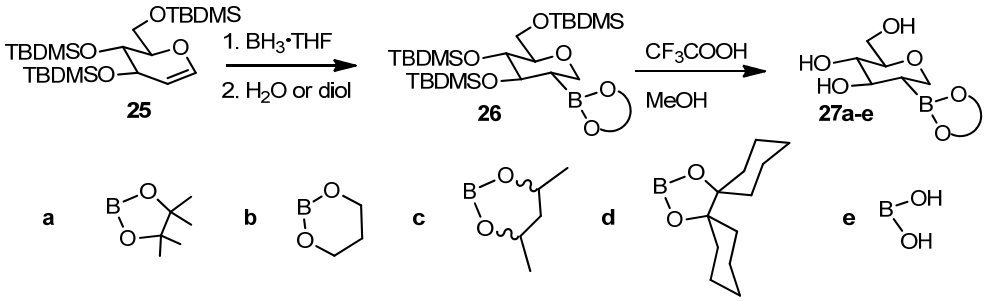
The final *galacto* analog **18** was demonstrated to be a cyclic boronic acid monoester by MS, which slowly decomposed in solution giving an elimination reaction through the opening of hemiacetal and boronic acid monoester (Scheme 3B).

The corresponding *gluco* derivative was not obtained due to a fast elimination reaction of the boronic acid with the adjacent hydroxyl group to give **23**. The stable derivative **24** (Scheme 3, box), obtained through a different synthetic pathway, was found to be stable with the anomeric position locked in methyl glucoside, thus avoiding the opening of the hemiacetalic ring. Boron acid was again present as a cyclic monoester with the hydroxy group at position 4.

In 2018, Aoki's group reported the synthesis and biological evaluation of 1,2-dideoxy-D-glucopyranos-2-ylboronic acid as shown in Scheme 4 [36].

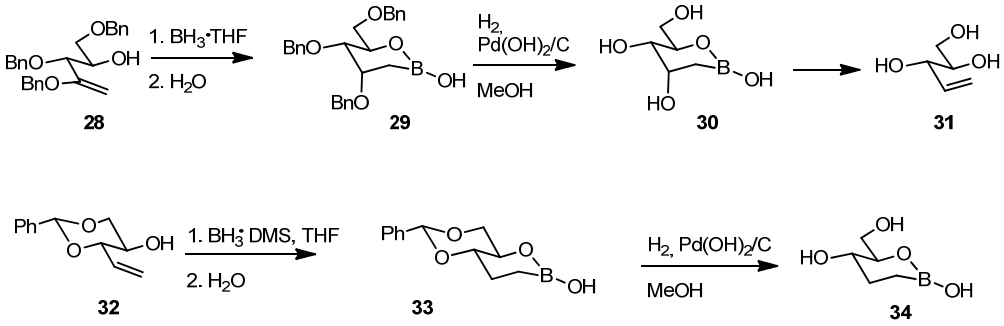
Toxicity and intracellular uptake of **27a–e** were evaluated under normal and hypoxic conditions. The most promising compounds **27a,d,e** were further investigated for the uptake, in comparison with BPA and BSH, either in the presence of a GLUT1 inhibitor or in competition with D-glucose. The results strongly suggest that absorption of these products is achieved through GLUT1. Finally, as it is known that D-glucose phosphorylation increases its retention inside the cells, compounds **27a** and **27e** were submitted to the reaction with ATP in the presence of hexokinase showing that, while **27a** was almost unreactive, **27e** was

slowly phosphorylated. All these results indicate that **27e** could be a lead compound for the development of other related derivatives with better performance.



Scheme 4. Synthesis of 2-borono-1,2-dideoxy-D-glucose analogs.

A further report on boronic acid analogs of monosaccharides describes the synthesis of the hexose analogs **30** and **34** [37] (Scheme 5) bearing the boron atom at the anomeric position. As already reported for other sugar boronic acids, compound **30** gave a slow elimination reaction to the alkenol **31**, while **34** was shown to be very stable.



Scheme 5. Synthesis of anomeric boronic acid analogs.

It is interesting to note that no elimination reaction, or other instability issues, was observed for compound **27e** (Scheme 4), despite the presence of the hydroxyl group adjacent to the boronic acid. The stability of **27e** can be attributed to the rigidity of the structure, which could hamper the β-elimination reaction, which probably requires a periplanar conformation. To summarize, it appears from literature data that β-hydroxyboronic acids are usually unstable, giving β-elimination reactions. The tendency to elimination is facilitated by either acidic or basic conditions but appears to require a coplanar arrangement of hydroxyl and boronic acid groups. On the other hand, the conversion of β-hydroxyl to a β-alkoxy group and/or the boronic acid to an ester increases stability.

To conclude, a breakthrough towards sugar boronic acids has been opened: these compounds clearly show stability issues, but the structural requirements to obtain stable compounds have been established, leaving the topic open for future work which may deserve further investigation.

3.2. Exploiting the Interaction between Sugar and Boronic Acids

It is well known for a long time that boric and boronic acids form quite stable complexes through the covalent boron–diol interaction, with the reversible formation of boronic esters between boronic acid and a sugar diol, the stability being dependent on many factors; e.g., [38,39]. Cyclic esters of boronic acids with a diol are stable enough to allow their use as protecting groups [40,41]. Recent developments and integration of boron chemistry with other techniques improved the binding affinity towards different targets, allowing the development of sensors for specific monosaccharides [42].

Within the context of BNCT, these interactions have been exploited in two different ways: on one side the interactions between nanoparticles bearing boronic acids with tumor

glycan structures were exploited for delivery; in another approach, the delivery was studied exploiting the interaction between a sugar-containing polymer and the BPA through the formation of cyclic boronic esters generating boron rich polymers.

According to the first approach, different boron-rich nanoparticles were obtained by reacting acrylamidophenylboronic acid with chitosan, dextran, or bovine serum albumin (BSA). These nanoparticles show relevant tumor-targeting ability due to the preferential interaction with sialic acid overexpressed in tumor glycans [43]. As an example, nanoparticles were generated from BSA and polyacrylamidophenylboronic, which demonstrated good tumor targeting and significant retention in tumors compared with nanoparticles without boronic acid. Additionally, nanoparticle sizes around 110 nm were observed to be optimal. Coating of the nanoparticles with polyethyleneimine-polyethylene glycol (PEI-PEG) copolymer and further decoration with cyclic Arg-Gly-Asp (cRGD) (Figure 4) significantly increased the circulation time of the particle and their accumulation at the tumor site on a murine hepatoma model [44].

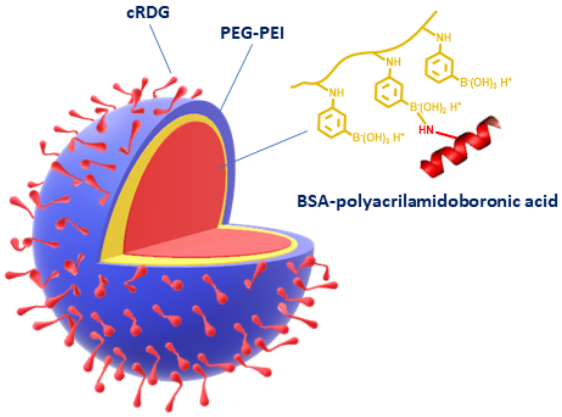


Figure 4. Nanoparticles based on boronic acid for sialic acid-targeting.

Following the second approach, the group developed a block copolymer of PEG-poly(L-lysine) (PEG-PK) decorated with D-fructose (Figure 5) [45]. The polymer was obtained by reaction of $MeOPegNH_2$ with *N*6-trifluoroacetyl-L-lysine *N*-carboxyanhydride, followed by deprotection of the ω-amino groups and their functionalization with 2,3:4,5-di-*O*-isopropylidene-β-D-fructopyranose through the formation of a carbamate by the action of carbonyldiimidazole (CDI). Exploiting the strong affinity of BPA for D-fructose, the polymer was loaded with BPA, assuming complete fructose derivatization (Figure 5A).

Part of the polymer was labeled with a fluorescent probe to study the subcellular distribution of the polymer. An extensive biological study including biodistribution, subcellular distribution, cellular uptake and retention, tumor uptake, and tumor biodistribution demonstrated that polymer is internalized by endocytosis mediated by Lat1 (L-amino acid transporter) (Figure 5B) and superior performance of polymer-bound BPA with respect to BPA-fructose. Among other observations, it was shown that BPA is released from the polymer within the cells and particularly close to lysosomes, due to the reversible nature of the complexation between BPA and fructose.

In a further example, sodium tetraborate was allowed to react with sodium hyaluronate in solid-state synthesis to form a borate complex, for which possible ways of coordination of borate with hyaluronic acid in the complex were proposed [46]. The complex was characterized by FT-IR and NMR spectroscopies. Although no biological data are presented, the complex has potential use as a BNCT agent exploiting the interaction between hyaluronic acid and its CD44 receptor.

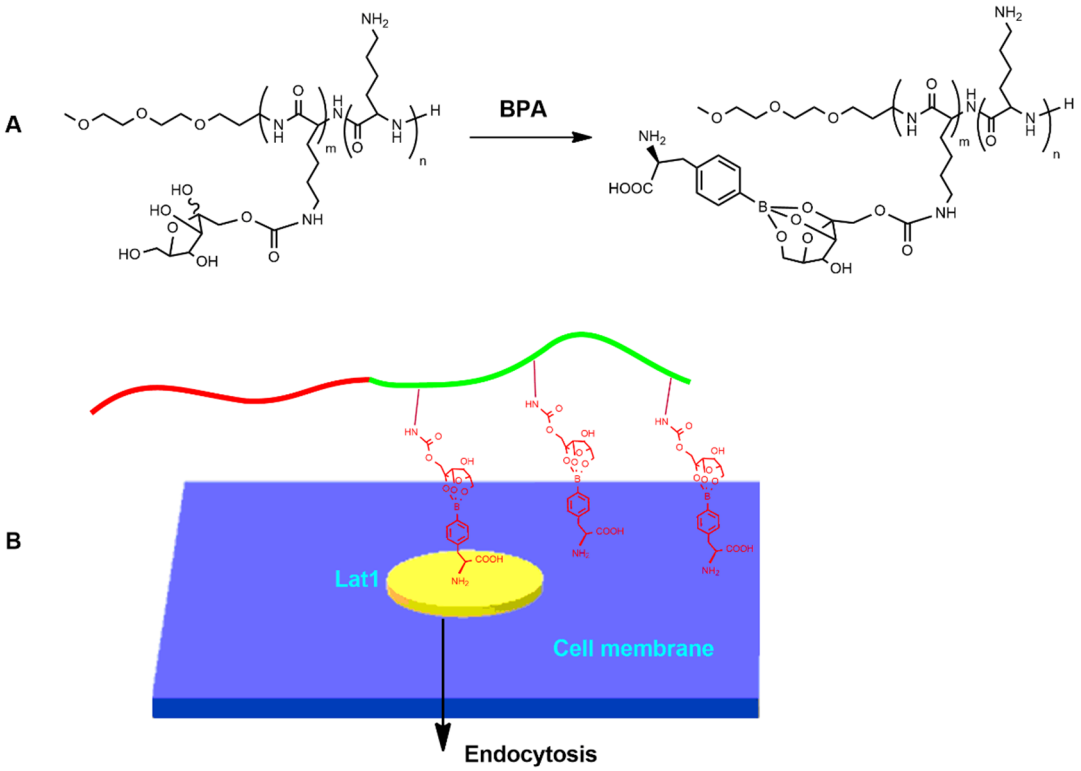


Figure 5. (**A**): Loading of the polymer with BPA; (**B**): internalization of the boronated polymer through Lat1.

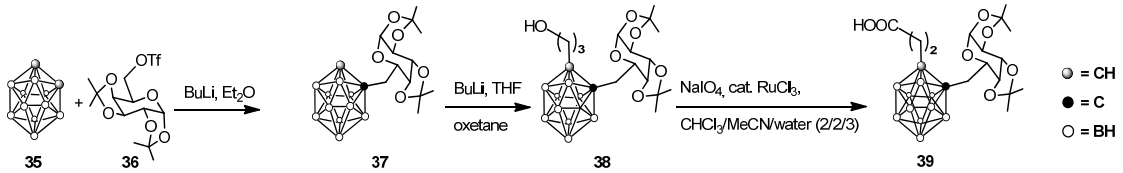
4. Sugars and Boron Clusters

4.1. Sugar-Conjugated Carboranes

As previously described, the interest in carboranes conjugated to sugars was raised at the end of the last century, and the research in this area is still lively. There are two main reasons to conjugate a carborane to sugars: carboranes are highly hydrophobic and the sugars have the role to give an adequate solubility to the compounds; moreover, the introduction of a sugar moiety would allow exploiting the D-glucose facilitative transporters (GLUTs), a family of sugar transporters. It is now well established that tumor cells switch their energy supply from the normal oxidation of D-glucose to less efficient aerobic glycolysis, even in the presence of oxygen and fully operative mitochondria. This process is known as the Warburg Effect [47].

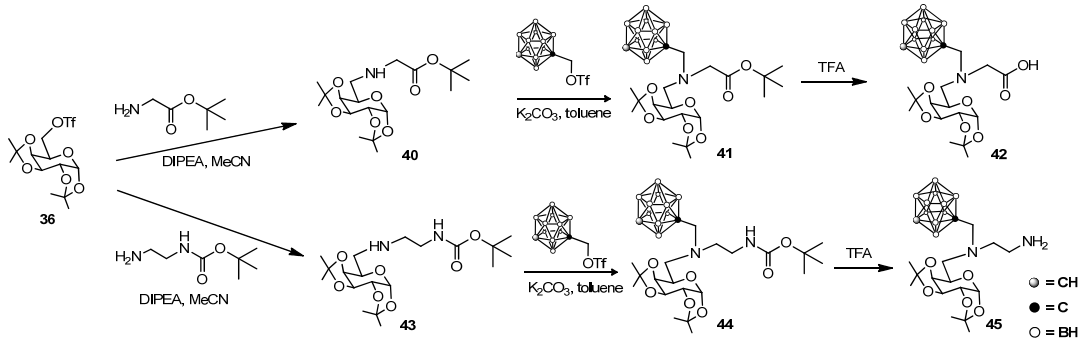
Increased rate of glycolysis is associated with increased uptake of D-glucose (and other sugars) by the tumor cells, and, as a consequence, with overexpression of GLUTs. This approach has already been exploited for cancer targeting and treatment by conjugation of sugars with chemotherapic drugs [48].

The group of Hey-Hawkins has been interested in the derivatization of dicarba-*closo*-dodecaboranes, ranging from glycosylphosphonates [49] to sugar-containing *ortho*-carbaborane-9-thiol, for a long time [50]. More recently, a building block containing galactose and an arm for peptide conjugation was described [51]. The reaction of lithiated *ortho*-carborane with bis-isopropylidene-protected α-D-galactopyranose 6-triflate **36** gave **37**. The installation of a propionyl appendage was obtained by lithiation of **37**, reaction with oxetane, and perruthenate oxidation. The carboxyl part can then be used for further conjugation (Scheme 6).



Scheme 6. Synthesis of a carborane-based building block.

It is interesting to note that although the silyl protection of ortho-carborane is usually used to guarantee monosubstitution, here the appropriate conditions for monoalkylation of unprotected ortho-carborane have been set. In an evolution of this approach, two building blocks for the conjugation of carboranes to biomolecules were described (Scheme 7). The reaction of α-D-galactopyranose 6-triflate **36** with glycine t-butyl ester or with mono-Boc-ethylenediamine gave derivatives **40** and **43**.



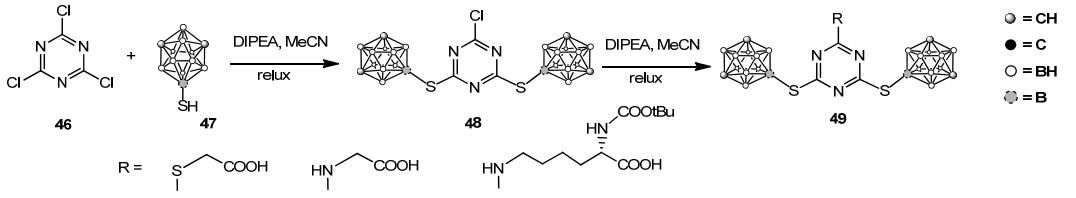
Scheme 7. Synthesis of sugar-carborane building blocks for peptides conjugation.

Alkylation of **40** and **43** with 1-(trifluoromethanesulfonylmethyl)-*meta*-carborane followed by removal of t-butyl groups eventually furnished carboxy- and amino-functionalized products **42** and **45**.

Compounds **42** and **45** were further derivatized with 7-amino-4-methylcoumarin and with folic acid, respectively, which are two selected biomolecules that play roles in cancer treatment [52].

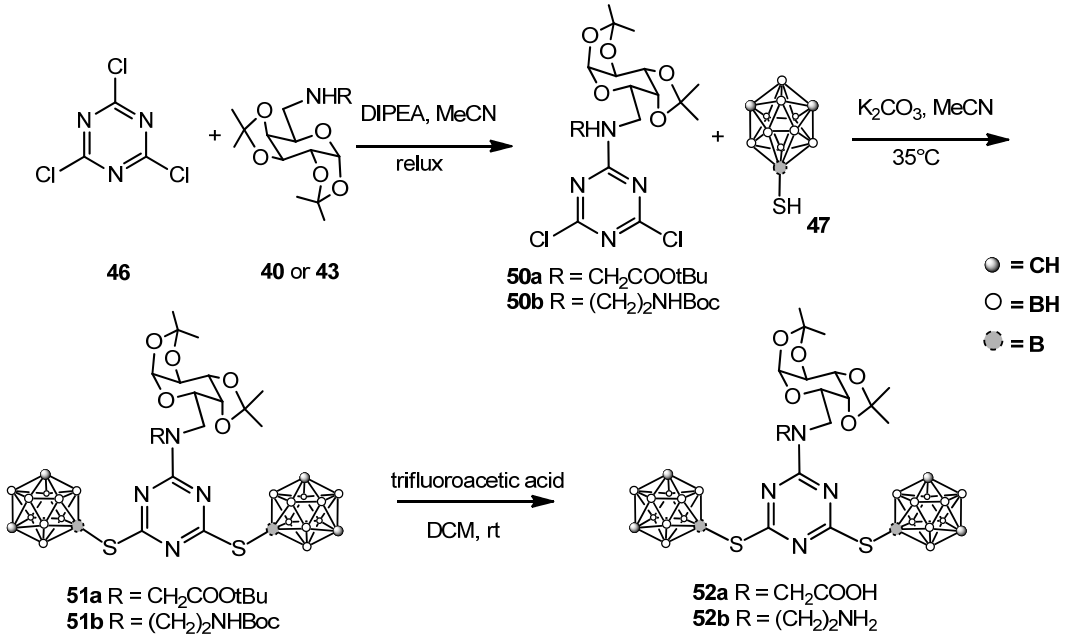
Starting from a previously proposed approach [53], the same group exploited cyanuric chloride **46** and 9-mercapto-*meta*-carborane **47**, which has a highly nucleophilic thiol group, as a platform to quickly generate compounds with chemical diversity and high boron loading.

After an initial demonstration of the synthetic feasibility, two units of 9-mercapto-*meta*-carborane and some simple nucleophiles (Scheme 8) were introduced on a triazine core [54].

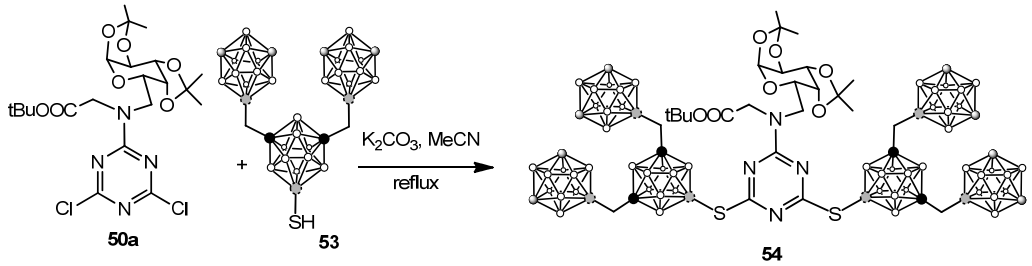


Scheme 8. Triazine-based building blocks.

More complex derivatives containing a galactose unit were obtained exploiting previously developed sugar-containing building blocks and 9-mercapto-*meta*-carborane **47** (Scheme 9) or a newly developed tris-cluster derivative **53** of **47** (Scheme 10) [55,56].



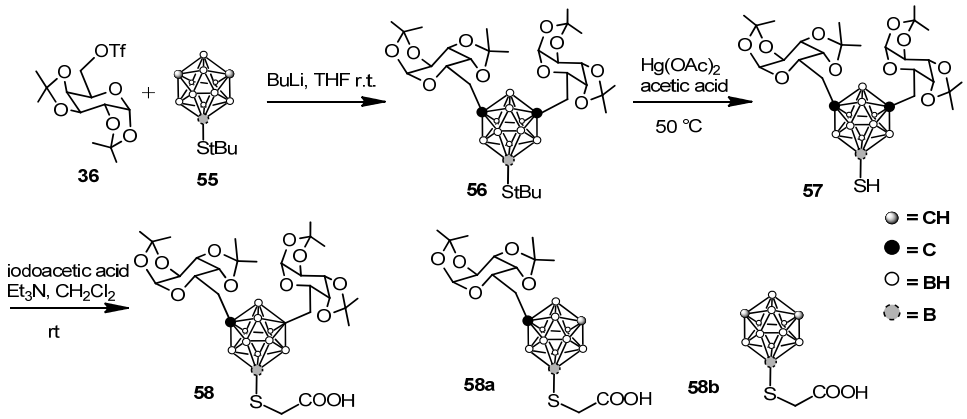
Scheme 9. Sugar-containing triazine-based building blocks.



Scheme 10. High boron loading sugar-containing triazine-based derivative.

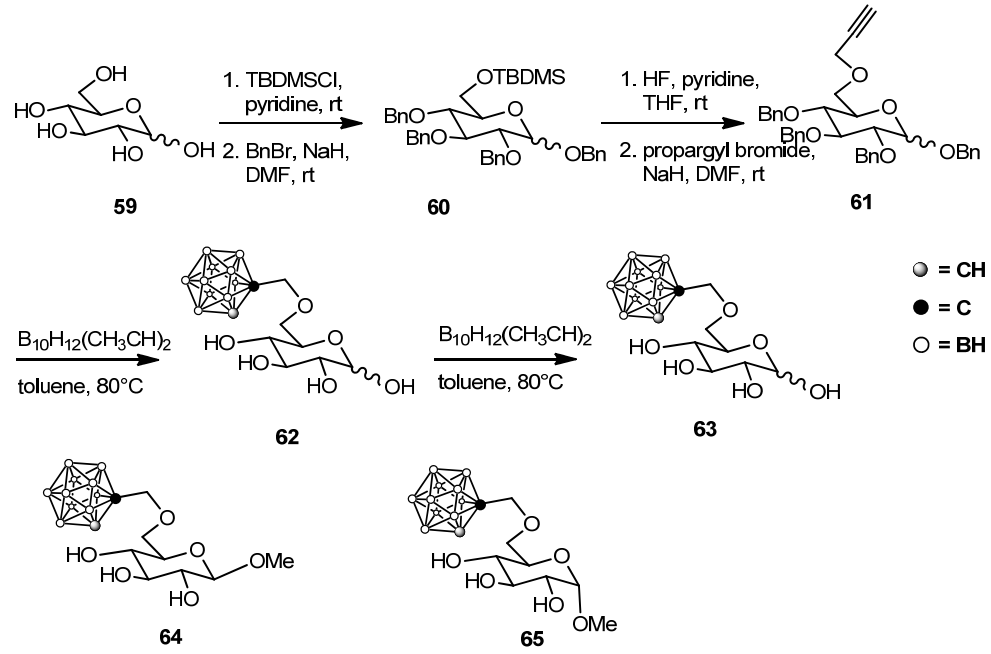
Compound **47** was also used as a scaffold and decorated with two galactosyl moieties and a carboxymethyl group which allowed the conjugation with neuropeptide Y (NPY), known to be recognized by tumor-overexpressed G protein-coupled receptor (GPCR) [57]. Compound **47** was protected as t-butyl thioether **55** then alkylated with galactosyl triflate **36** after deprotonation of the cage carbon atoms with n-butyllithium (Scheme 11). Thiol deprotection and alkylation with iodoacetic acid afforded **58**. Compounds **58a** and **58b** were obtained in an analogous way and were coupled to the lysines of NPY peptide by a combination of automated and manual solid-phase peptide synthesis (SPPS), generating a series of products with different boron loading and sugar content. The isopropylidene-protecting groups of galactose were removed during the final cleavage of the peptide from the resin.

The thus-obtained products showed an increased water solubility, increasing sugar moieties without affecting significantly the binding to the receptor. Moreover, the sugars prevented aggregation and prolonged the plasmatic life of the conjugate. From a preliminary screening, a selected conjugate containing 8 clusters and 16 galactose units was chosen for further study. It was not toxic and exhibited high selectivity for receptor subtypes and uptake into HEK293 and MCF7 cells. In particular, the conjugate showed selectivity for the hY_1R G-protein-coupled receptor subtype (EC50 18 nM) with respect to the hY_2R subtype (EC50 >1000 nM). Resazurin-based toxicity assay showed no toxicity on MCF7 cells for a concentration up to 10 μM for 48 h. HEK293 and MCF7 cells uptake was also studied by labeling the conjugate with TAMRA, demonstrating the internalization of the conjugate in cells expressing the hY_1R receptor (no boron quantification was given).



Scheme 11. Synthesis of the building blocks for NPY conjugation by SPPS.

In a similar work, a peptidic ligand for gastrin-releasing peptide receptor (GRPR) was decorated with the same building block **58** and similar results to those obtained using NPY. The most interesting aspect is the demonstration that the exchange of L-galactose for D-galactose prevents the uptake of the conjugate by liver cells uptake, which shows an even higher selectivity. This observation, together with the very low toxicity of the conjugate, is promising, as one of the issues of BNCT is the clearance of the boron agent by the liver and kidney. Usually, BPA is typically administered in a dose of 250–330 mg BPA/kg body weight, although higher doses have been used [58]. Compounds able to accumulate into the tumors and escape clearance can be administered in a lower dose, allowing the design of more complex compounds, as in the present case. When a compound is expected to require being administered in high doses, the simplest synthesis would be planned to avoid a prohibitively high cost of the boron agent. Following this approach, the group of Ekholm developed the synthesis of D-glucose derivatives bearing a carboranylmethyl substituent in position 6, as illustrated in Scheme 12 for compound **63**. Compounds **64** and **65** were obtained analogously [59]. The compounds showed low toxicity, high cellular uptake, and surprisingly, compound **63** had high water solubility, not only when compared with BPA but also compared to **64** and **65**.



Scheme 12. Synthesis of the carboranylmethyl-substituted D-glucose derivatives.

In fact, compound **63** was 500 times more soluble than compound **64**. Docking calculations and competition experiments between the glucoconjugates and [^{14}C]-D-glucose in the human CAL 27 cell line demonstrated that, at least for compounds **63** and **64**, the affinity for GLUT1 was in the μM range, in contrast to the low mM-affinity displayed by D-glucose, so it is expected that compounds **63** (and **64**, if solubility problems can be solved) can target GLUT1 in vivo, competing with free D-glucose. Finally, compounds **63–65** performed much better than BSH or BPA in cell-uptake studies. The exploration was further extended to D-glucose derivatives bearing the carboranylmethyl group in positions other than 6 [60]. The synthesized products are shown in Figure 6.

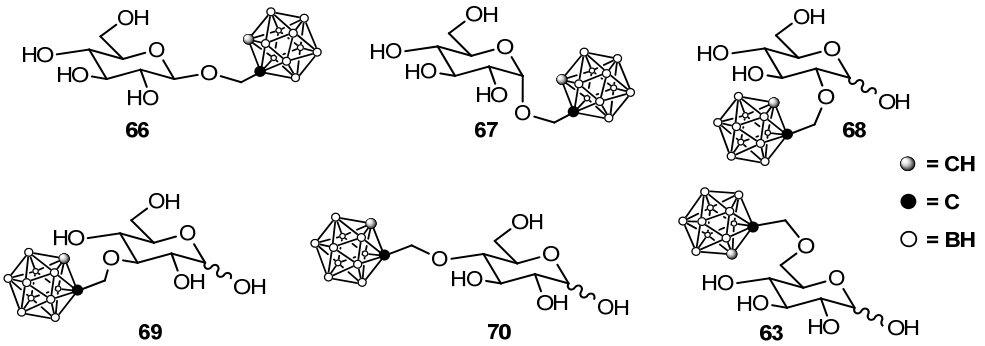


Figure 6. Carboranylmethyl D-glucose derivatives substituted on positions other than 6.

Affinity studies performed as described previously revealed that all the derivatives had better capability to target GLUT1 than D-glucose, with compounds **70** and the previously studied **63** as the best-performing products. However, studies on the cellular uptake revealed that compound **68** gave the highest accumulation in the CAL27 cell line. Another important point addressed by this study was the phosphorylation of this series of derivatives. It was demonstrated that any of the compounds were phosphorylated by human hexokinase. This result can be read in two ways: first, it can be deduced that these compounds do not enter in D-glucose metabolic pathways, thus diminishing the concern on possible interferences with regular glucose metabolism; on the other hand, as phosphorylation increases the retention of the compounds into the cells, it has to be demonstrated that these compounds have a retention time compatible with the therapy. Therefore, it is still too early to draw definite conclusions regarding the potential of these derivatives in vivo, but the results suggest progressing to the in vivo stage.

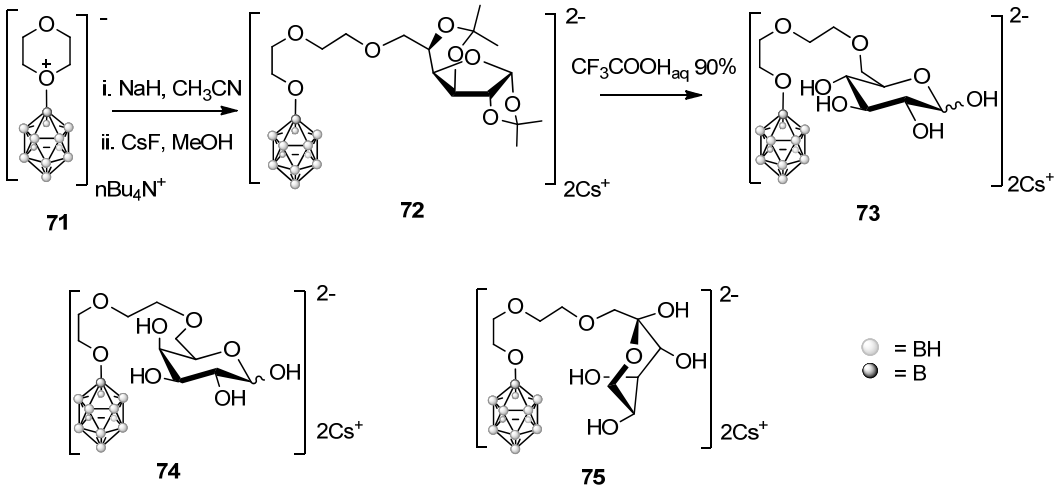
Apart from small molecules, *m*-carborane-containing self-assembled nanoparticles were also generated from a polyacrylate-polycaprolactone (PCL) block copolymer decorated with D-galactose units as targeting moiety and a near-infrared (NIR) cyanine dye at the PCL end [61]. MTT assay with HepG2 cancer cells that overexpress galactose receptors showing almost 100% viability at 250 μg/mLpolymer concentration after 3 days. Fluorescence imaging of the same HepG2 cells after 6 h of incubation showed evident fluorescence distributed in the cytoplasm confirming the endocytosis of the nanoparticle. In the absence of free D-galactose almost no endocytosis is observed, confirming the role of galactose receptors for internalization of the nanoparticles.

4.2. Sugar-Conjugated Dodecaborates

Some sugar derivatives containing dodecaborate clusters also appeared recently in the literature. A possible problem related to dodecaborate-sugar conjugates is the presence of a charge on the boron cluster, which can interfere with transport proteins.

Dodecaborate derivatives of D-glucose, D-galactose and D-fructose were obtained by reaction of isopropylidene protected sugars with the oxonium salt of *closo*-dodecaborate **71** [15] giving the desired conjugates **73–75** in good yields and a few synthetic steps (Scheme 13) [62]. The synthesis is illustrated for the preparation of compound **73**, the syntheses of **74** and **75** following the same scheme. It is interesting to note that when benzyl

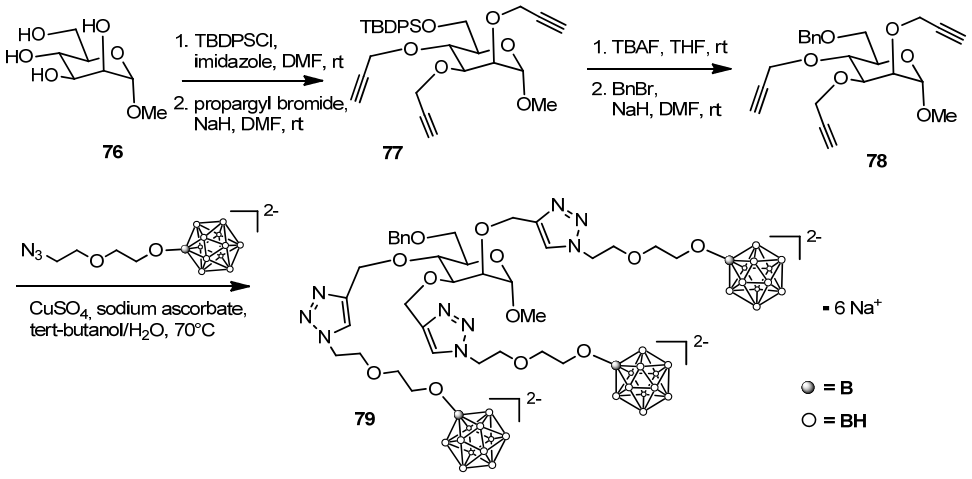
protecting groups were used instead of isopropylidene, it was not possible to remove them by standard hydrogenolysis.



Scheme 13. Synthesis of dodecaborate-derivatives of monosaccharides.

Compounds **73–75** showed no toxicity in human fibroblasts. Boron uptake was measured on the A549 lung cancer cell line but no significant uptake was measured. The reason for the absence of any uptake is not easy to explain. One reason could be because GLUTs are reluctant to transport charged sugar derivatives, although, in the present case, the charge is quite far from the sugar part. Further investigations would be required to better understand this point, such as the use of structurally similar but neutral analogs (e.g., compounds bearing a carborane instead of a dodecaborate) as well as the testing on other cell lines.

In a more recent example, D-mannose was used as a scaffold for the synthesis of derivatives containing three dodecaborate clusters (Scheme 14) [63].



Scheme 14. Synthesis of tri-dodecaborate-derivatives of D-mannose.

Starting from mannoside **76**, protection of the 6-OH and propargylation of the remaining hydroxyl groups gave intermediate **77.** The silyl group in position 6 of the mannose moiety was exchanged with a benzyl group or with a fluorescent probe (not shown) and the three propargyl groups submitted to a "click" reaction to give the final compound **79**. **79** (and its fluorescent analog) was extensively studied in vitro and in vivo, showing low toxicity, acceptable accumulation but high retention in tumor cells, although also the clearance from blood was quite slow. The mechanism of uptake and retention is not clear,

but it appears evident that it does not involve sugar transport proteins, as mannose, the core of the compound, is buried by all the dodecaborate clusters. The compound is interesting regardless and deserves further investigation.

Finally, a potential agent for BNCT was obtained from dextran by allylation of the polymer, reaction with BSH, and derivatization with an antibody against epidermal growth factor receptor 1 (anti-EGFR1 Fab) (Figure 7) [64].

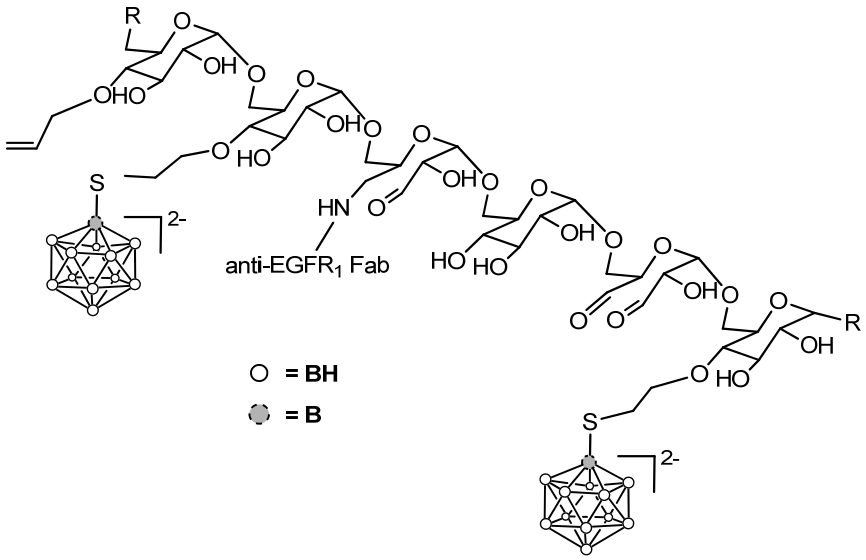


Figure 7. Boronated dextran conjugated with anti-EFGR1 antibody.

Some of the synthesized compounds with high boron loading gave interesting results in terms of internalization in vitro and of biodistribution in mice.

4.3. Sugars and Metallacarboranes

Metallacarboranes are molecular clusters consisting of carbon and boron atoms. They consist of two semi-cages of dicarbollide, each carrying two negative charges which "sandwich" a metallic cation. The remaining negative charge is displaced throughout the nanometric structure and is counterbalanced by a counter-ion (for example, see the chemical structure of COSAN $[Co(C_2B_9H_{11})_2]^-$) [65]. An octylglucopyranoside surfactant named C8G1 was chosen as the model because it self-assembles into the water and creates a hydrated glucose-based interface. The authors reported that COSAN strongly interacts with C8G1 to form mixed aggregates in equilibrium [66]. COSAN derivatives have shown some surfactant properties, associated with a more hydrophobic feature that provides the ability to cross biological membranes, opening up opportunities in the pharmaceutical field, including BNCT.

COSAN derivatives are also capable of strongly binding CDs, specifically β-CDs and γ-CDs. Their encapsulation showed significant alterations of photophysical and electrochemical properties, allowing the translocation of several COSAN derivatives through lipid bilayer membranes [67].

5. Conclusions

With the availability of several accelerators for BNCT which will increase the number and the reliability of the clinical trials, the need for better boron-delivery agents is becoming more urgent. Although many problems are well known which could hamper the development of these agents, the research in this field is still active and will increase in the future. As with many other conventional antitumor drugs, and for BNCT, predictably there will not be a universal boron carrier, but more compounds will probably be needed for the treatment of different tumors.

Among the many classes of compounds that can be exploited as boron carriers for BNCT, carbohydrate-containing boron agents are a category that is strongly stimulating the research in this field. On the one hand, the hydrophilic character of sugars guarantees an increase in the solubility of the caborane clusters. On the other hand, they can be exploited to target the agent towards tumors that overexpress GLUT proteins. The relevant amount of activity in the use of carbohydrates within the development of boron carriers for BNCT, together with the promising results obtained in many cases and the learning from failure in others, should stimulate further activity in the field and help to drive the research towards the most promising derivatives. We are expecting that an increasing amount of data from in vitro and in vivo studies will help to focus the research towards more promising compounds to make BNCT a routine cancer treatment modality.

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