NEW DEVELOPMENTS IN THE MEDICINAL CHEMISTRY OF CARBORANES

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Dedicated to Professor Bohumil Štíbr on the occasion of his 70th birthday.

The advancements in the synthetic chemistry of carboranes and metallacarboranes have given rise to diversified uses in medicinal chemistry, resulting in many new medical applications. An overview of the medicinal chemistry of carboranes is presented emphasizing the use of nanoparticles, dendrimers, porphyrins and carbohydrates as boron carriers. A review with 80 references.

Keywords: Carboranes; Metallacarboranes; Medicinal chemistry; Nanoparticles; Dendrimers; Porphyrins; Carbohydrates.

Carboranes are electron delocalized clusters that contain both boron and carbon atoms. Icosahedral dicarbaboranes ($C_2B_{10}H_{12}$) are the most commonly encountered carborane clusters. As can be seen in Fig. 1, there are three isomers, 1,2-$C_2B_{10}H_{12}$ (*ortho*-), 1,7-$C_2B_{10}H_{12}$ (*meta*-) and 1,12-$C_2B_{10}H_{12}$ (*para*-); all of which are commercially available. All the three icosahedral carboranes are chemically and thermally very stable. In general, the *ortho*-carborane derivatives can be prepared from the reaction of decaborane with various acetylenes; the corresponding *meta* and *para* isomers can be obtained via thermal isomerization of the respective *ortho*-carboranes. The hydrogens attached to the cage carbons of the carboranes are acidic and can be removed by reaction with strong bases, which allows further derivatization of the clusters. Similarly, these icosahedral carboranes having electron rich boron atoms can also be functionalized by Lewis acid catalyzed

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Friedel–Craft type reactions. These factors combine to make icosahedral carboranes attractive building blocks in the areas of material science, medicine and catalysis[2].

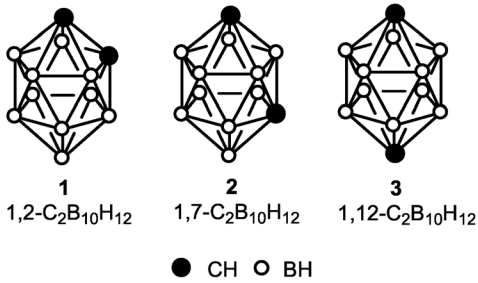


FIG. 1
Icosahedral carboranes

Over the last two decades, icosahedral carboranes have been widely used in the medicinal chemistry research because of their high boron content and stability to catabolism. The medicinal chemistry involving carboranes are mainly focused on the treatment of cancer via boron neutron capture therapy (BNCT). This is a bimodal treatment which involves a cancer specific boron drug and a beam of low energy (thermal) neutrons of sufficient intensity for neutron capture to take place within the treated tissues[2]. The boron neutron capture reaction, $^{10}B(n,\alpha)^{7}Li$, involves a ^{10}B atom capturing a thermal neutron giving an excited ^{11}B that undergoes a rapid fission reaction producing high energy $^{4}He^{2+}$ (α-particle) and $^{7}Li^{3+}$ ions (Fig. 2, Eqs (1) and (2)); this was first characterized in 1935, shortly after the discovery of the neutron[3]. The neutron capture cross-section of ^{10}B is 3838 barn, which is orders of magnitude higher than the normal constituent atoms of the tissue. The therapeutic dose of ^{10}B required to kill a cancer cell is ~10^9 atoms per cell. An important requirement for an effective BNCT therefore depends on selectively directing the requisite concentrations of ^{10}B to the cancerous

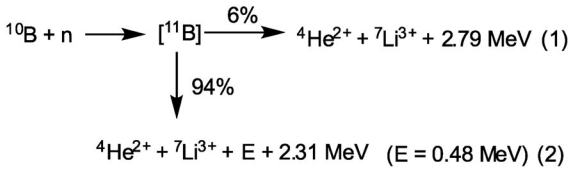


FIG. 2
The boron-neutron capture reactions

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[4].

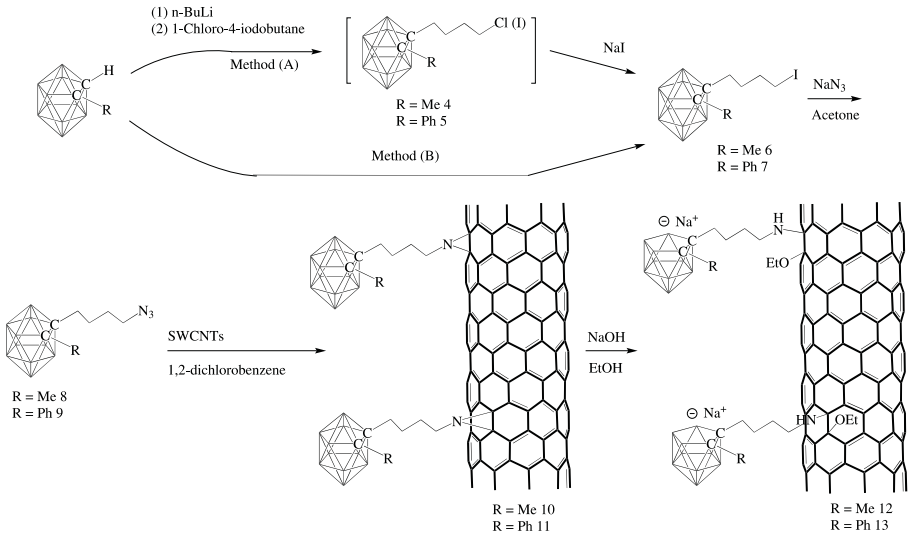
Although BNCT has always been closely associated with the treatment of fatal malignant brain cancers such as glioblastoma multiforme[5], now it is being extended to the treatment of melanoma[6], and head and neck cancer[7]. Boron neutron capture synovectomy (BNCS) can also be useful for treatment of rheumatoid arthritis[8]. The other medicinal applications of carboranes include imaging and as pharmacophores[2a]. There are a number of reviews available on the medicinal chemistry of carboranes and the rapidly growing applications of carboranes in the medicinal chemistry[9]. In this review we will focus on some of the newest boron drug delivery platforms as well as some other emerging areas in medicinal chemistry.

Carborane-Appended Nanoparticles

Nanomaterials of appropriate dimension can be used as effective drug delivery vehicles[10]. Nanoparticles can also be functionalized to accommodate multiple boron atoms and, therefore, can be administered at a relatively lower dose for effective BNCT. Therefore, syntheses of nanomaterials-based BNCT agents have received significant attention[11]. Nanomaterials-based drug vehicles generally show low cytotoxicity in the normal cells and can penetrate neoplastic cell membranes through capillaries into rapidly dividing tumor cells[12]. Such materials are also found to have favorable interaction with the brain blood vessel endothelial cells of mice[13] and so boron-containing nanomaterials have the potential to be effective BNCT agents. It has been found that liposomes with diameters > 50 nm have difficulty to penetrate the blood brain barrier (BBB)[14], thus the optimum dimension of the nanoparticles as drug delivery vehicles is also an important issue that needs to be considered. Some of the recent developments on the use of carbon nanotubes (CNTs) and magnetic nanoparticles as potential boron delivery platforms will be described in this section.

Since their discovery in 1991 [15], CNTs have been a very useful research commodity and have found a number of diverse applications[16]. The carbon nanotube is a cylindrical shaped allotrope of carbon and can be further classified into two categories, single-wall (SW) and multi-wall (MW) species. The CNTs possess a unique ability of being able to enter various cells with-

out showing any deleterious toxic side effects. For example, it has been reported that peptide-functionalized single-walled carbon nanotubes (SWCNTs) could pass through cell membranes and accumulate in the cytoplasm of 3T6, 3T3 fibroblasts and phagocytic cells, without showing cytotoxicity or inflicting other damage to the cell[17]. Similar results were obtained in HL60 cells, where it was found that functionalized SWCNTs can help transport large attached groups into cells without exhibiting cell cytotoxicity[18]. *In vitro* studies of folic acid and fluorescent tag-conjugated SWCNTs have also shown them to be effective in targeting HeLa cells, which are believed to stem from cervical cancer[19]. There are also reports on enhanced water solubility of CNTs through side-wall derivation with biologically important moieties[20]. These factors motivated us to explore the feasibility of using carborane-appended SWCNTs as boron delivery agents for use in BNCT [21]. *Nido*-carborane units were successfully attached to the side walls of single-wall carbon nanotubes to produce high boron content, water-soluble SWCNTs (Scheme 1)[21]. These were then used to treat mice bearing the EMT6 tumor cells, a mammary carcinoma. A favorable tumor-to-blood ratio of 3.12 and a boron concentration of 21.5 μg/g tumor were obtained after 48 h of administration. In addition, it was observed that retention in tumor tissue was higher than in the blood and other tissues in-



SCHEME 1
Syntheses of substituted carborane-appended SWCNTs

cluding lung, liver and spleen, which is favorable for BNCT. The low boron concentration in the other tissues shows that there is a preferential uptake by the tumor cells with a long retention time of over 48 h (Fig. 3). This is the most important requirement of a successful BNCT drug[21]. In addition to

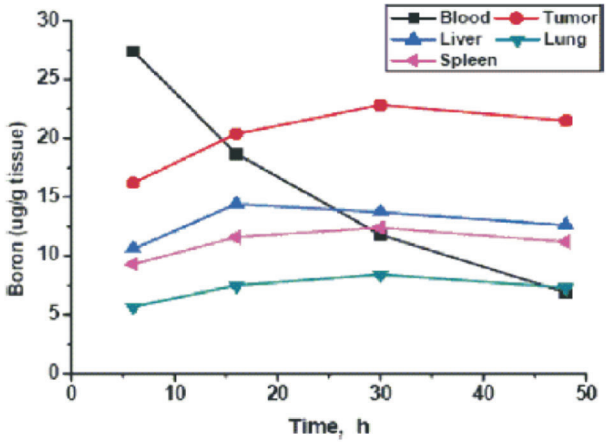


FIG. 3
Distributions of boron by **12** in saline in different tissues

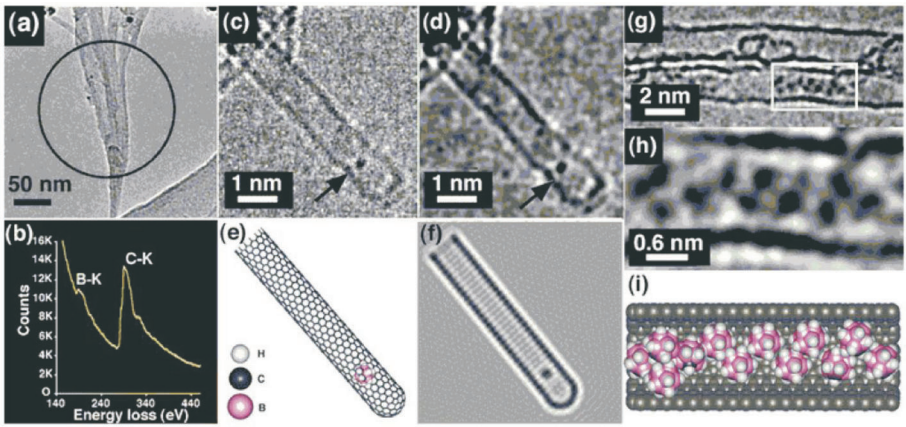


FIG. 4
a Low magnification HRTEM image of several bundles of SWNTs treated with *o*-carborane; b EELS spectrum obtained from indicated region in a; c and d HRTEM image and noise-filtered image of a discrete *o*-carborane molecule within the tip of a capped 1.2 nm diameter SWNT; e and f structure model and Scherzer focus simulation of a single *o*-carborane molecule within a SWNT tip; g and h HRTEM image obtained from a short chain of *o*-carborane molecules formed within a 1.6 nm diameter SWNT; i schematic representation of nanostructure in h

side wall attachments, it is also possible to encapsulate boron carriers in the empty cavities of CNTs [22]. Reportedly, *ortho*-carboranes were successfully encapsulated inside SWCNTs (Fig. 4)[23] which could be potentially useful as an effective carrier for BNCT treatment. To summarize, the use of CNTs in the next generation of BNCT drug delivery systems may improve the effectiveness of BNCT treatment and undesirable side effects could be reduced using CNTs as drug delivery agents. However, the long-term toxicity of carbon nanotubes needs to be completely assessed.

Recent literatures revealed functionalized boron-based nanomaterials such as boron nitride and boron carbide nanoparticles can also be useful as a boron source in BNCT [24]. Boron nanotube (BNT) could also be useful for BNCT. Rod and spherical boron nanoparticles were recently synthesized in our laboratory from non-toxic boron oxide powders ultrasonically smelted in liquid lithium (Fig. 5a)[25]. The first report on synthesis of single-wall boron nanotubes was made by Ciuparu et al.[26], and they managed to produce nanotubes with diameters of 3 nm and lengths of 16 nm (Fig. 5b). The boron nanotubes can lead to the creation of a series of other boron nanostructures, such as boron nanoribbons (Fig. 5c)[27] and nanowires (Fig. 5d)[28]. Study by Kuntsmann et al.[29] found new forms of radially constricted, single-wall, zigzag boron nanotubes which may serve as intermediates in the formation of an ideal nanotubular system. Although boron nanotubes can be potentially useful as boron drug delivery agents, issues such as large scale synthesis, development of strategies to functionalize boron nanotubes as well as to make them water soluble needs to be first addressed. Presently, most of the research work is focused on uncovering the characteristics of boron nanotubes and coming up with probable applications[30].

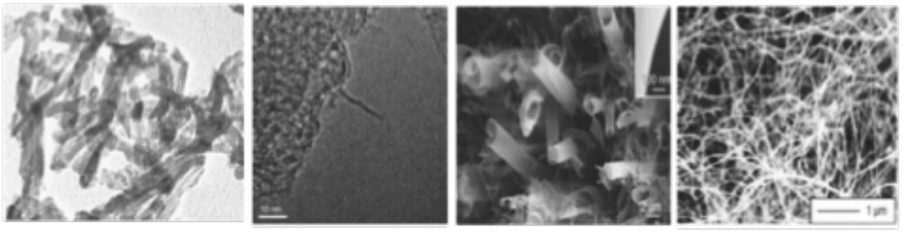
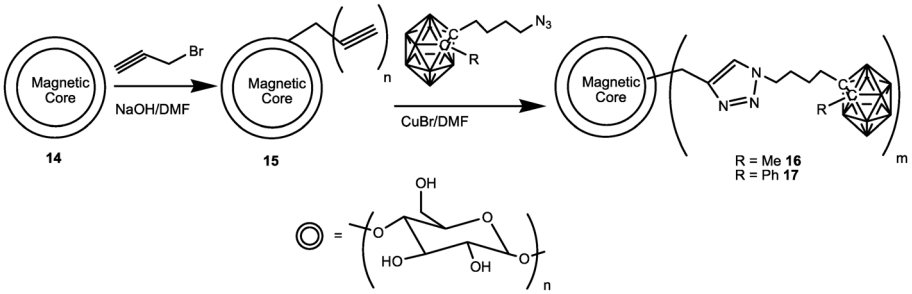


FIG. 5
a TEM image of boron nanotubes; SEM images of b boron nanotubes, c boron nanoribbons, and d boron nanowires

Biological and medicinal applications of magnetic nanoparticles (MNPs) in targeted drug delivery, thermotherapy of cancer and in magnetic resonance imaging (MRI) has shown promising results[31]. In magnetically targeted therapy, a drug is attached to a biocompatible magnetic nanoparticle carrier, and then it is injected into the patient in the form of ferrofluid. These particles are then directed to the target site within the body using an external magnetic field[31a]. The major advantage of this methodology is a smaller amount of the cytotoxic drugs which in turn reduces the associated side effects. This technique has also been examined as a means to target cytotoxic drugs to brain tumors. Studies have demonstrated that particles from a size of 10–20 nm to as large as 1–2 μm could be useful for this method[32].

Preliminary results on the synthesis of encapsulated magnetic nanocomposites with a high load of carborane cages along with their biodistrubutions was recently reported[33]. Commercially available magnetic nanoparticles of iron oxides matrixed with starch were enriched with the carborane cages, 1-R-2-butyl-*ortho*-$C_2B_{10}H_{10}$ (R = Me, **16**; Ph, **17**), using the click reaction[34]. Starch modified magnetic nanoparticles were first functionalized with alkyne moieties by reactions of free hydroxyl groups in starch with propargyl bromide, followed by the attachment of carborane azides via the Click reactions (Scheme 2)[33]. IR and ICP-OES analysis of the resulting nanocomposites confirmed the incorporation of carborane clusters. Tissue distribution studies of **16**, in Scheme 2, were then conducted in a mixed solution of DMSO/saline (v/v = 1/10) in mice. The boron concentrations in tumor reached a high value of 51.4 μg/g tumor with tumor/normal tissue ratios of around 10:1 in the presence of an external magnetic field (Fig. 6). Such high concentration of boron was maintained even after 48 h which is very essential for a successful BNCT[33].



SCHEME 2
Synthesis of carborane-containing encapsulated magnetic nanocomposites

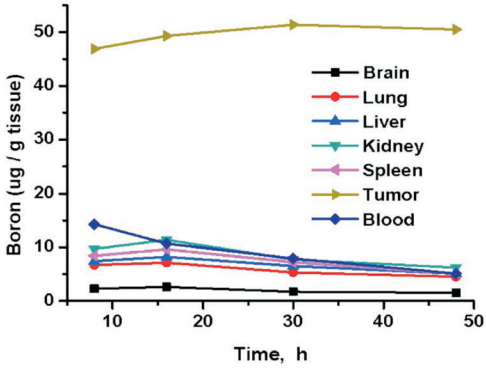


FIG. 6
Boron tissue distribution of **16** with external magnet

Carborane-Containing Dendritic Molecules

Dendrimers are globular macromolecules that have distinct structural features such as a symmetrical core, layers of branching units and surface groups. Dendritic macromolecules are conventionally synthesized by either a convergent approach, in which the growth of the dendrimer starts from the exterior and progresses inward to a core, or a divergent one that starts from the core and builds outward[35]. Dendritic macromolecules find a number of applications in biology and medicine[36]. Because of their high water solubility, monodisperse size, and uniform composition dendrimers are suitable candidates for the delivery of anticancer drugs and imaging agents[37]. Because of the dendrimer unique branching architecture and high number of surface functional groups, it can carry large payloads of therapeutic molecules to the cancer cells. Cellular uptake of dendrimers-based drug delivery systems has been proved to be significantly higher than found for linear polymeric carriers. Due to the leaky vasculature of tumor tissues, macromolecular and dendrimers-based drug delivery systems are preferentially transported to the tumor tissues and accumulate in them in a process known as the enhanced permeability and retention (EPR) effect[36a,38]. Therefore, incorporation of carboranes into dendritic macromolecules could be a viable approach for the delivery of boron to the tumor tissues. It has been estimated that a concentration of 30 μg of ^{10}B per gram tissue is necessary for effective BNCT [21]; this is a relatively high concentration and can be achieved using dendritic molecules containing multiple carborane clusters.

A water-soluble polysulfate carborane dendrimer **18** containing twelve *ortho*-carborane clusters (Fig. 7), was synthesized from its second generation polyalkyne dendrimer precursor by reaction with decaborane ($B_{10}H_{14}$). The water solubility imparting sulfate moieties were introduced by the reaction of the precursor carborane polyol compound with chlorosulfonic acid (Fig. 7). Polyamidoamine (PAMAM) dendrimer, which is designed to have a water-soluble backbone, is frequently used in drug delivery[39]. The PAMAM dendrimers are also biocompatible and nonimmunogenic with surface amine groups that can be easily modified to bind various molecules. Tumor boron concentrations of ~20 μg/g tumor in rats bearing the implants of the F98 glioma was achieved when a boron-containing PAMAM dendrimer was targeted at the epidermal growth factor receptor (EGFR)[40]. Other research groups have also used PAMAM based dendrimers for BNCT applications[41]. Parrot et al.[42] have synthesized aliphatic polyester dendrimers containing 16 carborane cages which could potentially be useful in BNCT.

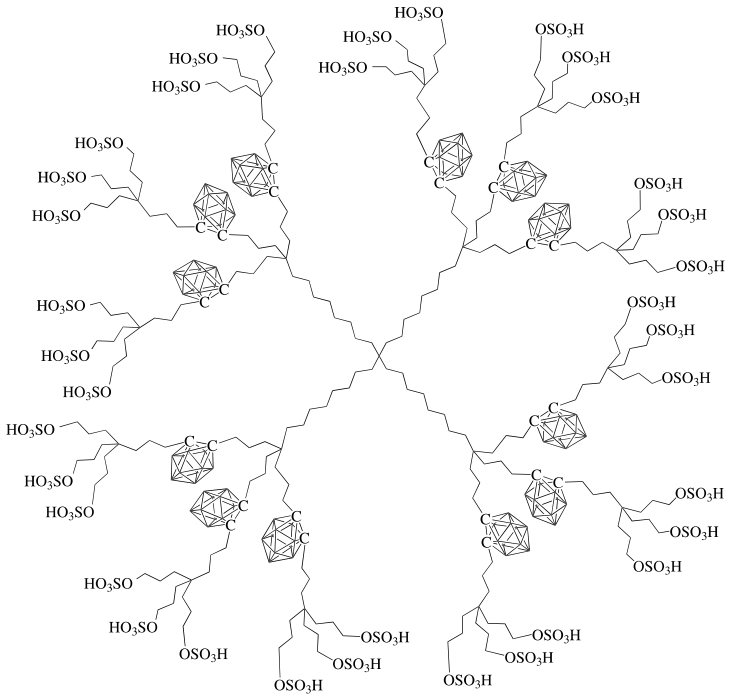


FIG. 7
Water-soluble polysulfate carborane dendrimer

Synthesis of carboranyl-carbosilane dendrimers in which *ortho*-carborane derivatives are bonded to the silicon atom through a propyl spacer has been reported (Fig. 8). In this case, the dendrimers **19** and **20** containing four and eight peripheral *ortho*-carborane clusters, respectively, were synthesized from their corresponding dendritic cores using a sequence of alkenylation, hydrosilylation and reduction reactions. The *ortho*-carborane clusters were then decapitated leading to highly charged water-soluble derivatives[43]. A number of other macromolecular boron-rich compounds were also synthesized by the same group[44].

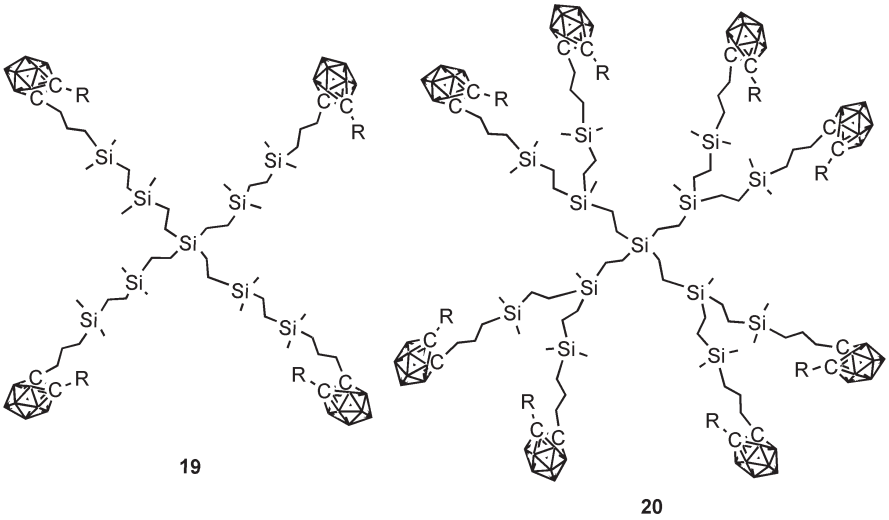
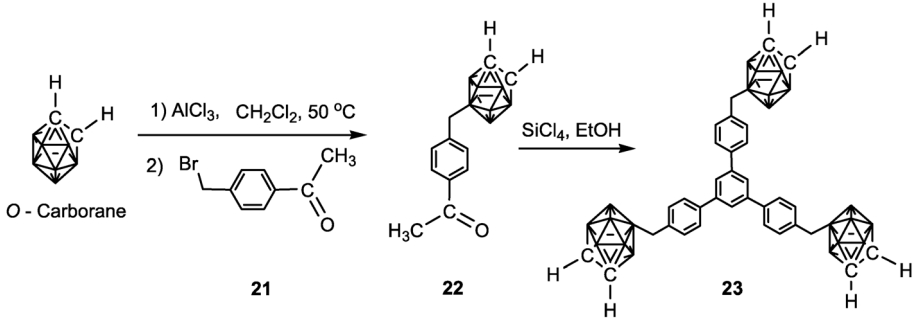


FIG. 8
Carbosilane dendrimers containing *o*-carboranes

Ortho-carborane clusters can be functionalized at both the boron and carbon atoms of the cages. Selective functionalization of *ortho*-carborane clusters can be achieved at the B(9) boron atom via electrophilic alkylation with alkyl halides and benzyl halides that contain electron withdrawing substituents such as NO_2, COOH, COOMe, and COPh [45]. We have synthesized the benzyl derivatives of the *ortho*-carborane (with benzylation at the B(9) position) containing an ethanone group on the benzene ring, as shown in Scheme 3.

Electrophilic benzylation of the *ortho*-carborane and its derivatives was obtained by refluxing a mixture of 1-[4-(bromomethyl)phenyl]ethanone (**21**) and *ortho*-carborane in dichloromethane in the presence of aluminum chloride that led to the formation of the B(9) substituted ketone **22**, which underwent facile trimerization with silicon tetrachloride and ethanol

to produce B_{cage} appended trimer **23** (Scheme 3). Functionalization of the acidic carborane protons of trimer **23** with 1-iodoheptane or trivinyl chlorosilane via its lithium salts was also possible, generating dendritic structured macromolecules[46].



SCHEME 3
Synthesis of the B_{cage}-appended symmetrical trimer

A series of C_3-symmetric C_{cage}-appended π-conjugated compounds containing three (**24–26**) to six (**27** and **28**) *ortho*-carborane clusters has also been synthesized by employing palladium catalyzed Suzuki coupling reactions, palladium catalyzed acetylation reactions followed by silicon tetrachloride mediated trimerization reactions (Fig. 9). Carborane-appended extended trimers (**25**, **26** and **28**) were found to be blue light emitting. A 22–70% enhancement of relative fluorescence quantum yields of carborane substituted extended π-conjugated compounds (**25** and **28**) was observed compared to the unsubstituted extended π-conjugated core. Decapitation of *ortho*-carborane clusters in methanolic sodium hydroxide solution led to the formation of highly charged *nido*-carborane-appended trimers (**29–33**) which were found to be water soluble. The water-soluble extended trimers (**30**, **31** and **33**) were also found to be fluorescent in water but with a reduced fluorescence intensity (Fig. 9). Such water-soluble fluorescent compounds may find some biological applications. These π-conjugated compounds containing multiple carborane clusters were found to be extremely thermally stable. It was also found that the addition of more *ortho*-carborane clusters to the π-conjugated systems increased their thermal stability[47].

After the synthesis of the cobaltabis(dicarbollide) anion, [3,3′-Co-(1,2-$C_2B_9H_{11}$)$_2$]$^-$, was reported by the Hawthorne research group[48], its high thermal and chemical stability has made it one of the most widely used

metallacarborane[49] in synthetic chemistry[50]. The synthesis of the zwitterionic oxonium derivative of the cobaltabis(dicarbollide) anion, [3,3′-Co-(8-$C_4H_8O_2$-1,2-$C_2B_9H_{10}$)(1′,2′-$C_2B_9H_{11}$)], ushered in a new area of research on the synthetic chemistry of monosubstituted cobaltacarborane complexes[51]. This compound has been shown to undergo dioxane ring opening reactions in the presence of a variety of nucleophilic reagents, such as fluoride, chloride and hydroxide anions, imide, cyanide and amines[52]. Recently, there are reports on the synthesis of dendritic macromolecules that contain multiple cobaltabis(dicarbollide) clusters. These dendritic molecules were synthesized employing hydrosilylation reactions with the

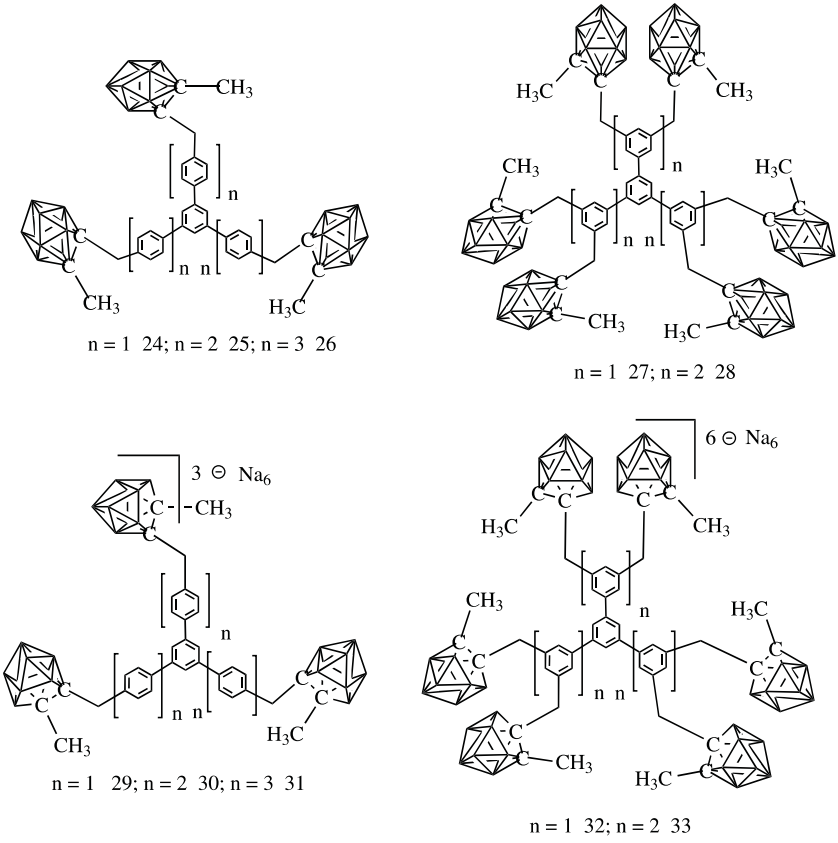


FIG. 9
C_3-symmetric C_{cage}-appended π-conjugated compounds

C_c-silyl substituted cobaltabis(dicarbollide) derivative Cs[1,1′-μ-SiMeH-3,3′-Co(1,2-$C_2B_9H_{10})_2$][53]. Metallodendrimers[54] are a class of globular macromolecules which find applications in molecular electronics[55], energy conversion[55d], sensing[56], and catalysis[57]. All these interesting applications of metallodendrimers led us to synthesize new classes of phenylene core-

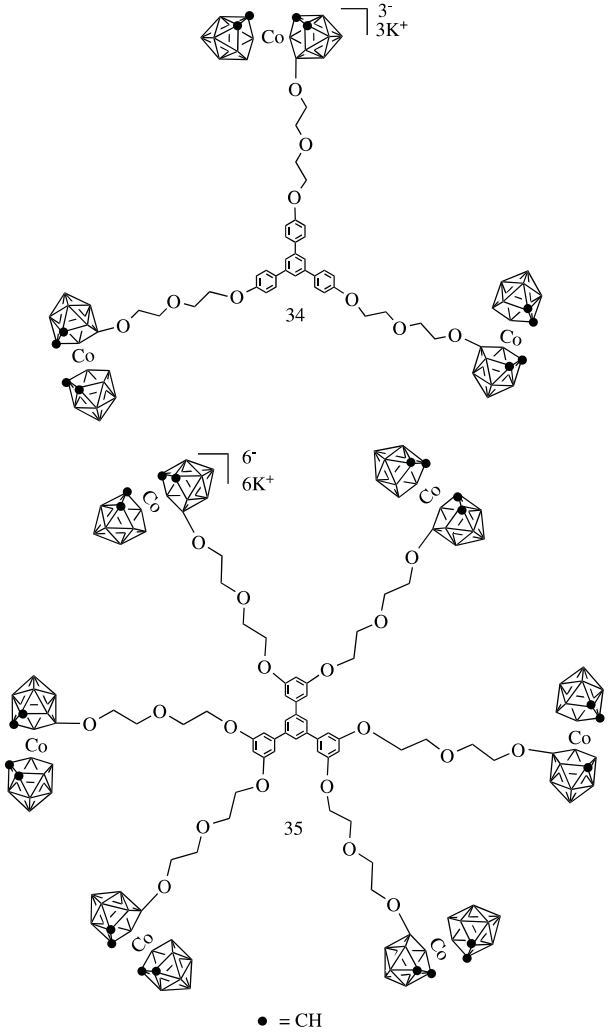
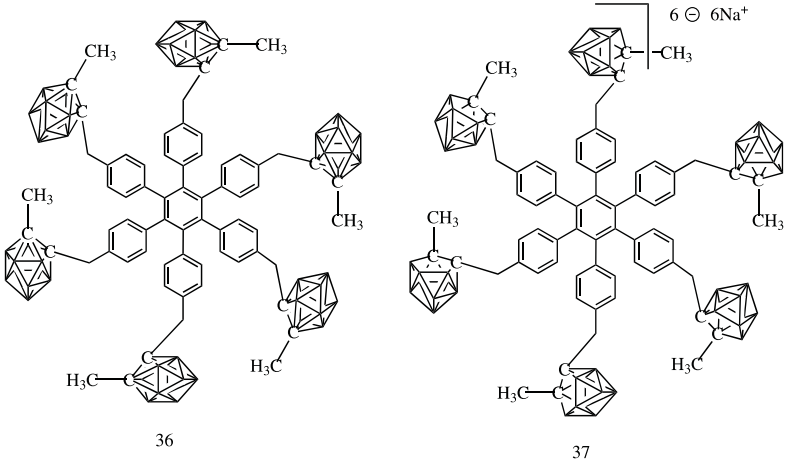


FIG. 10
Dendritic structured cobaltabis(dicarbollides)

based dendritic metallacarborane molecules containing three to six cobaltabis(dicarbollides), **34** and **35**, employing silicon tetrachloride and promoted cyclization of the corresponding keto precursors (Fig. 10)[58].

Cobalt catalyzed cycloaddition reactions of symmetrical alkynes usually generate C_6-symmetric hexaphenylbenzenes[59]. Synthesis of the star-shaped compound **36**, which contains six *ortho*-carborane clusters surrounding a hexaphenylbenzene core (Fig. 11), was synthesized in like manner. Compound **36** was then reacted in methanolic sodium hydroxide solution to decapitate the neutral *closo*-carboranes to yield their corresponding [*nido*-$C_2B_9H_{12}$]$^-$ cages, as shown for **37**, imparting water solubility[60]. Attaching suitable tumor targeting units[2a] to this boron-rich macromolecular compound, in its water-soluble form, may be useful as a platform for boron drug delivery.



36 37

FIG. 11
Boron-rich C_6-symmetric stars-shaped compounds

Carborane-Porphyrin Conjugates

The advancement of the synthetic chemistry of porphyrins and related macrocycles has resulted in the production of a number of such molecules[61]. Porphyrin-like macrocycles are a major class of phototherapeutic agents and have been clinically used for treatment of cancer via photodynamic therapy (PDT). There are different mechanisms that have been suggested for the uptake of such molecules into tumor tissues. In general, porphyrins are able to diffuse into tumor tissues as monomers or small aggregates through the plasma membrane of tumor cells and it has been

found that hydrophobic porphyrins can do so very efficiently[62]. Due to their tumor targeting efficiency porphyrins are often conjugated with carboranes for possible use in BNCT applications. There are a number of reviews on such carborane-porphyrin conjugates[2,9,63]. Here we will discuss some recent reports on the carborane-porphyrin conjugates and their applications in cancer therapy.

The synthesis and biological properties of a novel carboranyl-containing chlorin **38** that can find application as a dual sensitizer in the PDT and BNCT treatment of cancer is recently reported. This was found to be non-toxic in the dark but showed extensive photosensitizing ability both *in vitro* and *in vivo* and also exhibited significant photosensitizing activity against highly pigmented melanotic melanoma tumors in mice (Fig. 12)[64]. Conjugates of chlorin e_6 with *closo*-dodecaborate and cobaltabis(dicarbollide) anions, **39** and **40**, were also synthesized employing click methodology. *In vitro* studies on A549 human lung adenocarcinoma cells revealed that the synthesized boronated conjugates could accumulate in cancer cells, but their intracellular concentration was not sufficient enough for effective photodynamic and boron neutron capture therapy (Fig. 12)[65].

Water-soluble *meso*-substituted porphyrin **41** (Fig. 13) containing 36 boron atoms was tested for its accumulation by B16F1 murine melanotic

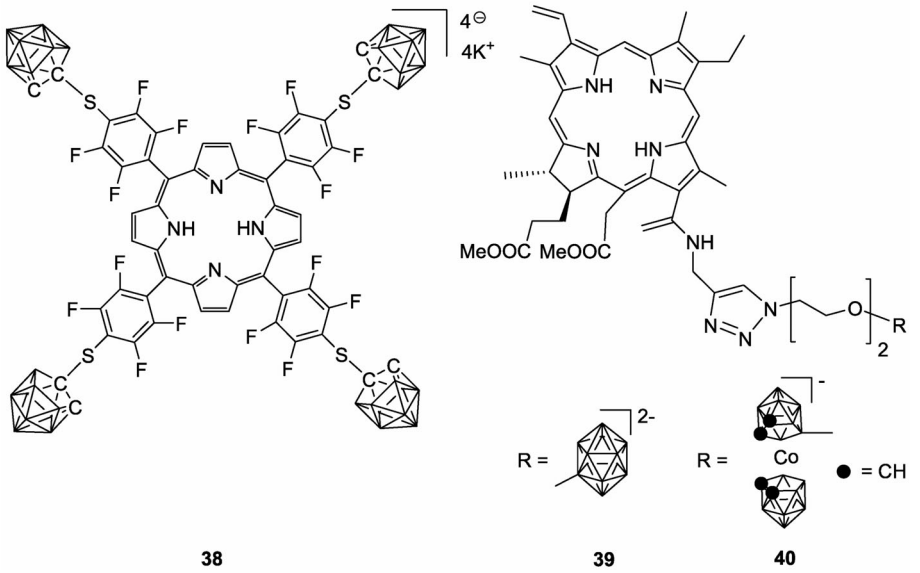
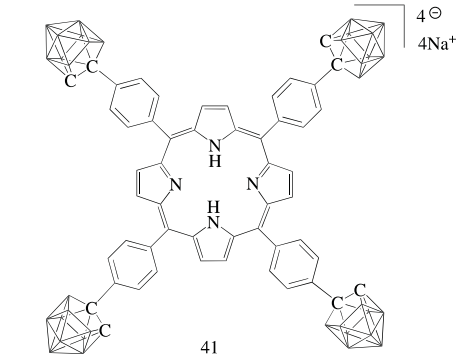


FIG. 12
Boron-enriched chlorines for PDT and BNCT



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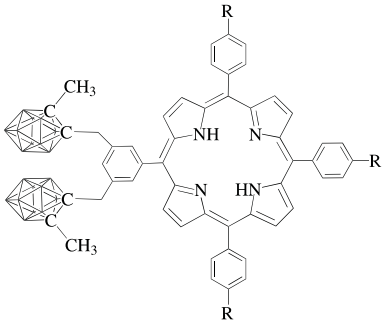

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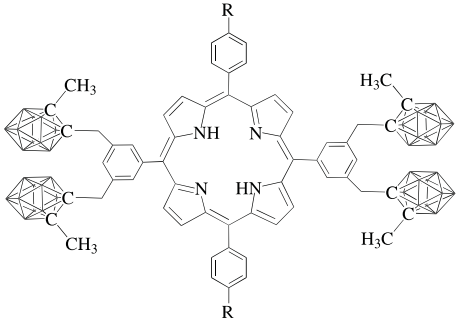

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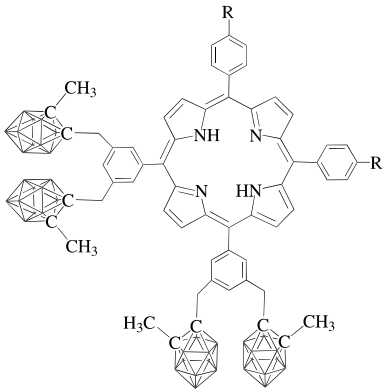
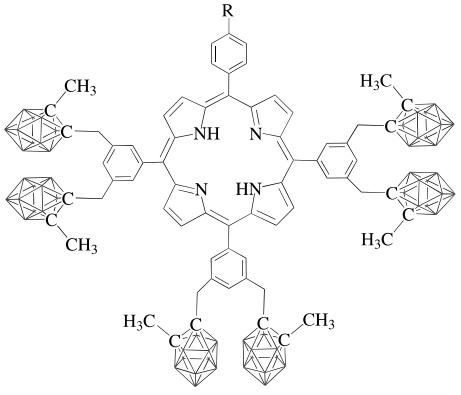


44a-d



45a-d

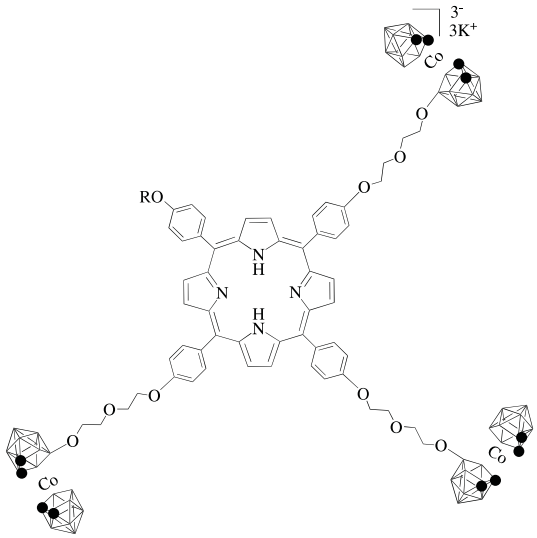
a: R = NMe_2
b: R = $PO(OEt)_2$
c: R = NMe_3^+
d : R = $PO(OH)_2$

FIG. 13
Carborane-appended porphyrins for potential therapeutic applications

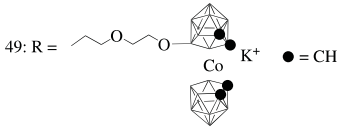
melanoma cells. The concentration of **41** increased with the incubation time reaching up to 0.4 nmol per mg of cell protein after 24 h of incubation. The fluorescence microscopy study showed predominant intracellular accumulation of **41**. A significant photosensitising efficiency was also observed for **41** and more than 95% cell mortality was observed upon irradiation with red light. Porphyrin **41** was also found to be accumulated by the tumor tissue of C57BL/6 mice bearing a subcutaneously transplanted melanotic melanoma[66]. The mice were subjected to a neutron source either after 0.5 h after intratumoral administration or at 24 h after intravenous injection. During this time period, 60 and 6 ppm of ^{10}B was found to be accumulated in the tumor tissues and irradiation of thermal neutrons delayed the growth of the tumor for 5–6 days[67]. Thus boron-loaded porphyrins like **41** could act as both PDT and BNCT agents and can be administered even to a very aggressive and radioresistant tumor such as melanotic melanoma[66,67].

A number of carboranyl porphyrins, **42–45**, containing either amine or phosphonic acid functionalities and 2–6 *ortho*-carborane clusters have been synthesized (Fig. 13) and, *in vitro* studies using human carcinoma HEp2 and human glioblastoma T98G cells, show that these porphyrins are non-toxic in the dark up to 100 μM concentrations, and that a tetracarboranyl porphyrin bearing two quaternary ammonium groups, **44c** is the most efficiently taken up by cells within a short time period of about 8 h, followed by a dicarboranyl porphyrin bearing three phosphonic acid substituents, **42d**. All these carboranyl porphyrins were found to deliver the desired therapeutic amounts of boron to T98G cells[68]. A number of porphyrin-cobaltacarborane conjugates have also been synthesized and their cellular uptake and potential BNCT applications assessed[69].

A series of four porphyrin-cobaltacarborane conjugates, **46–49**, were synthesized, containing 3–4 cobaltabis(dicarbollide) anions linked by $O(CH_2CH_2O)_2$ groups to the porphyrin macrocycle and one of them containing a HIV-1 Tat 48-60 peptide sequence linked via a low molecular weight polyethylene glycol (PEG) spacer (Fig. 14). The cellular uptake, cytotoxicity, and preferential sites of intracellular localization of the conjugates were evaluated in human HEp2 cells. Compound **46–49** were found to be non-toxic in the dark at the concentrations studied. Upon exposure to low light dose only compound **48** was found to inhibit cell proliferation up to 30% at a concentration of 10 μM. The cellular uptake was dependent on the number of carborane cages and was significantly enhanced by the presence of the cell penetrating peptide sequence HIV-1 Tat 48-60; all these porphyrin-cobaltacarborane conjugates were preferentially localized in the



46: R = CH_3
47: R = CH_2CO_2H
48: R = $CH_2CONH(CH_2CH_2O)_7CH_2CH_2NHCOCH_2OCH_2CONH$-GRKKRRQRRRPPQNH$_2$



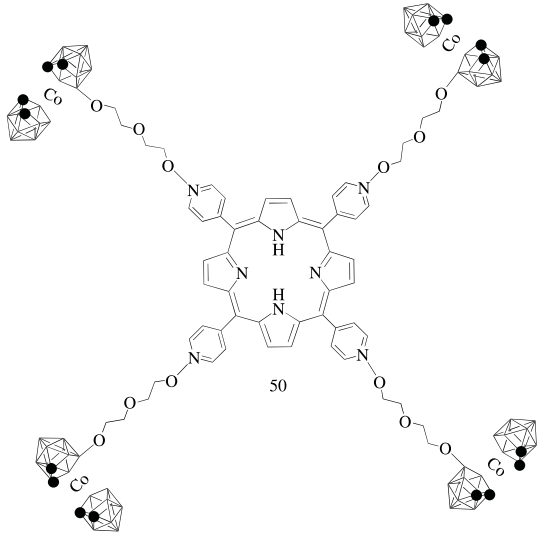


FIG. 14
Porphyrin-cobaltacarborane conjugates

cell lysosomes[69a]. In another report, the syntheses of five new porphyrin-cobaltacarborane conjugates and their cellular uptake, cytotoxicity, and subcellular localization have been studied[69b]. The synthesis of these compounds was carried out via a one-step reaction between a nucleophilic *meso*-pyridyl containing porphyrin and zwitterionic cobaltacarborane [3,3′-Co(8-O(C_2H_4)$_2$O-1,2-$C_2B_9H_{10}$)(1,′2′-$C_2B_9H_{11}$)]. One of the five compounds is **50** in Fig. 14. Among others in the series, compound **50** that contains four cobaltabis(dicarbollide) clusters showed highest accumulation in the cells indicating the number and distribution of cobaltacarborane residues linked to the porphyrin macrocycle has a significant effect on the cellular uptake of the conjugates[69b].

Carborane-Carbohydrate Conjugates

There are a number of reports on the synthesis of carborane-carbohydrate conjugates over the last two decades for tumor targeted boron delivery. The synthesis of carborane-carbohydrate conjugates and their use in BNCT was recently reviewed[70]. Due to the presence of carbohydrate-specific receptor proteins on the surface of tumor cells[71], the combination of carbohydrate and carboranes could enhance their uptake into tumor tissues. Secondly, the use of carbohydrates containing multiple hydroxyl groups could help to compensate for the hydrophobicity of the carboranes, make them water soluble and thereby could enhance their uptake into tumor tissues[2a]. Here we will discuss some of the recent reports on carborane-containing carbohydrates and their use as boron drug delivery platform.

Facile synthesis of highly water-soluble carbaboranediyl bis(glycophosphonates) and corresponding phosphonothioates was recently reported (Fig. 15). These compounds are also found to show low cytotoxicity and therefore could find potential medicinal applications[72]. Compounds **51** and **52** were synthesized from *meta*-carboranediyl bis(phosphonite); first synthetic investigation towards these target compounds was carried out by the same research group and was previously reported[73]. Tetra-D-galactosylated carboranediyl bis(phosphonates) containing four galactose moieties **53–55** were also synthesized in like manner. However, these were synthesized from a different starting materials possessing four dimethylamido groups[72]. The synthesis of bis(glycophosphonates) and phosphonothioates of *meta*- and *para*-carboranes as shown in Fig. 15 was then extended to the bis-(*meta*-carborane) to increase the boron content in such compounds (Fig. 16). Employing similar methodology as reported in their previous work, compounds **56** and **57** contain two galactose moieties and compounds **58** and

59 possessing four galactose moieties were synthesized[74]. Compounds **56** and **57** were also found to be water soluble but to a lesser extent than mono-cage compounds **51–55**.

^{18}F-labeled analogue of glucose (^{18}F-FDG) is used to detect sites of increased glucose metabolism using positron emission tomography (PET)[75]. Therefore, a carborane-glucose conjugate could be a useful combination for their general use as radiopharmaceuticals. Carborane-glucose derivatives in which the cluster is linked to the C_1 position of the glucose moiety was prepared and reacted with the $[Re(CO)_3]^+$ core to get the compound **60** (Fig. 17)[76a]. A new method was also developed for the synthesis of radiolabelled ^{99m}Tc-metallacarborane in water under mild reaction condition and reported by the same research group[76b]. In order to develop model plat-

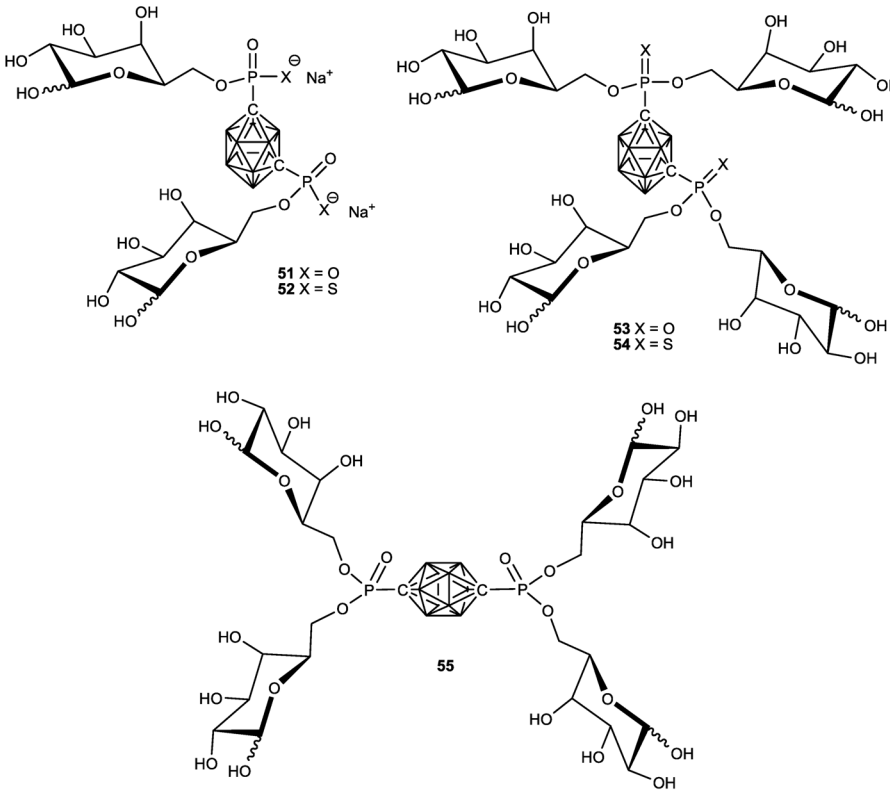


FIG. 15
Carborane-containing water-soluble bis(phosphonate), bis(phosphonothionate), and bis(glycophosphonate)

forms for targeted radiopharmaceuticals, a series of carborane-carbohydrate derivatives were prepared in which a single ligand can be tagged with two different classes of radionuclides. A *nido*-carborane linked to glucose was synthesized and then the cage was labelled with a radiometal (^{99m}Tc) and a radiohalogen (^{125}I) in good radiochemical yield. The rhenium **62a** and ^{99m}Tc-metallacarborane derivative **62b** were prepared using microwave-assisted reactions and the iodinated derivatives **61a** and **61b** were prepared using efficient oxidative labelling methods (Fig. 17). The fully characterized nonradioactive rhenium and iodinated compounds were used as the reference standards to demonstrate that the isolated radioactive compounds

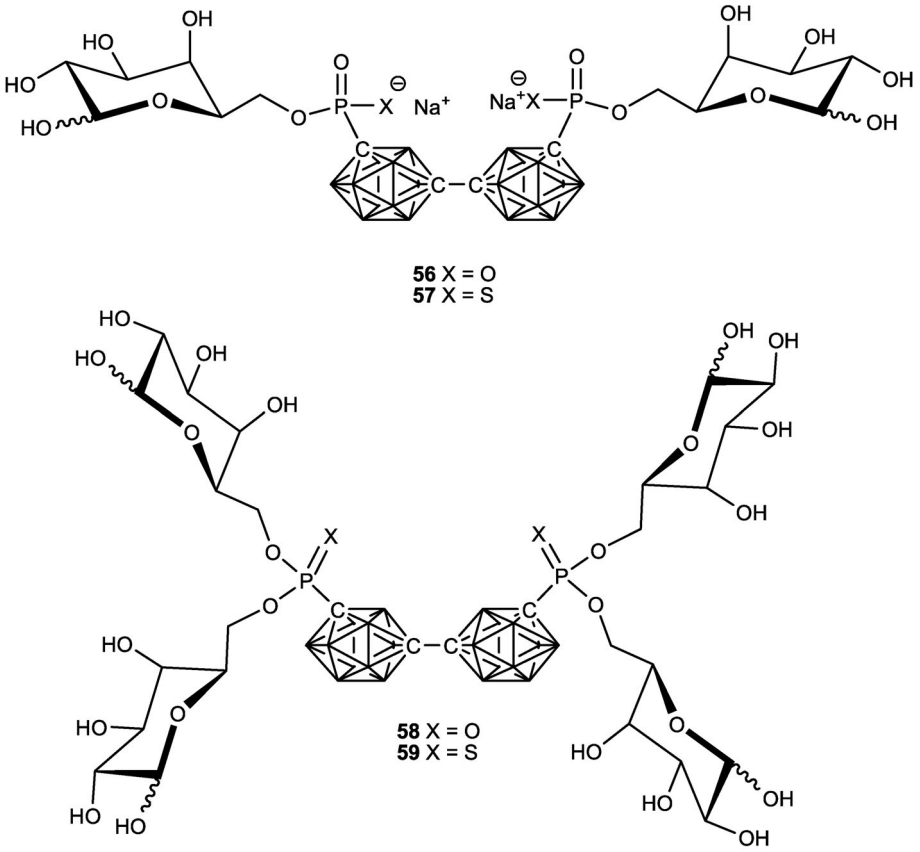


FIG. 16
Bis(carborane)-bridged bis(glycophosphonates) and phosphonothioates

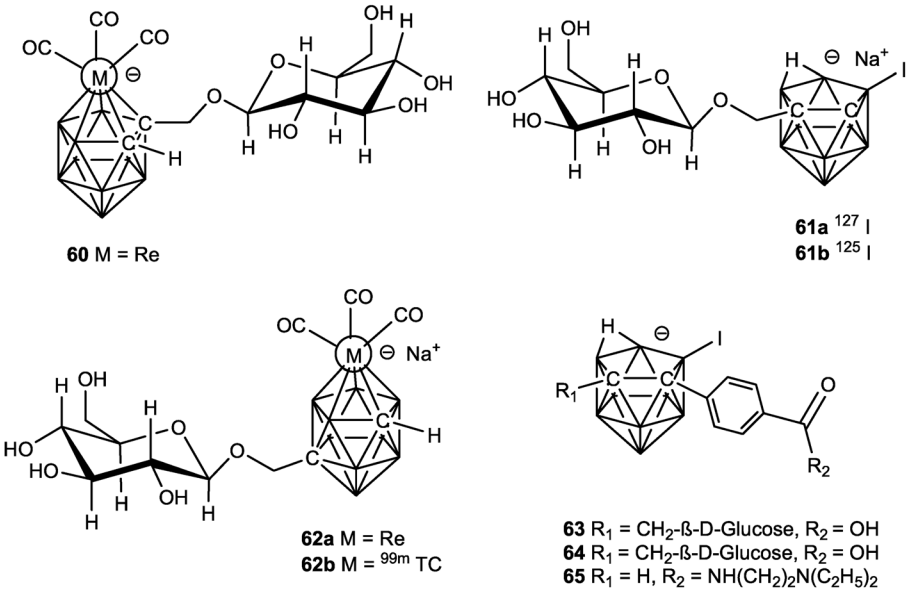


FIG. 17
Carborane-carbohydrate conjugates for radiopharmaceuticals

were indeed the desired target compounds. This work demonstrated the advantage of using carborane ligand system which can be labelled with both radiohalogens and radiometals and thus can be potentially useful in developing targeted radiopharmaceuticals[77]. A number of other radiohalogen (^{125}I) containing water-soluble carboranyl derivatives containing glucose, benzoic acid and polyamine moieties, **63–65**, were also developed as potential molecular radioimaging and therapy agents[78].

Derivatives of Cobaltabis(dicarbollide)

The human immunodeficiency virus (HIV) protease is responsible for cleavage of the polyprotein precursors necessary for the production of new viral particles and thus plays vital role in HIV replication cycle. Chemical inhibition and inactivation of protease block the infectivity of the virus and thus form the basis for antiviral drug design for the treatment of AIDS [79]. The use of cobaltabis(dicarbollide) anion **66** and its derivatives **67–70** (Fig. 18) have been recently evaluated for their use as inhibitors of HIV protease[79b,80]. The kinetic analysis reveals the cobaltabis(dicarbollide) derivatives compete with the peptide substrate and binds to the active cleft of the enzyme. The

parent cobaltabis(dicarbollide) anion **66** shows tight inhibition *in vitro* and micromolar antiviral potential. The derivative **67** and symmetrical derivatives **68–70** showed much improved inhibition activity. Compounds **68** and **70** were found to be the most potent inhibitors in the series[79b,80].

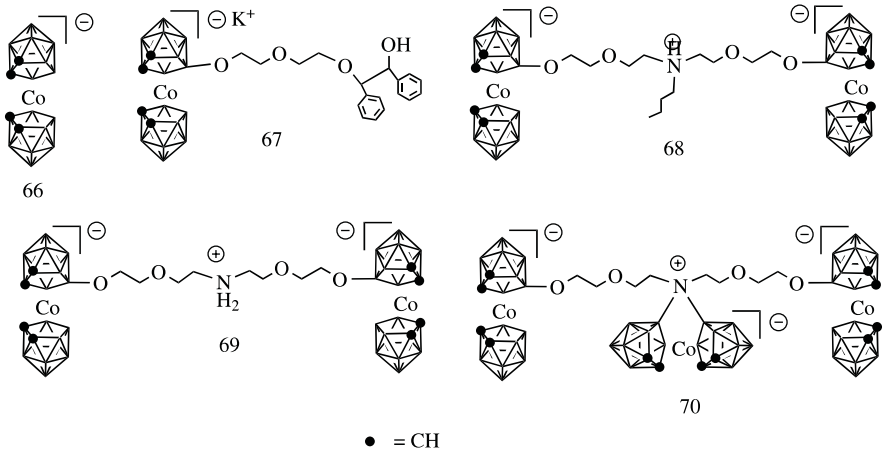


FIG. 18
Derivatives of cobaltabis(dicarbollide) for HIV protease inhibition

CONCLUSION

The work covered in this review demonstrates some recent applications of boron clusters, specifically icosahedral carboranes and cobaltabis(dicarbollide) in the field of medicinal chemistry. The medicinal chemistry involving carboranes should not be centered just on their use in cancer therapy via BNCT. All other possible medicinal applications need to be explored such as their use in the preparation of new inorganic pharmaceuticals and in the development of targeted therapeutic agents. The unique properties of carboranes such as hydrophobicity and size can also be exploited for their use as pharmacophores.

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