Top Heterocycl Chem (2015) 34: 31–52
DOI: 10.1007/7081_2013_111

Published online: 8 June 2013

Synthesis of Carborane-Containing Porphyrin Derivatives for the Boron Neutron Capture Therapy of Tumors

N.V.S. Dinesh K. Bhupathiraju and M. Graça H. Vicente

Abstract The treatment of malignant brain tumors using conventional therapies and surgery often leads to tumor recurrence and/or unwanted side effects. Boron neutron capture therapy (BNCT) is a binary and localized form of treatment for brain tumors and other difficult-to-treat cancers that uses nontoxic boron-containing agents. Boronated porphyrins and derivatives constitute a class of highly promising third-generation boron delivery agents for BNCT. These stable, tumor-specific, and fluorescent macrocycles can be synthesized with high boron content, can deliver therapeutic amounts of boron to target sites, and allow tumor detection and treatment planning by optical imaging. In addition, boronated porphyrins have shown low toxicity and enhanced tumor selectivity and retention times compared with clinically approved BNCT agents, BSH and BPA. In this article the synthesis of carboranyl-containing porphyrins and derivatives for application in BNCT is reviewed, with special emphasis on macrocycles reported in the last decade. Current strategies for enhancing the biological efficacy of BNCT agents involve their association with tumor-targeting molecules, such as polyamines and peptides, for improved tumor selectivity and accumulation.

Keywords BNCT · Carborane · Chlorin · Phthalocyanine · Porphyrin

Contents

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1 Introduction

Boron neutron capture therapy (BNCT) is a binary therapy that involves the irradiation of ^{10}B-containing tumors with low energy thermal neutrons [1–4]. The nuclear capture reaction produces excited ^{11}B nuclei which spontaneously fission to give high linear-energy transfer (high-LET) alpha and ^{7}Li particles, γ radiation and release of about 2.4 MeV of kinetic energy, as shown in Fig. 1. The high-LET particles produced during the fission reaction have limited path lengths in tissue (5–9 μm), therefore making BNCT a localized form of treatment, able to destroy ^{10}B-containing malignant cells in the presence of ^{10}B-free healthy cells. In addition, the much lower nuclear cross-sections of biologically abundant nuclei ^{12}C (0.0034 barn), ^{1}H (0.33 barn), and ^{14}N (1.8 barn) in comparison with ^{10}B (3,838 barns) limit interference with the ^{10}B(n,α)^{7}Li capture reaction. Although the natural abundance of the boron-10 isotope is 20%, it can be incorporated at the 95–96% level into BNCT agents from ^{10}B-enriched starting materials.

BNCT clinical trials in brain tumor patients started about 50 years ago at the Brookhaven National Laboratory and the Massachusetts Institute of Technology (MIT), using neutron beams with limited tissue penetration of up to 4 cm. Modern nuclear reactors, such as the MIT research reactor, use epithermal neutron beams that can reach up to 10 cm, allowing the treatment of deep seated tumors [4]. Currently, there are two clinically approved BNCT agents, the sodium salt of the sulfhydryl boron hydride $Na_2B_{12}H_{11}SH$ (BSH, **1**) and L-4-dihydroxy-borylphenylalanine (BPA, **2**), used either alone or in combination for the treatment of malignant brain tumors, melanomas, and squamous cell carcinomas (Fig. 2) [5–9]. For example, BNCT using ^{18}F-labeled BPA assisted by positron emission tomography (PET) was recently used to treat recurring head and neck cancer, with significant improvement of the mean patient's survival time [9]. Although BSH and BPA have demonstrated low toxicity and efficacy in BNCT clinical trials, improved boron delivery agents with higher tumor selectivity and ability to deliver therapeutic amounts of boron (>20 μg/g tumor) to target tumors with low systemic toxicity have been the focus of intense research [4]. These so-called third-generation boron delivery agents include boronated amino acids, proteins, antibodies, nucleosides, sugars, lipids, liposomes, nanoparticles, and porphyrin derivatives [10, 11]. Among these, boronated porphyrins are particularly promising due to their demonstrated (1) low dark toxicities, (2) high uptake and retention in tumors, (3) high tumor-to-blood and tumor-to-normal tissue boron concentration ratios, (4) delivery of therapeutic amounts of boron to tumors, (5) ability to produce cytotoxic oxygen species upon light activation, which is the basis for their use in photodynamic therapy (PDT) [12, 13] and the possibility of using PDT in combination with BNCT, (6) ability for DNA and RNA binding, and (7) fluorescent properties, which facilitate the quantification of tissue-localized boron and treatment planning [14–16]. The neutral isomeric carboranes

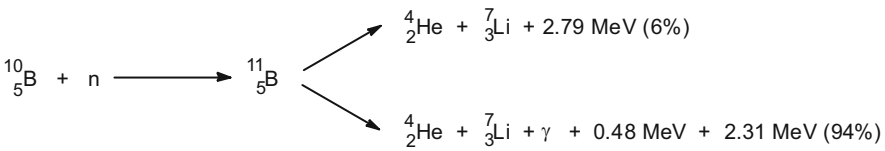


Fig. 1 The $^{10}B(n,\alpha)^{7}Li$ neutron capture and fission reactions

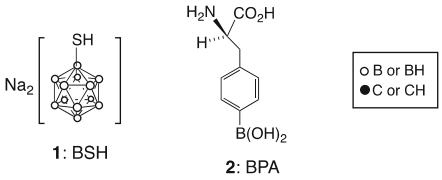


Fig. 2 Boron delivery agents in BNCT clinical trials

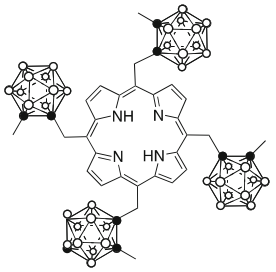
ortho-, *meta*-, and *para*-$C_2B_{10}H_{12}$, the anionic *closo*-carborane $CB_{11}H_{12}^-$ and the open-cage *nido*-$C_2B_9H_{12}^-$ (obtained from base-induced deboronation of *ortho*-carborane), and the bis(dicarbollide) $[3,3'\text{-}Co(1,2\text{-}C_2B_9H_{11})_2]^-$, have been the clusters of choice for attachment to porphyrin macrocycles because of their high boron content, amphiphilic properties, and their high photochemical, kinetic, and hydrolytic stabilities. In this chapter we review the synthesis of carboranyl-containing porphyrins and derivatives that have been reported for application in BNCT, with particular emphasis on the macrocycles reported in the last decade.

2 Synthetic Strategies and Early Reported Macrocycles

The synthesis of porphyrins **3** and **4**, among other *meso*-tetracarboranylporphyrins, were first carried out in 1978 by Haushalter and Rudolph [17, 18]. Porphyrin **3** was prepared in 11% yield by Rothemund condensation of pyrrole with 1-methyl-2-methylformyl-*ortho*-carborane, and porphyrin **4** was obtained from the reaction of pre-formed *meso*-tetra(4-aminophenyl)porphyrin with the corresponding *ortho*-methylcarborane acid chloride. The *closo*-carboranylporphyrins **3** and **4** were subsequently converted into their corresponding *nido*-carborane derivatives by base-induced removal of a boron atom from each *ortho*-carborane cage, using a mixture of pyridine and piperidine. About a decade later several groups reported the synthesis of carboranylporphyrins for application as boron delivery agents for BNCT [19–24]. These macrocycles were obtained from commercially available protoporphyrin-IX or hematoporphyrin-IX precursors, via functionalization of the vinyl, hydroxyethyl or the propionic side chains, producing VCDP (**5**) [21], **6** [22, 23],

BOPP (**7**) [19, 20] and **8** [24]. VCDP was prepared in about 40% yield from mercuration of Zn(II)-deuteroporphyrin-IX dimethyl ester, followed by reaction with vinyl-*ortho*-carborane in the presence of $LiPdCl_3$, demetallation and final deboronation and ester hydrolysis using KOH in methanol. BOPP was obtained in 85% yield by reacting bis(1,2-dihydroxyethyl)-deuteroporphyrin-IX dimethyl ester with the corresponding acid chloride of *ortho*-carborane in the presence of DMAP, followed by ester hydrolysis using dilute HCl.

Carborane-functionalized phthalocyanines were first reported by Soloway and coworkers [25], which carried out the functionalization of a tetrasulfonylchloride-phthalocyanine with *para*-aminophenylcarborane, giving a mixture of regioisomeric phthalocyanines.



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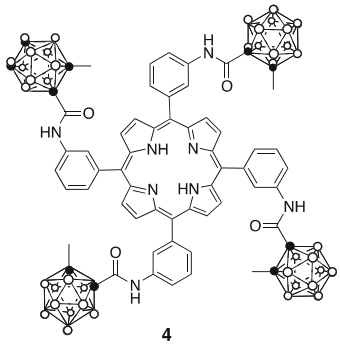

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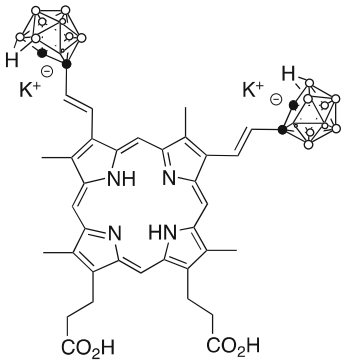
In the early 2000s several other carboranyl-containing porphyrins and phthalocyanines were reported [26–35]. These macrocycles were prepared using the following strategies: (1) functionalization of a pre-formed macrocycle, (2) cyclotetramerization of bononated pyrroles, or by (3) condensation of boronated aldehydes with pyrroles and dipyrromethanes. In the synthesis from pyrrole and aldehyde precursors, the Rothemund [36], Adler [37], and Lindsey [38] condensation conditions have all been reported. The highest yields are obtained with Lindsey's method which employs mild conditions, usually using $BF_3{\cdot}OEt_2$ or TFA as the acid catalyst at room temperature to form the porphyrinogen, followed by oxidation to porphyrin using 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) or *para*-chloranil (2,3,5,6-tetrachlorobenzoquinone). The total synthesis from boronated pyrroles and/or aldehydes is usually employed for the preparation of symmetric macrocycles, such as *meso*-tetraarylporphyrins of high boron content. On the other hand, unsymmetric systems are most often prepared by direct functionalization of a pre-formed macrocycle, obtained either by total synthesis or from a natural source (heme, chlorophyll-*a*). This approach is usually employed for the synthesis of carboranylporphyrin derivatives bearing a tumor-targeting moiety and can lead to high yields of the target macrocycles, as will be discussed in the following sections.



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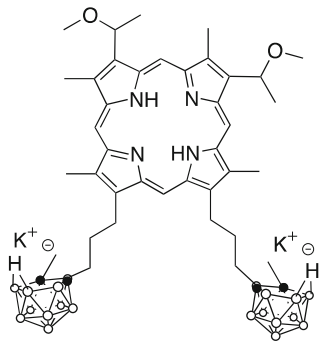

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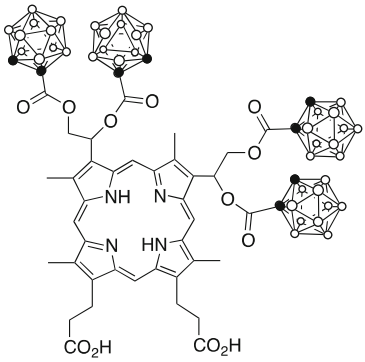

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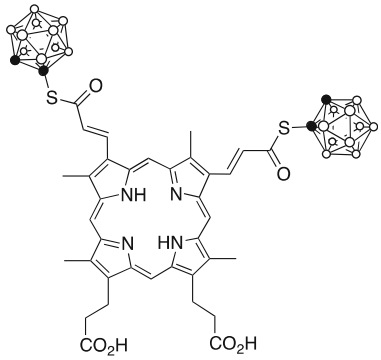

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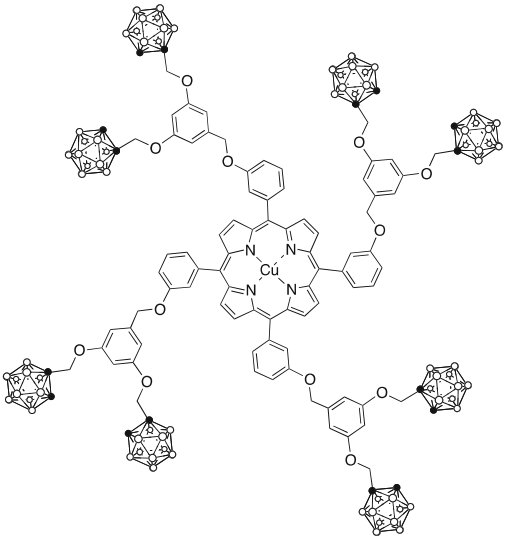
3 Recent Synthesis of Carboranyl-Containing Porphyrin Derivatives

3.1 Symmetric Carboranyl-Porphyrins and Chlorins

Symmetric carboranylporphyrin derivatives have been prepared either by total synthesis from boronated monomeric precursors, or from functionalization of a pre-formed symmetric porphyrin. Both metal-free and metallated derivatives, usually containing Zn(II), Cu(II), or Ni(II) ions, have been reported. Zn(II)-porphyrins often show enhanced photosensitizing properties, whereas Cu(II)-porphyrins show reduced photosensitization and allow tumor detection using PET (^{64}Cu) or SPECT (^{67}Cu).



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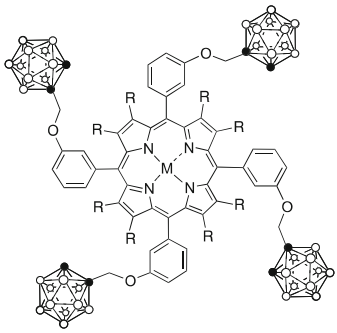
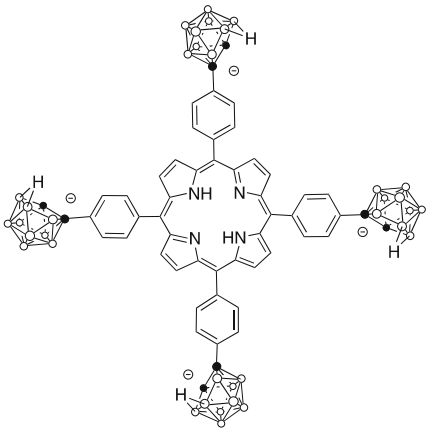


10: R = CH_2CO_2Me; M = Cu or Ni
11: R = H; M = Cu
12: R = Br; M = Cu



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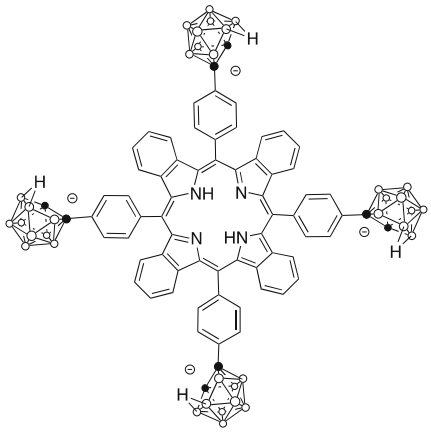

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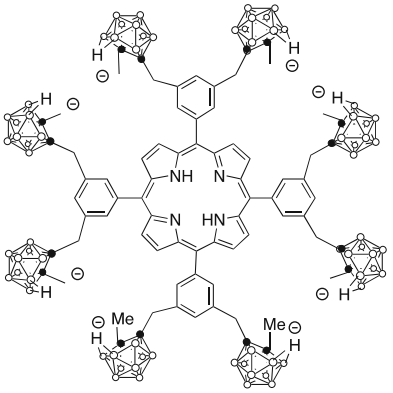
Cu(II)-porphyrin **9** was synthesized using Lindsey's method by condensation of 3-(3,5-di-*ortho*-carboranyl-methoxybenzyloxy)benzaldehyde with pyrrole in the presence of $BF_3{\cdot}OEt_2$ followed by copper insertion using Cu(II) acetate, in 20% overall yield [39]. Using a similar strategy, porphyrins **10**–**12** were prepared, from reaction of pyrrole or a β-substituted pyrrole with a boronated benzaldehyde, followed by metal insertion, and in the case of **12**, by bromination of CuTCPH (**11**)

in pyridine at room temperature [40, 41]. A more soluble derivative of CuTCPH (**11**) containing four hydroxy substituents at the *meta*-positions of the *meso*-phenyl groups was prepared in about 30% yield using similar condensation and metallation conditions [39]. The resulting tetrahydroxy-CuTCPH was obtained by dealkylation of the corresponding tetramethoxyporphyrin using BBr_3.

Using Lindsey's condensation conditions, H_2TCP **13** in both ^{10}B-enriched and non-enriched forms were synthesized by condensation of pyrrole with *para*(*ortho*-carboranyl)benzaldehyde using $BF_3{\cdot}OEt_2$ as catalyst, followed by oxidation with DDQ and deboronation with pyridine/piperidine 3:1, in about 50% yield [26, 29, 42–44]. An alternative but low-yielding reported synthesis of this porphyrin involves the functionalization of a pre-formed tetra(4-iodophenyl)porphyrin with *ortho*-carborane via Cu(I)-catalyzed coupling [45]. The tetrabenzo-carboranylporphyrin **14** was prepared by condensation of tetrahydroisoindole with *para*(*ortho*-carboranyl) benzaldehyde under Lindsey's conditions, followed by metallation with $CuCl_2$, oxidation to tetrabenzoporphyrin using excess DDQ, demetallation with conc. H_2SO_4, and final deboronation of the *ortho*-carboranes using tetrabutylammonium fluoride in THF, in about 30% overall yield [46, 47].



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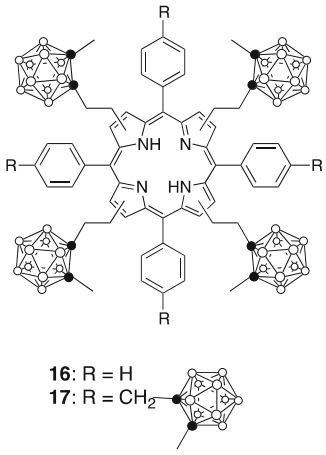
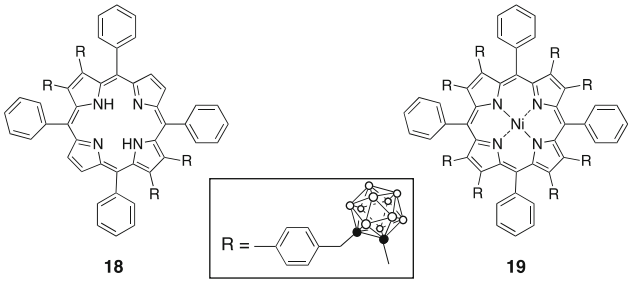


16: R = H
17: R = CH_2

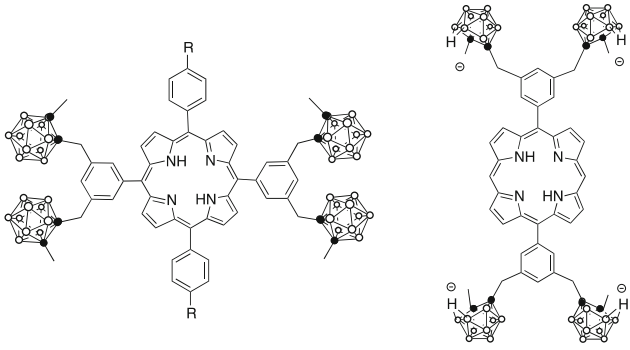
The octa-*ortho*-carboranylporphyrin **15** of high boron content was synthesized in about 10% yield from condensation of pyrrole with bis[3,5-(methyl-*ortho*-carboranyl)methyl]benzaldehyde using TFA as the acid catalyst, followed by oxidation with *para*-chloranil and deboronation of the *ortho*-carborane cages [26, 48, 49].

meso-Tetraaryl-carboranylporphyrins **16** and **17** bearing carborane cages on the β-pyrrolic positions of the macrocycle have been synthesized from carboranyl-pyrroles and aldehydes under Lindsey's conditions, in 49% and 20% yields, respectively [50, 51]. Condensation of the boronated pyrrole with benzaldehyde,

or a boron-containing benzaldehyde in the presence of $BF_3{\cdot}OEt_2$, gave the target porphyrins as regioisomeric mixtures after oxidation with *para*-chloranil. Pure β-substituted carboranylporphyrins **18** and **19** were also synthesized in good yields (18–78%) by direct functionalization or pre-formed tetra- and octa-bromoporphyrins, using a Pd(0)-catalyzed coupling reaction in anhydrous toluene, excess carboranylmethylphenyl boronic acid, and anhydrous K_2CO_3 [52].



18 **19**



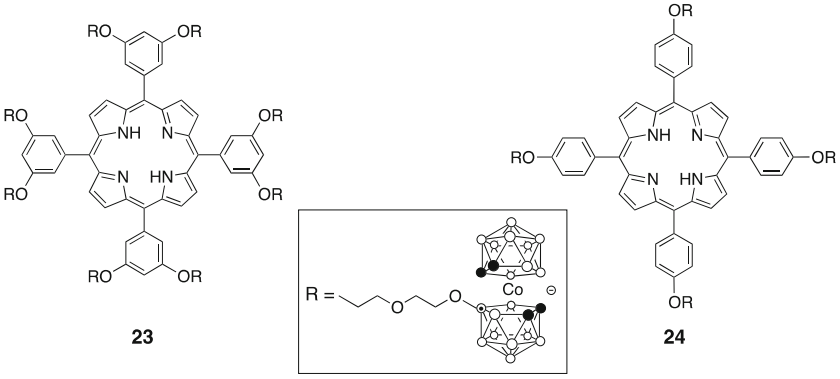
20: R = $PO(OH)_2$
21: R = NMe_3I

22

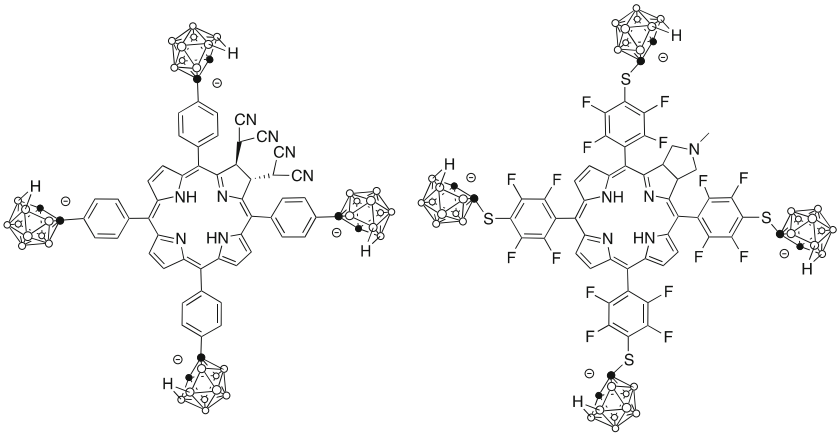
Using a MacDonald [2+2] condensation [53] between bis[3,5-(methyl-*ortho*-carboranyl)methyl]benzaldehyde and various dipyrromethanes, a series of carboranylporphyrins, including **20**–**22**, were prepared in 4–40% yields [54–56]. The lower yields obtained were due to acid-catalyzed scrambling during the condensation reaction. The water-soluble carboranylporphyrins were obtained by cleavage and hydrolysis of phosphonic esters using bromotrimethylsilane (to give **20**), by quaternization of the peripheral amine groups with methyl iodide (to give **21**), or by deboronation of the *ortho*-carboranes with pyridine/piperidine 3:1 (to give **22**).

Symmetric porphyrins **23** and **24** were synthesized in very high yields (>90%) from the reaction of the corresponding pre-formed *meso*-hydroxyphenylporphyrins

with zwitterionic [3,3′-Co(8-$C_4H_8O_2$-1,2-$C_2B_9H_{10}$)(1′,2′-$C_2B_9H_{11}$)] [57, 58]. Nucleophilic groups on the porphyrin macrocycle, such as hydroxy and pyridyl, efficiently open the dioxane ring of [3,3′-Co(8-$C_4H_8O_2$-1,2-$C_2B_9H_{10}$)(1′,2′-$C_2B_9H_{11}$)], producing porphyrins bearing Co(III) bis(dicarbollide) linked via a short PEG linkage [57–62]. In the absence of these groups, metal-free porphyrins produce the corresponding mono- and di-alkylated derivatives [61]. Since the Co(III) bis(dicarbolide) is negatively charged, porphyrins **23** and **24** are octa- and tetra-anionic, respectively. On the other hand, when pyridylporphyrins are used as the starting materials for the ring opening reaction of [3,3′-Co(8-$C_4H_8O_2$-1,2-$C_2B_9H_{10}$)(1′,2′-$C_2B_9H_{11}$)], zwitterionic carboranylporphyrins are formed [57, 61, 62].



23 **24**



25 **26**

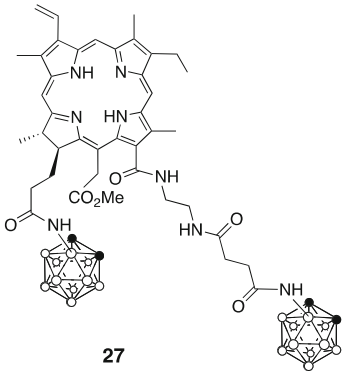
Symmetric boronated chlorins are obtained from functionalization of symmetric porphyrin precursors. For example, boronated *trans*-chlorin **25** was synthesized from the corresponding *meso*-tetra(4-*ortho*-carboranylphenyl)porphyrin (the *closo*-carboranylporphyrin precursor of porphyrin **13**) [63, 64], via Cu(II) complexation and nitration at a β-pyrrolic position using copper(II) nitrate in acetic acid/acetic anhydride, followed by demetallation using 2% H_2SO_4 and reaction with malononitrile in the presence of K_2CO_3. Base-induced deboronation of *ortho*-carborane cages of the chlorin using pyridine/piperidine 3:1 gave compound **25** in 41% overall yield.

Boronated chlorin **26** was synthesized from *meso*-tetra(pentafluorophenyl)porphyrin in 48% overall yield [65]. The fluorinated porphyrin was first converted into the corresponding chlorin using *N*-methylglycin in toluene, and then the *para*-fluoro groups were substituted in the presence of excess mercapto-*ortho*-carborane under mild conditions (K_2CO_3 and KF at room temperature), to give boronated chlorin **26**.

3.2 Unsymmetric Carboranyl-Porphyrins and Chlorins

The preferred methodology for the preparation of unsymmetric macrocycles is by direct functionalization of naturally occurring and readily available porphyrins (such as protoporphyrin-IX) and chlorins (such as methyl pheophorbide-a). Alternatively, unsymmetric synthetic porphyrins, usually formed by mixed aldehyde condensations, can undergo functionalization with appropriate carboranyl-containing reagents. For example, carboranylporphyrins **5–8** were prepared via functionalization of protoporphyrin-IX or its derivatives (hematoporphyrin-IX or deuteroporphyrin-IX), with appropriately substituted carborane cages. On the other hand, chlorophyll-*a* derivatives pheophorbide-a, pyropheophorbide-a, and chlorin-e_6 have been functionalized with carborane cages, mainly via their carboxylic acid substituents, to produce, for example, chlorins **27–32**. Chlorin **27** was prepared by nucleophilic opening of the exocyclic ring of methyl pheophorbide-a with ethylenediamine, followed by acylation of the free amine group with succinic anhydride and conjugation of the resulting carboxylic group with 3-amino-*ortho*-carborane in the presence of DCC in dichloromethane/pyridine [66–69]. Hydrolysis of the ester group at the 17^3 position using 70% aqueous TFA gave a free carboxylic group which was conjugated under similar conditions to give chlorin **27** [66]. Alternatively, the ethylene amine derivative of pheophorbide-a can undergo alkylation reactions with *ortho*-carboranylmethyl triflate or the cesium salt of *closo*-carboranylmethyl triflate in THF to give the corresponding chlorins in yields ranging from 12% to 88% [67–69].

Chlorin **28** was also prepared from the same pheophorbide-a ethylene amine precursor by ring opening reaction of zwitterionic [3,3′-Co(8-$C_4H_8O_2$-1,2-$C_2B_9H_{10}$)(1′,2′-$C_2B_9H_{11}$)] giving chlorin **28** in 61% yield [70, 71].



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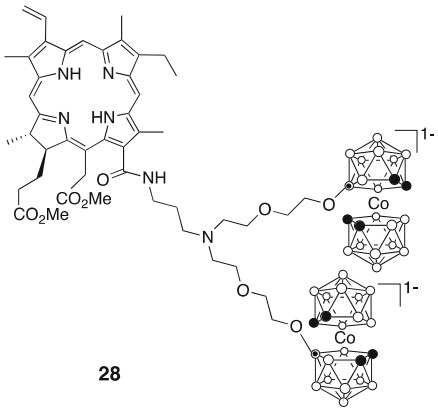

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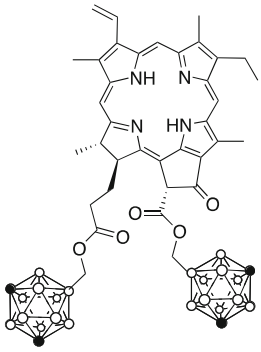

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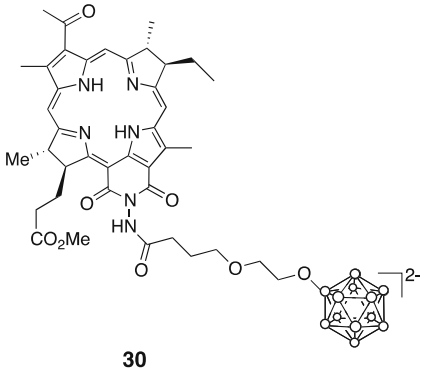

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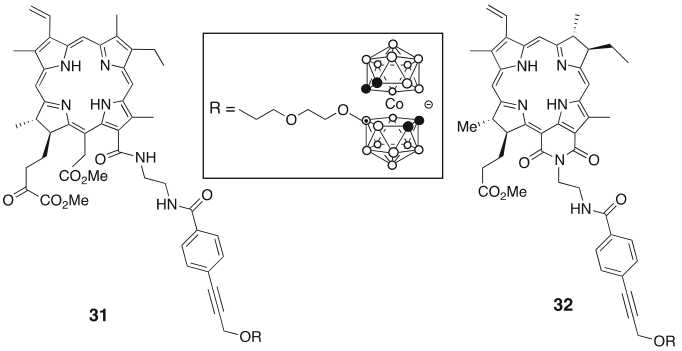
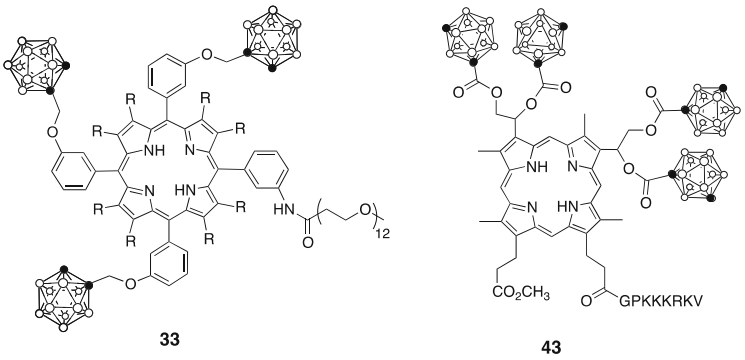
Other carborane-conjugates of methyl pheophorbide-a were obtained by transesterification of one or both of the methoxycarbonyl groups with carboranyl alcohols, using I_2 in refluxing toluene or 2-chloro-1-methylpyridinium iodide and DMAP for the mono-carboranyl conjugates, or $[Bu_2Sn(OH)(OTf)]_2$ in refluxing toluene for the di-carboranyl conjugates such as **29**, in yields up to 80% [72]. Ester, thioester, and amide derivatives of pyropheophorbide-a have also been prepared from the corresponding alcohol, thiol, or amine carboranes respectively, using either di-*tert*-butylpyrocarbonate and DMAP for the coupling reaction [73] or oxalyl chloride and $[Me_4N]_2[B_{12}H_{11}SH]$ [74].

The synthesis of bacteriochlorin derivative **30** involved the nucleophilic ring opening reaction of the oxonium derivative of the *closo*-dodecaborate dianion [75, 76]. Using an alternative strategy, **31** and **32** were prepared from the

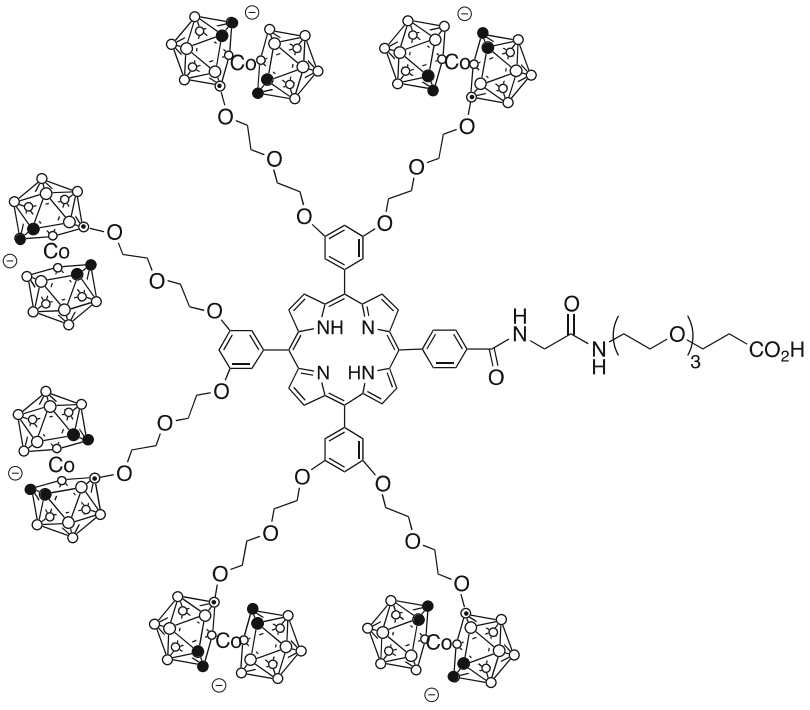
corresponding amine-containing macrocycles, by reaction with *para*-iodobenzoyl chloride followed by a Sonogashira coupling reaction with Co(III)-bis(dicarbollide) containing a terminal acetylene group, using 5:1 triphenylphosphine and $Pd_2(dba)_3$ in benzene/DIPEA at 60°C [77].



In order to increase the tumor uptake and overall biological efficacy of boronated porphyrins, the conjugations of unsymmetric systems to a cell-targeting moiety, such a peptide, polyethyleneglycol (PEG) or polyamine, have been investigated. The conjugation of PEG groups to biologically active molecules is a strategy often used for enhancing their aqueous solubility, serum life, and tissue permeability. On the other hand, polyamines are found in high concentrations in rapidly proliferating tumor cells due to up-regulation of the polyamine transport system, and their conjugation to biologically active molecules generally increases tumor selectivity and uptake. Another strategy used for increasing intracellular drug delivery is via conjugation to certain peptide sequences, in particular arginine- and/or lysine-rich cell-penetrating peptides (CPP) or nuclear localizing sequences (NLS), which are known to increase tumor cell uptake and nuclei-targeting.



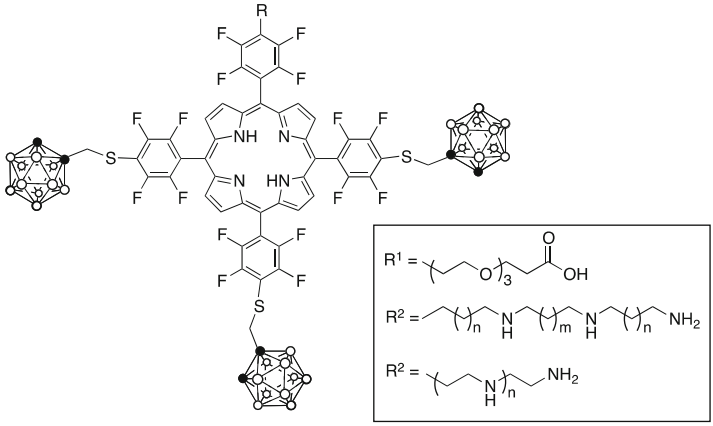
Porphyrin **33** containing three *ortho*-carboranes and a poly(ethylene glycol) group was synthesized in low yields by conjugation of the corresponding tri (carboranyl)porphyrin bearing a free amino group with a poly(ethylene glycol) monomethyl ether (MeOPEG550) chloroformate [78]. A higher yield was recently achieved for the synthesis of pegylated porphyrin **34** of larger boron content, via conjugation of a low molecular weight tri-PEG group to a *meso*-tetraarylporphyrin bearing six Co(III)-bis(dicarbollides) [60]. The precursor porphyrin was prepared by a mixed condensation of 3,5-dimethoxybenzaldehyde and methyl 4-formylbenzoate with pyrrole using Lindsey's method, followed by deprotection of the methoxy and ester groups with BBr_3 in 10% overall yield. The resulting free carboxylic acid group was conjugated to glycine *tert*-butyl ester followed by functionalization of the six hydroxyl groups with zwiterionic [3,3′-Co(8-$C_4H_8O_2$-1,2-$C_2B_9H_{10}$)(1′,2′-$C_2B_9H_{11}$)] and deprotection using TFA in 65% yield (three steps). Porphyrin **34** was obtained by conjugation of the PEG *tert*-butyl ester using HATU/HOBt/DIEA and deprotection with TFA in 19% overall yield.



34

Recently, boronated porphyrin **35** bearing a tri-PEG was prepared in higher yields using an alternative conjugation procedure, involving nucleophilic substitution of

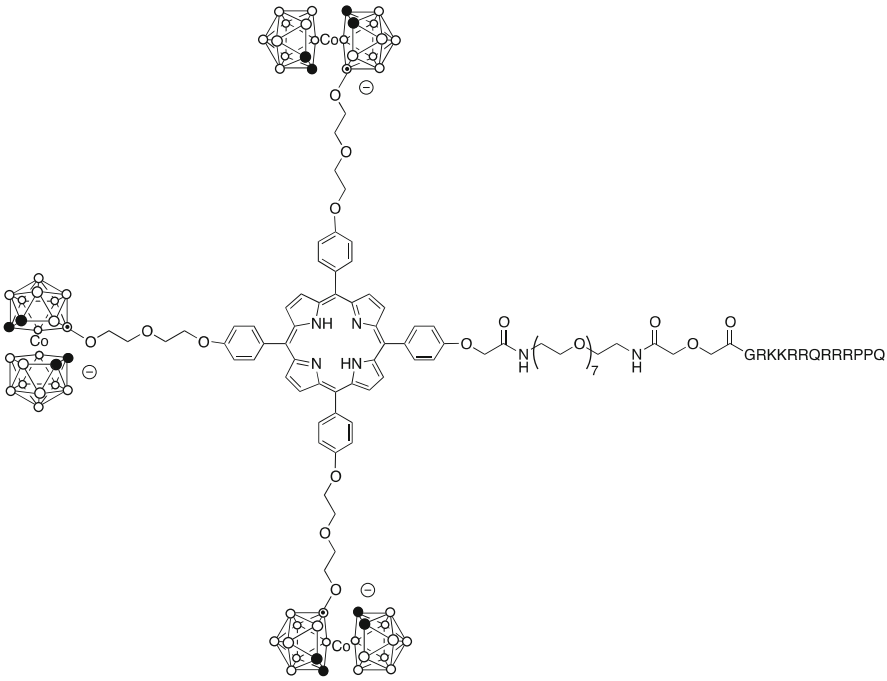
the *para*-fluoride of a pentafluorophenylporphyrin precursor [79]. Using this methodology, boronated porphyrins **36**–**42** bearing linear polyamines were also synthesized in high yields [79]. The tricarboranylporphyrin precursor to porphyrins **35**–**42** was obtained in 30% yield from reaction of *meso*-tetra(pentafluorophenyl) porphyrin with 1-mercaptomethyl-*para*-carborane. Conjugation of this porphyrin with the corresponding Boc-protected polyamines or *tert*-butyl-protected PEG using NMP at 100°C, followed by deprotection with TFA gave porphyrins **35**–**42** in >90% yields.



35: R = R^1
36: R = R^2, n = 0, m = 1
37: R = R^2, n = 1, m = 1
38: R = R^2, n = 1, m = 2
39: R = R^2, n = 1, m = 0
40: R = R^3, n = 2
41: R = R^3, n = 3
42: R = R^3, n = 4

The BOPP derivative **43** (as regioisomeric mixture) conjugated to a NLS was synthesized from *m*-BOPP (*meta*-carborane analogue of BOPP) by conjugation of a mixture of mono-methyl ester *m*-BOPP to the NLS peptide on rink amide resin, using HATU as the coupling agent [80].

Porphyrin **44** containing the cell-penetrating peptide HIV-1 Tat (48-60) with the sequence GRKKRRQRRRPPQ was prepared by conjugation of a porphyrin bearing three Co(III)-bis(dicarbollides) and a free carboxylic acid with the pegylated peptide on PAL-PEG-PS resin using HOBt/TBTU/DIPEA [59]. After cleavage from the solid support and deprotection using a mixture consisting of TFA/TIS/H_2O/phenol 88:2:5:5, porphyrin **44** was obtained in 8% yield.



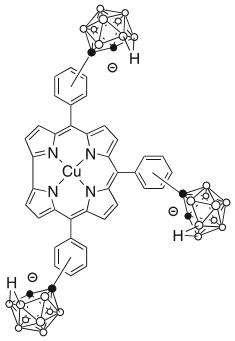
44

3.3 Carboranyl-Containing Corroles and Phthalocyanines

Corroles are tetrapyrrolic macrocycles with a direct pyrrole–pyrrole link. The total synthesis of tricarboranylcorroles **45** with the *nido*-carborane groups at *para*- or *meta*-phenyl positions was reported from the corresponding carboranyl-benzaldehydes and pyrrole, in about 10% yield [81]. The Lindsey method was used for the condensation reaction using excess of pyrrole (10 equiv.) to minimize the formation of the porphyrin. The insertion of Cu(III) ion using copper acetate in methanol was followed by fluoride-induced deboronation to give corroles **45** in quantitative yields.

The syntheses of several boron-containing phthalocyanines, including **46**–**52**, have been reported, both by tetramerization of a boron-substituted phthalonitrile and by direct functionalization of a pre-formed macrocycle. The total synthesis method is usually preferred, due to the poor solubility of these systems in most solvents, which renders the functionalization of the macrocycle difficult. However, in the case of *ortho*-carborane-containing phthalocyanines, functionalization of a pre-formed macrocycle is the preferred method because the basic conditions used during phthalocyanine synthesis often lead to degradation of the *ortho*-carborane cages. Zn(II)-phthalocyanines **46** were obtained as mixtures of regioisomers by

cyclotetramerization of the corresponding 3- or 4-*ortho*-carboranylphthalonitriles at 200°C, in the presence of zinc(II) acetate [82, 83].



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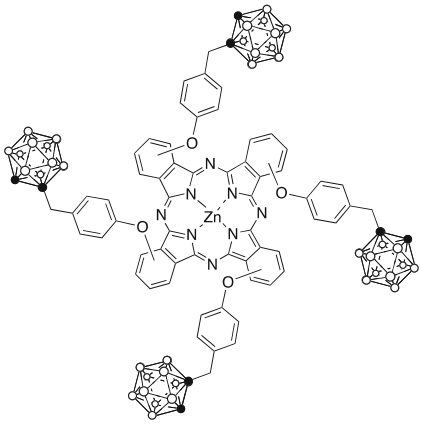

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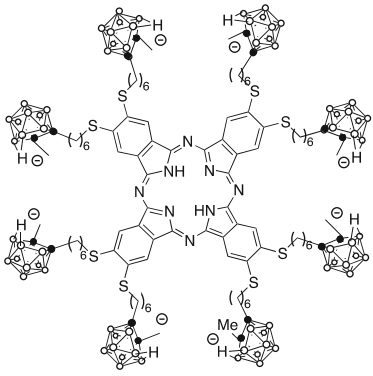

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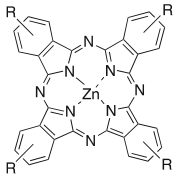
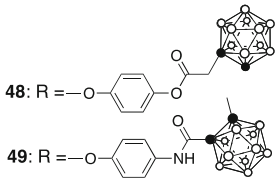
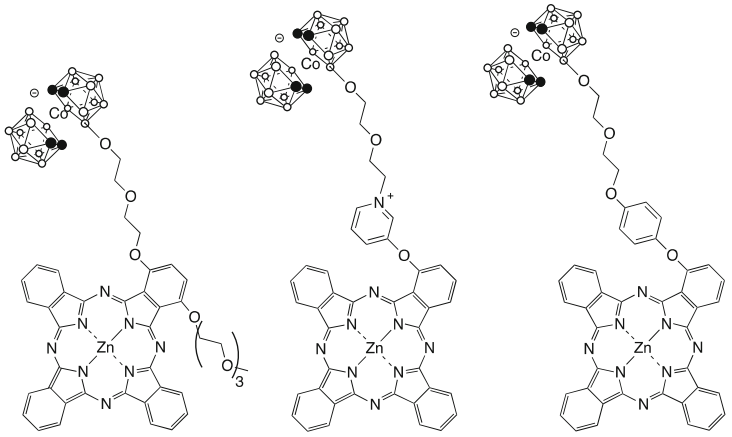




The symmetric and octa-anionic phthalocyanine **47** was synthesized in 30% yield via tetracyclization of the corresponding carborane-containing phthalonitrile in the presence of DBU and *n*-BuOH at 140°C [84]. The carboranylphthalonitrile was prepared by base-catalyzed aromatic nucleophilic substitution of 4,5-dichlorophthalonitrile with thiol-carborane.

Phthalocyanines **48** and **49**, as mixtures of regioisomers, bearing four *ortho*-carboranes were synthesized using the two strategies described above, by fuctionalization of a pre-formed macrocycle and by tetramerization of the corresponding carborane-containing phthalonitriles [85]. The former method gave the target compounds in 13–20% yields while self-condensation of the phthalonitrile

precursors gave only 1–10% yields. Regioisomerically pure phthalocyanines **50**–**52** were prepared by condensation of the corresponding boronated phthalonitrile with 30-fold excess of 1,2-dicyanobenzene, to produce the A_3B-type carboranylphthalocyanines as the only product in addition to the symmetric A_4-type phthalocyanine, which was removed by filtration [86, 87]. The carborane-containing phthalonitriles were prepared by nucleophilic ring opening of zwitterionic [3,3′-Co(8-$C_4H_8O_2$-1,2-$C_2B_9H_{10}$)(1′,2′-$C_2B_9H_{11}$)] by phenoxy- or pyridyl-functionalized phthalonitriles under basic conditions.



50 **51** **52**

4 Conclusions and Outlook

Over 100 boron-containing tetrapyrrolic macrocycles have been synthesized for application in BNCT following two main methodologies: by total synthesis from boronated monomeric precursors or from functionalization of a pre-formed macrocycle. However, only a few of these boronated macrocycles have been evaluated in preclinical biological investigations. The early reported carboranylporphyrins BOPP and CuTCPH were shown to deliver therapeutic amounts of boron to tumor-bearing mice, with high tumor-to-blood and tumor-to-brain boron concentration ratios [19, 34, 35, 39–41, 88–94]. Several other boronated macrocycles containing hydrolytically stable carbon–carbon linkages between the macrocycle and carborane groups (e.g., H_2TCP and H_2DCP) and/or higher amount of boron by weight than BOPP and CuTCPH (e.g., H_2OCP) were also shown to have low mice toxicity, and to deliver therapeutic amounts of boron to tumor-bearing mice [47, 54, 60, 65]. All other boronated porphyrin derivatives have only been evaluated in preliminary cellular studies, and their in vivo biological properties are still unknown.

Alternative routes for the in vivo administration of boronated porphyrin derivatives have been investigated with the aim to increase permeability across the BBB and tumor uptake. A very promising methodology is convection-enhanced delivery (CED), which is able to deliver extremely high amounts of boron (>100 μg/g) to intracerebral animal tumors, with very high tumor-to-normal brain and tumor-to-blood boron ratios, and no systemic toxicity [95–97].

Among the porphyrin derivatives, boronated chlorins, corroles, bacteriochlorins, and phthalocyanines can be used as dual BNCT and PDT sensitizers because of their absorptions of near-IR light that penetrates deeper into human tissues. The combination of the BNCT and PDT therapies could lead to higher efficacy of tumor treatment via the targeting of different mechanisms of tumor cell destruction. However, current clinical development of BNCT and investigation of the biological properties of new boron delivery agents are slow for a variety of reasons, including readily availability of adequate neutron sources and cost. Nevertheless, the outlook for BNCT is bright since this binary therapy offers new hope for otherwise untreatable cancers.

Acknowledgments The support from the US National Institutes of Health (grant number R01 CA 098902) is acknowledged.

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http://www.springer.com/978-3-662-43996-8

Applications of Porphyrinoids
Paolesse, R. (Ed.)
2014, VII, 177 p. 127 illus., 29 illus. in color., Hardcover
ISBN: 978-3-662-43996-8