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Boron-Containing Protoporphyrin IX Derivatives and Their Modification for Boron Neutron Capture Therapy: Synthesis, Characterization, and Comparative In Vitro Toxicity Evaluation

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Abstract: A novel series of boronated porphyrins for potential use in boron neutron capture therapy (BNCT) and photodynamic therapy (PDT) for tumor suppression is described. Protoporphyrin IX {i.e., bis(α-methyl-β-pentylethylether)protoporphyrin IX, and bis(α-methyl-β-dodecanylethylether)-protoporphyrin IX} bearing polyhedral borane anions ($B_{12}H_{11}SH^{2-}$, $B_{12}H_{11}NH_3^-$, or $B_{12}H_{11}OH^{2-}$) were synthesized with reasonable yields. Modification of the protoporphyrin IX structure was achieved by variation of the lengths of the alkyl chains (pentyl and dodecanyl) attached through ether linkages to the former vinyl groups. The goal of this modification was to develop boronated porphyrins with chemical and physical properties that differed from those of protoporphyrin IX. Performance of an MTT assay with each derivative revealed that the synthesized boronated porphyrins showed low cytotoxicities in a variety of cancer cells. Of these compounds, $B_{12}H_{11}NH_2^{2-}$-conjugated porphyrin induced a significant increase in the level of boron accumulation and PDT efficacy against HeLa cells.

Keywords: BNCT · boron · cluster compounds · photodynamic therapy · porphyrinoids

Introduction

Boron neutron capture therapy (BNCT)[1] and photodynamic therapy (PDT)[2] are two bimodal therapies with the potential to control local recurrences of malignant tumors. Both rely on the selective uptake and/or retention of a sensitizer molecule by the target cells and activation of that sensitizer by application of an external radiation source. PDT depends upon photosensitization of porphyrins and use of red laser light, which catalyzes the conversion of molecular oxygen into rapidly reactive cell toxins.[3] BNCT acts on similar principles, but makes use of the high capture cross-section of the boron-10 nucleus for thermal neutrons. An excited ^{11}B nucleus decays to yield highly energetic ^4He and ^7Li with a microscopic range of 5–9 μm. These particles can palliate or ablate ^{10}B-rich tumors. The quantity of sensitizer required for successful therapy has been estimated to be around 20–30 ppm boron.[1c,4]

The family of dyes most extensively studied with respect to PDT and BNCT are the porphyrins and related macrocycles (e.g., chlorines, phthalocyanines, and porphyrazines).[1c,5] In many aspects, these drugs appear to act similarly. For a porphyrin to be useful in either of these therapies, it should be accumulated or retained in the tumor tissue in preference to the surrounding healthy tissue. There are several uptake mechanisms for porphyrins into tumor cells,[6] but there exists no general rule for the nature of the structure/uptake correlation. The compounds currently used for clinical trials of BNCT applied to malignant brain tumors are the sodium mercaptoundecahydrododecaborate $Na_2B_{12}H_{11}SH$ (BSH) and the amino acid *p*-boronophenylalanine (BPA), which yield tumor/blood boron concentration ratios of 1:1 and 3:1, respectively.[7,8] It would be useful if combinations of these and/or new boron carriers could achieve higher tumor-selective ratios without undesirable chemotoxicity.

Strategies for achieving this goal focus on obtaining higher boron concentrations in the tumor and better selectivity of the boron carrier for tumor cells than for blood and normal tissues. A variety of boronated porphyrins designed to have a higher weight proportion of boron per molecule than BPA have been synthesized.[9–12] Previous studies have

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shown that the tetrakis-carborane carboxylate ester of 2,4-bis-(α,β-dihydroxyethyl)deuteroporphyrin IX (BOPP) is one such porphyrin. It contains ~30% boron by weight and appears to be a good boron carrier in different glioma animal models.[13] The pharmacokinetic behavior of BOPP, in contrast both with that of BPA and with that of BSH, in both small and large animals, as well as in humans, is characterized by a relatively slow rise in tumor boron levels over a period of several hours or even days.[13,14]

The disadvantages of BOPP are as follows: i) it has toxic side effects, most notably thrombocytopenia, which limits the dose that can be tolerated by humans, ii) relative boron levels reached in human tumors are insufficient to permit clinically effective BNCT, and iii) the plasma pharmacokinetic behavior of BOPP in humans is characterized by a prolonged clearance phase, giving rise to potentially toxic metabolites and cutaneous photosensitivity.[15]

Another strategy tested in an attempt to optimize this treatment was through the investigation of a boronated porphyrin (BOPP) in combination with BPA (a cocktail of two BNCT drugs). The results showed that the combination of BOPP and BPA gave much higher tumor boron concentrations and better tumor selectivity than either drug administered alone.[16] Recently, tetraphenylporphyrins containing polyhedral borane anions were synthesized, and their toxicological profiles in rats were determined.[17] The results showed that thrombocytopenia toxicity limited the dose of boronated porphyrins in mammals, which suggests that the toxicity may arise from the porphyrin moiety rather than from the borane or carborane moiety.

Here we report a series of protoporphyrin IX derivatives with systematically altered properties. These compounds differ from one another not only in the natures of the covalent bonds between the porphyrin and the dodecaborate anion components, but also in the lengths of the alkyl chains that chemically link the dodecaborate, through ether bonds, to the former vinyl groups of protoporphyrin IX (**1**, Figure 1).Variation of the alkyl chain lengths of the linkages, as well as testing with different borate moieties, are important for the creation of molecules that exhibit a wide spectrum of solubility.

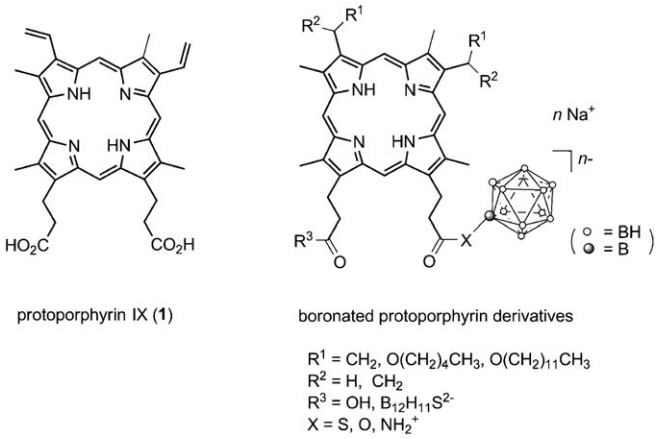


Figure 1. Schematic structures of protoporphyrin IX (**1**) and sodium salts of boronated protoporphyrin derivatives.

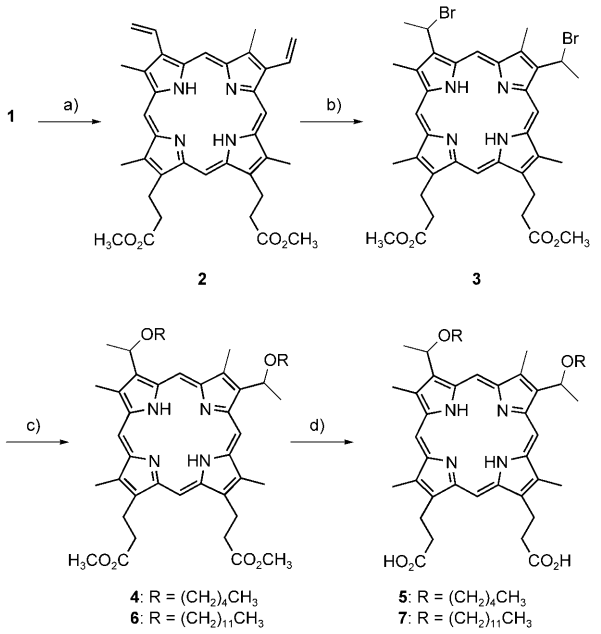
Results and Discussion

Synthesis: Naturally occurring porphyrin systems have occasionally been used for conjugation with boron clusters.[5c] Here we report the synthesis of a series of compounds with systematically varying properties. Esterification of commercially available **1** with H_2SO_4/MeOH (5%) for 18 h at −10 °C in the dark gave protoporphyrin IX dimethyl ester (PP-IX dimethyl ester, **2**).[18] Even on a scale of 1 g, yields of **2** exceeding 95% are routinely obtained. The vinyl groups in **2** were hydrobrominated with HBr/AcOH (25%) to yield the corresponding bis(α-methyl-β-bromo)protoporphyrin IX dimethyl ester **3** in >92% yield (Scheme 1). This very mild, clean method does not hydrolyze the ester side chains and produces virtually no side products. Treatment of **3** with pentan-1-ol and potassium carbonate (K_2CO_3) for 2 h at room temperature (RT) gave the corresponding ether compound {bis(α-methyl-β-pentylethylether)protoporphyrin IX dimethyl ester (**4**)} in 95% isolated yield. Incubation of **4** in a THF/MeOH/H_2O (1:1:1) mixture with LiOH·H_2O for 6 h resulted in cleavage of the dimethyl esters to give bis(α-methyl-β-pentylethylether)protoporphyrin IX **5** in 87% yield with no evidence of ether bond cleavage (Scheme 1). Similarly, bis(α-methyl-β-dodecanylethylether)protoporphyrin IX dimethyl ester (**6**) and bis(α-methyl-β-dodecanylethylether)protoporphyrin IX (**7**) were prepared in 97% and 90% yields, respectively, with dodecan-1-ol as the alcohol source (Scheme 1).

An alternative route for direct conversion of **1** into the corresponding ether compound (**5** or **7**) without esterification of the free carboxylic acid groups is also possible, but this method, although it saves time, results in only a 55% isolated yield.

One of the goals of our synthetic work was the successful preparation and characterization of a structurally diverse series of water-soluble dodecaborate anions derived from compounds **1**, **5**, and **7**. Polyhedral borane anions (such as $B_{12}H_{11}SH^{2-}$, $B_{12}H_{11}NH_3^-$, or $B_{12}H_{11}OH^{2-}$)[19,20] are often the clusters of choice for binding to porphyrins because of their known chemistry, hydrophilic properties, high boron contents, and chemical stabilities. Moreover, the carboxylic acid group was chosen for the linkage chemistry largely as a result of the breadth of stable derivatives that could potentially be formed from known polyhedral dodecaborate anions. As a result, amide, thioester, and oxoester derivatives were successfully prepared and characterized (Figure 1).

Activation of the carboxylic acid groups of the porphyrins **1**, **5**, or **7** with oxalyl chloride allowed the attachment of $[(CH_3)_4N]_2B_{12}H_{11}SH$ (BSH), to give surprisingly stable thioesters. This reaction was utilized to prepare bis(tetramethylammonium)protoporphyrin IX monothioester undecahydro-

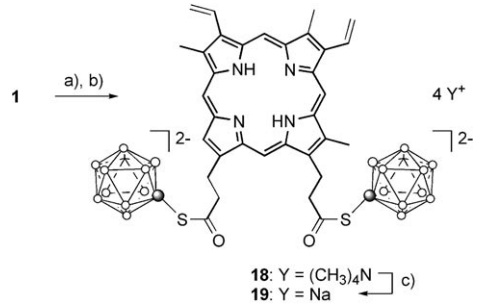


Scheme 1. Synthesis of long-chain PP-IX derivatives **5** and **7** from **1**. a) H_2SO_4/MeOH (5%), −10°C, 18 h. b) HBr/ACOH (25%), RT, 2 h. c) ROH, CH_2Cl_2, K_2CO_3, RT, 1 h. d) LiOH, MeOH/H_2O/THF, RT, 6 h.

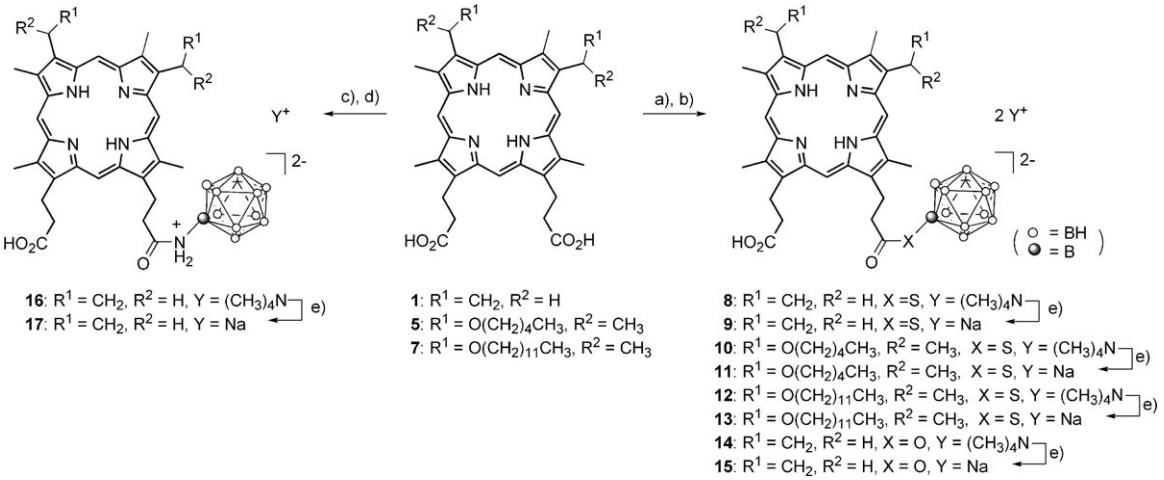
closo-dodecaborate (**8**), bis(tetramethylammonium)bis(α-methyl-β-pentylethylether)protoporphyrin IX monothioester undecahydro-*closo*-dodecaborate (**10**), or bis(tetramethylammonium)bis(α-methyl-β-dodecanylethylether)protoporphyrin IX monothioester undecahydro-*closo*-dodecaborate (**12**) in reasonable yields (Scheme 2). One of the most important requirements of BNCT agents is water solubility. The transformation of the tetramethylammonium salt into the sodium salt is the simplest way to increase the water solubility of a BSH-containing porphyrin. The compounds **8**, **10**, and **12** were highly water-soluble when converted from the tetramethylammonium salts used in the synthesis into their sodium salts (compounds **9**, **11**, and **13**, respectively) by ion-exchange chromatography.

In a similar approach, the oxoester (bis(methyltriphenylphosphenium)protoporphyrin IX monooxoester undecahydro-*closo*-dodecaborate, **14**) was prepared by coupling $(MePh_3P)_2B_{12}H_{11}OH$ (BOH) to the acid chloride of compound **1** (Scheme 2). The water-soluble sodium salt (**15**) was obtained by ion exchange. Synthesis of **14** by the procedures of Kahl et al.[17] is also possible, but the yield of the product was very low. The amide (bis(tetramethylammonium)protoporphyrin IX monoamide undecahydro-*closo*-dodecaborate, **16**) was synthesized afterwards to determine whether it could improve upon the biological properties of **1** (Scheme 2). Ion exchange afforded the sodium salt **17**, which was water-soluble.

Similarly to **9**, tetrakis(tetramethylammonium)protoporphyrin IX bis(thioester) undecahydro-*closo*-dodecaborate (**18**) was prepared in 74% yield from the acid chloride of **1** and BSH (Scheme 3). As in the cases of the lipophilic tetramethylammonium salts, this compound was also converted into the water-soluble sodium salt (**19**) by ion exchange prior to administration. The advantage of a com-



Scheme 3. Synthesis of compound **19**: a) CH_2Cl_2, $(COCl)_2$, RT, 1 h. b) $[(CH_3)_4N]_2B_{12}H_{11}SH$, CH_3CN, C_5H_5N, RT, 72 h. c) Ion-exchange with Amberlite 120R (Na^+ form).



Scheme 2. General pathway for the synthesis of anionic boronated porphyrins **8**, **10**, **12**, **14**, and **16**: a) CH_2Cl_2, $(COCl)_2$, RT, 1 h. b) $B_{12}H_{11}XH^{2-}$ (X = S or O), CH_3CN, C_5H_5N, RT, 72 h. c) CH_2Cl_2, $(COCl)_2$, RT, 1 h. d) $[(CH_3)_4N]B_{12}H_{11}NH_3$, DMF, NaH, C_5H_5N, RT, 72 h. e) Ion-exchange with Amberlite 120R (Na^+ form).

pound such as **19**, bearing such a high percentage of boron by weight (~27%), is that it can potentially deliver high (therapeutic) quantities of boron to tumor targets with tolerable toxicity.

These results are interesting because these compounds differ in the natures of the functional groups linking the porphyrin carboxylic group and the dodecaborate anion, the resulting overall charges of the porphyrin-borane conjugates, and the lengths of the ether chains. The structures and purities of the new compounds were confirmed by ^{11}B, ^{1}H, and ^{13}C NMR spectroscopy, IR, UV/Vis, and fluorescence spectroscopy, mass spectrometry, and elemental analysis (see Experimental Section).

Spectroscopic characterization: The ^{1}H NMR spectra of compounds **3**–**17** were consistent with their proposed structures, showing the expected features and correct integration ratios. We observed high-field shifts of the CH components of the former vinyl groups in compounds **3**–**7** from 7.58 ppm to ca. 6.1 ppm. Large deviations in the positions of these signals were observed in compounds **3**–**7**, as would be expected. Moreover, the chemical shifts of the CH_2 components of the former vinyl groups were also changed, from 7.25 ppm to ca. 2.2 ppm, indicating the presence of the saturated form (CH_3 groups). In addition, the ^{13}C NMR spectra showed high-field shifts of ca. 18 ppm for the CH carbon atoms of compounds **4**–**7** (74.2 ppm) relative to compound **1** (56.2 ppm). Other NMR spectroscopic data for the series of compounds (**5**, **7**, and **10**–**13**) were similar, although there were some minor variations in the proton shielding as the alkoxy groups changed (see Experimental Section).

Polyhedral borane anions of the types $B_{12}H_{11}SH^{2-}$, $B_{12}H_{11}OH^{2-}$, and $B_{12}H_{11}NH_3^-$ were easily identified by NMR spectroscopy, because their ^{11}B NMR spectra presented a characteristic shielding pattern over the quite remarkable range of ca. −22 to +7 ppm, showing only minor differences in the overall ^{11}B cluster shielding patterns. The spectra of all boronated porphyrins (**8**–**19**) showed 1:5:5:1 patterns typical of monosubstituted B_{12} derivatives.

Evidence in support of structures **2**–**7** was also obtained by mass spectrometry. The ESI-MS spectra of these compounds in MeOH showed molecular ion peaks—$[M]^+$ or $[M+1]^+$—consistent with the formula of each compound. The boronated porphyrins **8**–**15**, **18**, **19**, and **16**–**17** showed the molecular ion peaks—($[M]^-/2$) and ($[M]^-$)—attributable to the typical pattern of boron isotopes (^{10}B and ^{11}B, respectively).

The UV/Vis absorption spectra of all porphyrins in CH_3CN or H_2O (10 μM) each contained a high-energy Soret band (peak position = ca. 410 nm) and lower-energy Q-bands (peak positions = ca. 515, 535, 585, 635 nm) arising from π–π* transitions, typical for the protoporphyrin IX (**1**) framework. However, emission spectral studies in ethanol each showed an emission fluorescence band at ca. 635 nm for compounds **1**, **9**, **15**, **17**, and **19**, caused by the bathochromic shift of 10 nm in relation to the BOPP, **11**, and **13** emission bands at ca. 625 nm. The fluorescence quantum yields (Φ_f) of compounds **1**, **9**, **11**, **13**, **15**, **17**, and BOPP were calculated relative to rhodamine 101 in ethanol as a standard ($\Phi_f = 1.00$)[21a] by the comparative method.[21b,c] Free protoporphyrin IX (**1**) showed a Φ_f value of 0.1, whereas BOPP, **11**, and **13** showed Φ_f values of 0.091, 0.095, and 0.093, respectively. Conjugation of the propanoic acid group of **1** with dodecaborate anions enhanced the fluorescence of **1** only slightly more than BOPP (Φ_f = ca. 0.12). Presumably, the binding of the carborane ester or alkoxy moieties at the former vinyl groups of **1** locked the rotational mobility of **1** in a rigid structure, whereas compounds **9**, **15**, **17**, and **19** did not bind significantly to **1**.

The IR spectra of compounds **5** and **7** showed absorption bands in the 3585–3565 cm^{-1} and 1745 cm^{-1} regions, characteristic of the free OH and C=O groups, respectively, of free diacids. However, the boronated porphyrins (**8**–**17**) each showed two different vibrational frequencies for the C=O bonds {ν(C=O)}, at ca. 1725 and 1685 cm^{-1}, indicating substantial electron donation from the borane anion into the linkage group. Moreover, the vibrational frequencies of the B−H bonds {ν(B−H)} or the B−B bonds {ν(B−B)} were not found to be sensitive to conjugation with the boron cluster. For compounds **8**–**19**, ν(B−H) lay in the 2495–2500 cm^{-1} range, whereas ν(B−B) varied from 1050 to 1080 cm^{-1}. Of the frequencies associated with the $B_{12}H_{12}^{2-}$ moiety {ν(B−H) 2486 to 2462 cm^{-1}; ν(B−B) 1073 to 1057 cm^{-1}},[22] only slight differences between the compounds were found, indicating that intracluster bonding was not perturbed by the substitution of the icosahedron.

Biology: Boronated porphyrins are an important class of tumor-localizing agents in two bimodal therapies for cancer: BNCT and PDT. The boronated porphyrins are characterized by several desirable properties: i) they are easily synthesized, pure, and well-characterized drugs, ii) they are stable in vivo and are tumor-specific, iii) they yield high tumor/blood and tumor/normal tissue boron concentration ratios, and iv) they are minimally toxic.

In view of the above desirable characteristics, we prepared and characterized a series of porphyrins bearing polyhedral borane anions. We first examined the cell toxicities of the synthesized boronated porphryins toward a variety of cancer cells by means of an MTT—3′-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide—assay. Of the boronated porphyrins, the BSH-conjugated porphyrin **9** showed low cytotoxicity in relation to its alkylated compounds **11** and **13** and BOPP (Table 1). Furthermore, the BOH- and BNH_2-conjugated porphyrins (**15** and **17**) also exhibited lower levels of cytotoxicity than BOPP toward various cancer cells, with the exception of C6 cells (Table 1). We also examined the cytotoxicity of porphyrin **19**, with two polyhedral borane anions in the molecule: conversely, the more hydrophilic porphyrin **19** (IC_{50} = 182.9 μM) was found to be more cytotoxic toward C6 cells than porphyrin **9** (IC_{50} = 382.2 μM). These results indicate that conjugation of only one polyhedral borane anion to porphyrin resulted in reduced cytoxicity.

Table 1. Cytotoxicities in IC_{50} [μM] of boronated porphyrins.

Porphyrin	HeLa	C6	B16	CT26	HepG2	HCT15	HCT116
9	306.7±13.9	382.2±35.4	533.3±1.4	382.6±6.5	811.1±6.0	404.4±4.3	436.2±20.2
11	161.8±15.9	75.8±2.8	138.9±3.5	124.3±10.6	214.7±15.9	142.2±1.4	88.3±6.6
13	51.9±2.2	69.1±0.6	81.0±12.5	107.7±7.2	182.9±9.7	169.3±12.8	94.7±2.2
15	196.4±25.7	69.2±6.7	241.2±9.2	359.1±9.0	248.2±2.7	235.7±18.9	212.8±4.6
17	227.2±14.9	246.8±9.8	301.3±4.7	374.4±5.5	658.7±4.1	233.5±1.3	285.1±5.1
BOPP	95.9±15.1	114.1±5.1	167.6±7.1	182.2±1.3	175.1±1.3	175.7±8.4	128.3±14.4

The various cancer cells were incubated for 72 h in the presence of each boronated porphyrin, and the ratios of viable cells were determined by MTT assay. The drug concentration required to inhibit cell growth by 50% (IC_{50}) was determined from semilogarithmic dose-response plots, and results represent the means ±SDs of triplicate samples.

We next examined the levels of intracellular accumulation of the boronated porphyrins through determination of boron concentrations in HeLa cells by ICP-AES (inductively coupled plasma atomic emission spectroscopy). As shown in Figure 2, the accumulations of boron increased with increasing concentration of boronated porphyrins. The accumulated boron concentrations obtained with compounds **9** and **11** were similar to that seen with BOPP. Interestingly, compounds **13**, **15**, and **17** each showed a fourfold increase in selective accumulation relative to other compounds. The assays with compounds **9**, **11**, and **13** showed that cell uptake increased with increasing porphyrin lipophilicity. Furthermore, fluorescence imaging after treatment for 3 h revealed that compound **17** and BOPP accumulated mainly in the cytosol (Figure 3).

Table 2 shows the PDT response driven by boronated porphyrins and BOPP in HeLa cells. Concentrations of 14.4, 2.71, 4.97, 0.6, 0.21, and 4.83 μM for compounds **9**, **11**, **13**, **15**, **17** and BOPP, respectively, did not induce cytotoxicity, whereas the boronated porphyrins reduced cell viability. Of the compounds, BOH- and BNH_2-conjugated porphyrins (**15** and **17**) showed activities more potent than that of BOPP, with IC_{50} values of 0.60 and 0.21 μM, respectively. However, the BSH-conjugated porphyrin (compound **9**) displayed a threefold reduction in PDT efficacy relative to BOPP. These results suggest that the PDT efficacies of boronated compounds, determined by cell viability, were correlated with the levels of cell accumulation in the cases of compounds **15** and **17**.

Conclusions

We have demonstrated a very simple, efficient, and practical strategy for the synthesis of novel water-soluble boronated porphyrins in good to high yields. Functionalized porphyrins are very useful precursors in advanced boronated porphyrin synthesis, which explains the current interest in finding efficient synthetic methods for the preparation of these species. Importantly, these new structurally varied boronated porphyrins displayed a wide spectrum of water solubilities and surprising spectroscopic properties with extremely stable and nontoxic *closo*-borane anions. These improvements indicate the potential to decrease the compounds' plasma half-lives relative to those of previously investigated boronated porphyrins such as BOPP. Furthermore, we found that the boronated porphyrins exhibited low cytotoxicities and high levels of accumulation and induced potent PDT effects with a variety of cancer cell lines. These encouraging results suggest the possible application of these compounds for combined BNCT and PDT tumor suppression.

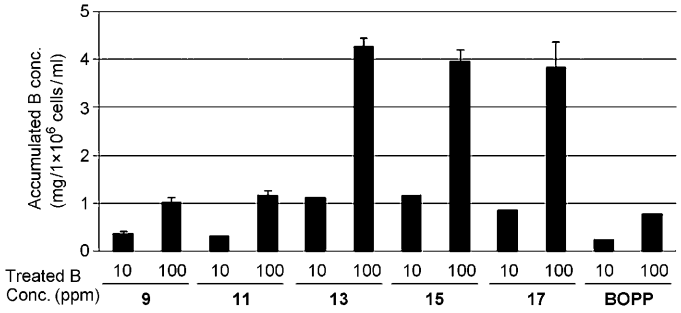


Figure 2. Intracellular uptake of boronated porphyrins. Various cancer cell types were incubated for 3 h in the presence of each boronated porphyrin. After incubation, the cells were digested and their boron contents were determined by inductively coupled plasma atomic emission spectroscopy (ICP-AES).

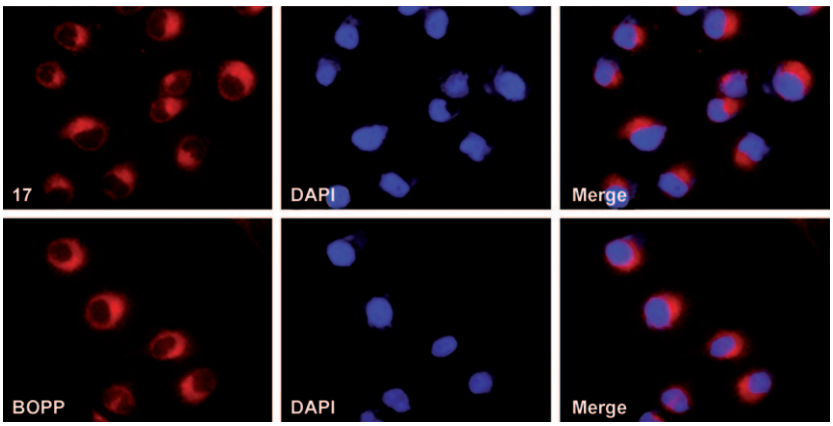


Figure 3. Fluorescence imaging of boronated porphyrins in HeLa cells. The cells were incubated for 3 h either with compound **17** or with BOPP (100 mM). After incubation, the cells were washed three times with PBS, and the boronated porphyrins were detected by fluorescence microscopy. The cell nuclei were stained with DAPI, shown in blue.

Table 2. PDT effects of boronated porphyrins.

Porphyrin	IC_{50} [μM]	Porphyrin	IC_{50} [μM]
9	14.4 ± 0.30	**15**	0.60 ± 0.06
11	2.71 ± 0.14	**17**	0.21 ± 0.04
13	4.97 ± 0.24	BOPP	4.83 ± 0.75

HeLa cells were incubated for 3 h in the presence of each boronated porphyrin and were then irradiated for 5 min with a xenon lamp (400–800 nm, average 2.4 mW cm^{-2}). After further incubation for 12 h, the ratios of viable cells were determined by MTT assay. The drug concentrations required to inhibit cell growth by 50% (IC_{50}) were determined from semilogarithmic dose-response plots, and results represent the means ± SDs of triplicate samples.

Experimental Section

Materials and methods: ^{1}H NMR and ^{13}C NMR spectra were measured with Jeol JNM-AL 300 (300 MHz) and Varian Unity-Inova 400 (400 MHz) spectrometers. ^{1}H NMR and ^{13}C NMR chemical shifts are expressed in parts per million (ppm, δ units), and coupling constants are expressed in hertz (Hz). ^{11}B NMR spectra were recorded with a JEOL JNM-AL 300 spectrometer (96.3 MHz) and the chemical shifts are reported in δ units relative to external $BF_3{\cdot}Et_2O$ in $CDCl_3$. IR spectra were measured with a Shimadzu FTIR-8200 A spectrometer. UV/Vis spectra were measured with a Shimadzu 2450 PC spectrophotometer over the 300–700 nm wavelength range. Elemental analyses were performed with a Perkin–Elmer 2400 automatic elemental analyzer. The fluorescence (excitation and emission) spectra were determined with a Jasco FP-6500 PC spectrophotometer. Electron spray ionization (ESI) mass spectra were recorded with a Shimadzu LCMS-2010 eV spectrometer. Analytical thin-layer chromatography (TLC) was performed on glass plates (Merck Kieselgel 60 F_{254}, layer thickness 0.2 mm). Samples were visualized with the aid of UV light (254 nm), I_2, or $KMnO_4$. Column chromatography was performed on silica gel (Merck Kieselgel 70–230 mesh). Preparative thin layer chromatography (TLC) was carried out with 0.75 mm layers of silica gel G (Merck, GF_{254}) made from water slurries on glass plates of dimensions 20 × 20 cm^2, followed by drying in air at 100 °C. All reactions were performed in darkness in dry solvents and under argon with use of standard Schlenk techniques. Most chemicals were of analytical grade and were used without further purification. BOPP, PP-IX dimethyl ester (**2**), $[(CH_3)_4N]_2B_{12}H_{11}SH$, $[(CH_3)_4N]B_{12}H_{11}NH_3$, and $(MePh_3P)_2B_{12}H_{11}OH$ were prepared as described in the literature[9d,18–20] and stored at −20 °C.

Bis(α-methyl-β-pentylethylether)protoporphyrin IX dimethyl ester (4): Compound **2** (1.0 mmol, 590 mg) was dissolved in HBr/acetic acid (25%, 30 mL) under argon and the mixture was stirred for 2 h. All volatile solvents were evaporated under vacuum to yield the green colored bis(α-methyl-β-bromo)PP-IX dimethyl ester (**3**). The resulting substance was directly dissolved in dichloromethane (50 mL). Pentan-1-ol (2.2 mmol, 194 mg) and K_2CO_3 (2.2 mmol, 304 mg) were added to the dichloromethane solution. The reaction mixture was again stirred under argon for 2 h and filtered, and the resulting filtrate was concentrated to dryness. The residue, consisting of the crude product, was then purified by repeated thin layer chromatography (TLC) on silica gel with CH_2Cl_2 and MeOH (17:3) as liquid phase to yield compound **4** as dark violet crystals. Yield (728 mg, 95%) as a dark violet solid; R_f = 0.45 (CH_2Cl_2/MeOH 17:3); ^{1}H NMR (300 MHz, [D$_6$]DMSO, 25 °C, TMS): δ = 10.58–10.36 (s, 4H; *meso*-H), 6.12 (m, 2H; α-CH), 4.28 (m, 4H; porphyrin-CH_2), 3.89, 3.82 (s, 6H; COOMe), 3.71, 3.69, 3.68, 3.62 (s, 12H; β-CH_3), 3.48 (t, J = 13.2 Hz, 4H; CH_2COOMe), 3.12 (4H; m, OCH_2), 2.22 (d, J = 7.0 Hz, 6H; CH_3), 1.75, 1.41, 1.21 (12H; m, CH_2), 0.78 (t, J = 12.9 Hz, 6H; CH_3), −3.95 ppm (s, 2H; NH); ^{13}C NMR (75 MHz, [D$_6$]DMSO, 25 °C, TMS): δ = 177.08 (2C; CO), 145.2, 144.98, 144.05, 143.87, 139.15, 136.85, 136.18, 125.03 (16C; C pyrrole), 98.54, 98.02, 97.98, 97.74 (4C; *meso*-C), 75.14, 73.16 (2C; O−CH), 61.27, 57.19 (2C; OCH_2), 47.86 (2C; COOMe), 31.98, 30.79 (2C; CH_2COOMe), 28.56, 28.06, 27.47, 27.17, 26.25, 25.74 (6C; $-CH_2-$), 23.21, 23.25 (2C; CH_2CH_2COOMe), 21.57, 21.65, 14.02, 13.63, 11.36, 11.86 ppm (8C; CH_3); IR (KBr disc): $\tilde{\nu}$ = 3310 w (CH), 2989 s, 2927 s (NH), 1755 s (C=O), 1710 s (C=C), 1605 s (NH), 1415 s (CH_3), 11495 s (CN), 2965 m, 2895 m, 1475 m, 1442 m, 1409 m, 1169 m, 1098 s, 752 m cm^{-1} (δ, γ of CH_2 groups); UV/Vis (CH_3CN): λ_{max} = 415, 523, 537, 594, 635 nm; MS (ESI, positive): m/z (%): 767 (100) $[M]^+$; elemental analysis calcd (%) for $C_{46}H_{62}N_4O_6$ (767.01):C 72.03, H 8.15, N 7.30; found: C 71.96, H 8.12, N 7.27.

Bis(α-methyl-β-pentylethylether)protoporphyrin IX (5): Compound **4** (1.0 mmol, 767 mg) was dissolved in a THF/MeOH/H_2O mixture (15 mL, 1:1:1). $LiOH{\cdot}H_2O$ (2.2 mmol, 92.3 mg) was added and the reaction mixture was stirred for 6 h at room temperature. The reaction mixture was filtered and the volume of the filtrate was reduced under vacuum (5 mL). HCl (1 N, 2 mL) was slowly added to this solution with stirring to precipitate the dark violet solid, which was filtered off and then washed with water (5 mL) to give **5**. Yield (642 mg, 87%) as a dark violet solid; ^{1}H NMR (300 MHz, [D$_6$]DMSO, 25 °C, TMS): δ = 10.65–10.43 (s, 4H; *meso*-H), 6.14 (m, 2H; α-CH), 4.33 (m, 4H; porphyrin-CH_2), 3.69, 3.67, 3.65, 3.63 (s, 12H; β-CH_3), 3.54 (t, J = 12.6 Hz, 4H; CH_2COOH), 3.08 (m, 4H; OCH_2), 2.17 (d, J = 8.0 Hz, 6H; CH_3), 1.73, 1.35, 1.16 (m, 12H; CH_2), 0.7 (t, J = 16.2 Hz, 6H; CH_3), −3.96 ppm (s, 2H; NH); ^{13}C NMR (75 MHz, [D$_6$]DMSO, 25 °C, TMS): δ = 175.11 (2C; CO), 147.2, 146.51, 145.79, 145.78, 140.02, 136.92, 136.28, 124.88 (16C; C pyrrole), 98.39, 97.97, 97.72, 97.36 (4C; *meso*-C), 74.05, 72.47 (2C; O−CH), 60.67, 56.61 (2C; OCH_2), 32.18, 30.4 (2C; CH_2COOH), 29.4, 29.21, 28.12, 27.7, 25.25, 25.08 (6C; $-CH_2-$), 22.32, 22.22 (2C; CH_2CH_2COOH), 21.99, 21.88, 13.92, 13.73, 11.2, 11.56 ppm (8C; CH_3); IR (KBr disc): $\tilde{\nu}$ = 3309 w (CH), 2987 s, 2927 s, 2860 s (OH/NH), 1745 s (C=O), 1706 s (C=C), 1600 s (NH), 1410 s (CH_3), 1145 s (CN), 2961 m, 2889 m, 1471 m, 1439 m, 1405 m, 1165 m, 1093 s, 749 m cm^{-1} (δ, γ of CH_2 groups); UV/Vis (CH_3CN): λ_{max} = 415, 520, 539, 595, 639 nm; MS (ESI, positive): m/z (%): 739 (100) $[M]^+$; elemental analysis calcd (%) for $C_{44}H_{58}N_4O_6$ (738.95):C 71.52, H 7.91, N 7.58; found: C 71.33, H 7.81, N 7.49.

Bis(α-methyl-β-dodecanylethylether)protoporphyrin IX dimethyl ester (6): This compound was prepared from **2** (1.0 mmol, 590 mg) and dodecanol (2.2 mmol, 410 mg) by the procedure described for **4**, to give **6** (934 mg, 97%) as a dark violet solid; R_f = 0.52 (CH_2Cl_2/MeOH 17:3); ^{1}H NMR (300 MHz, [D$_6$]DMSO, 25 °C, TMS): δ = 10.65, 10.57, 10.35, 10.12 (s, 4H; *meso*-H), 6.08 (m, 2H; α-CH), 4.34 (m, 4H; porphyrin-CH_2), 3.85, 3.79 (s, 6H; COOMe), 3.67, 3.64, 3.59, 3.50 (s, 12H; β-CH_3), 3.01 (m, 4H; CH_2COOMe), 2.56 (m, 4H; OCH_2), 2.13 (d, J = 6.0 Hz, 6H; CH_3), 1.71–1.17(m, 20H; CH_2), 0.83 (t, J = 13.2 Hz, 6H; CH_3), −3.95 ppm (s, 2H; NH); ^{13}C NMR (75 MHz, [D$_6$]DMSO, 25 °C, TMS): δ = 179.02 (2C; CO), 147.26, 147.05, 146.23, 145.14, 141.15, 134.65, 133.92, 124.95 (16C; C pyrrole), 99.21, 98.25, 97.65, 97.47 (4C; *meso*-C), 75.03 (2C; O−CH), 57.07 (2C; OCH_2), 48.35 (2C; COOMe), 31.47, 30.13 (2C; CH_2COOH), 29.01–25.36 (20C; $-CH_2-$), 24.99, 24.12 (2C; CH_2CH_2COOMe), 23.16, 22.06, 14.95, 13.14, 11.36, 11.43 ppm (8C; CH_3); IR (KBr disc): $\tilde{\nu}$ = 3310 w (CH), 3300 s, 2950 s (NH), 1755 s (C=O), 1681 s (C=C), 1609 s (NH), 1417 s (CH_3), 1152 s (CN), 2965 m, 2866 m, 1479 s, 1454 s, 1412 m, 1316 m, 1168 m, 1100 s, 885 m, 715 m cm^{-1} (CH_2 groups); UV/Vis (CH_3CN): λ_{max} = 419, 526, 538, 595, 639 nm; MS (ESI, positive): m/z (%): 963 (100) $[M]^+$; elemental analysis calcd (%) for $C_{60}H_{90}N_4O_6$ (963.38): C 74.8, H 9.42, N 5.82; found: C 74.69, H 9.38, N 5.77.

Bis(α-methyl-β-dodecanylethylether)protoporphyrin IX (7): This compound was prepared from **6** (1.0 mmol, 963 mg) by the procedure described for **5** to give **7** (842 mg, 90%) as a dark violet solid; ^{1}H NMR (300 MHz, [D$_6$]DMSO, 25 °C, TMS): δ = 10.59, 10.5, 10.47, 10.15 (s, 4H; *meso*-H), 6.07 (m, 2H; α-CH), 4.37 (m, 4H; porphyrin-CH_2), 3.71, 3.68, 3.65, 3.63 (s, 12H; β-CH_3), 2.95 (m, 4H; CH_2COOH), 2.61 (m, 4H; OCH_2), 2.18 (d, J = 6.0 Hz, 6H; CH_3), 1.85–0.81 (m, 20H; CH_2), 0.72 (t, J = 13.2 Hz, 6H; CH_3), −3.92 ppm (s, 2H; NH); ^{13}C NMR (75 MHz, [D$_6$]DMSO, 25 °C, TMS): δ = 177.82 (2C; CO), 148.78, 147.35, 146.33, 145.6, 141.12, 134.76, 133.73, 125.14 (16C; C pyrrole), 98.39, 97.97, 97.72, 97.36 (4C; *meso*-C), 74.72 (2C; O−CH), 56.17 (2C; OCH_2), 31.27, 30.56 (2C; CH_2COOH), 29.5–25.95 (20C; $-CH_2-$), 25.57, 24.29 (2C; CH_2CH_2COOH), 24.26, 22.06, 16.65, 13.92, 11.65, 11.54 ppm (8C; CH_3); IR (KBr disc): $\tilde{\nu}$ = 3310 w (CH), 3197 s, 2927 s, 2856 s (OH/NH), 1745 s (C=O), 1675 s (C=C), 1605 s (NH), 1415 s (CH_3), 1150 s (CN), 2965 m,

2856 m, 1475 s, 1452 s, 1405 m, 1313 m, 1165 m, 1100 s, 883 m, 705 m cm^{-1} (CH_2 groups); UV/Vis (CH_3CN): λ_{max} = 415, 523, 537, 593, 638 nm; MS (ESI, positive): *m/z* (%): 936 (100) $[M+1]^+$; elemental analysis calcd (%) for $C_{58}H_{86}N_4O_6$ (935.33): C 74.48, H 9.27, N 5.99; found: C 74.37, H 9.01, N 5.82.

Bis(tetramethylammonium)protoporphyrin IX monothioester undecahydro-*closo*-dodecaborate (8): Protoporphyrin IX (**1**, 0.16 mmol, 90 mg) was dissolved in anhydrous dichloromethane (10 mL) under argon in a 25 mL round-bottomed flask. Freshly distilled oxalyl chloride (8.2 mmol, 0.7 mL) was added to this solution, and the reaction mixture was stirred at room temperature for 1 h. The dichloromethane and unreacted oxalyl chloride were removed under vacuum. The resulting green solid of the porphyrin acid chloride was dissolved in anhydrous acetonitrile (15 mL). $[(CH_3)_4N]_2B_{12}H_{11}SH$ (0.25 mmol, 80 mg) and anhydrous pyridine (3.7 mmol, 0.3 mL) were added. This reaction mixture was stirred for 72 h and the volatile components were removed under vacuum. The crude product was purified by column chromatography (CH_2Cl_2/MeOH 17:3) to give **8**. Yield (71 mg, 51%) as a violet colored solid; R_f = 0.31 (CH_2Cl_2/MeOH 17:3); ^{1}H NMR (300 MHz, CD_3CN, 25 °C, TMS): δ = 10.29, 10.22, 10.2, 10.15 (m, 4H; *meso*-H), 8.49 (m, 2H; CH=CH_2), 6.45 (d, J = 16.0 Hz, 2H; CH=CH_2), 6.17 (d, J = 12.4 Hz, 2H; CH=CH_2), 4.32 (m, 4H; porphyrin-CH_2), 3.77, 3.73, 3.66, 3.64 (s, 12H; β-CH_3), 3.24 (m, 4H; CH_2COOH), 3.08 (s, 24H; $N(CH_3)_4$), 0.55–1.82 (br s, 11H; $B_{12}H_{11}$), −3.85 ppm (s, 2H; NH); ^{13}C NMR (75 MHz, CD_3CN, 25 °C, TMS): δ = 176.43, 176.69 (2C; CO), 145.39, 143.54, 142.37, 137.03, 136.85, 136.74, 130.61, 126.77 (16C; C pyrrole), 97.92–97.14 (4C; *meso*-C), 56.73, 56.6 (4C; CH=CH_2), 54.59 (8C; $N(CH_3)_4$), 31.27, 30.56 (2C; CH_2COOH), 23.28, 22.67 (2C; CH_2CH_2COOH), 13.45, 12.57, 11.56, 11.28 ppm (4C; CH_3); ^{11}B NMR (96.3 MHz, CD_3CN, 25 °C, BF_3·Et_2O): δ = −15.37, −11.97, −9.78, −5.49 ppm; IR (KBr disc): $\tilde{\nu}$ = 3587 s, 3375 s, 3228 s (OH/NH), 3025 w (CH), 2495 s (BH), 1725, 1685 s (C=O), 1618 s (C=C), 1605 s (NH), 1410 s (CH_3), 1152 s (CN), 1050 s cm^{-1} (B−B); UV/Vis (CH_3CN): λ_{max} = 417, 526, 535, 592, 637 nm; MS (ESI, negative): *m/z* (%): 359.22 (100) $[M]^-$/2; elemental analysis calcd (%) for $C_{42}H_{68}N_6B_{12}O_3S$ (868.62): C 58.20, H 7.91, N 9.70; found: C 58.05, H 7.73, N 9.49.

Ion exchange to form bis(sodium)protoporphyrin IX monothioester undecahydro-*closo*-dodecaborate (9): The bis(tetramethylammonium) salt of compound **8** (0.081 mmol, 71 mg) was dissolved in CH_3CN/H_2O (1:1 v/v; 50 mL) and then stirred overnight with Amberlite 120R previously generated in the Na^+ form (25 g). The dark red solution was filtered, and the resin was washed with CH_3CN/H_2O (1:1 v/v) until the filtrate was very pale pink. Acetonitrile was evaporated under reduced pressure and the water was then completely removed by freeze-drying to provide **9** as a violet crystalline powder. Yield (20 mg, 32%) as a violet solid; ^{1}H NMR (300 MHz, [D$_6$]DMSO, 25 °C, TMS): δ = 10.44, 10.34, 10.28, 10.25 (m, 4H; *meso*-H), 8.52 (m, 2H; CH=CH_2), 6.44 (d, J = 18.1 Hz, 2H; CH=CH_2), 6.21 (d, J = 9.6 Hz, 2H; CH=CH_2), 4.25 (m, 4H; porphyrin-CH_2), 3.74, 3.71, 3.65, 3.62 (s, 12H; β-CH_3), 3.13 (m, 4H; CH_2COOH), 0.55–1.81 (br s, 11H; $B_{12}H_{11}$), −3.84 ppm (s, 2H; NH); ^{13}C NMR (75 MHz, [D$_6$]DMSO, 25 °C, TMS): δ = 176.43, 176.69 (2C; CO), 145.39, 143.54, 142.37, 137.03, 136.85, 136.74, 130.61, 126.77 (16C; C pyrrole), 97.92–97.14 (4C; *meso*-C), 56.73, 56.6 (4C; CH=CH_2), 31.27, 30.56 (2C; CH_2COOH), 23.28, 22.67 (2C; CH_2CH_2COOH), 13.45, 12.57, 11.56, 11.28 ppm (4C; CH_3); ^{11}B NMR (96.3 MHz, [D$_6$]DMSO, 25 °C, BF_3·Et_2O): δ = −15.24, −11.85, −9.95, −5.65 ppm; UV/Vis (H_2O): λ_{max} = 411, 515, 535, 583, 637 nm.

Bis(tetramethylammonium)bis(α-methyl-β-pentylethylether)protoporphyrin IX monothioester undecahydro-*closo*-dodecaborate (10): This compound was prepared from **5** (0.16 mmol, 118 mg) and $[(CH_3)_4N]_2B_{12}H_{11}SH$ (0.25 mmol, 80 mg) by the procedure described for **8**, to give **10** (88 mg, 55%) as a deep red solid; R_f = 0.35; ^{1}H NMR (300 MHz, CD_3CN, 25 °C, TMS): δ = 10.65, 10.56, 10.49, 10.12 (s, 4H; *meso*-H), 6.16 (m, 2H; α-CH), 4.37 (m, 4H; porphyrin-CH_2), 3.74, 3.69, 3.66, 3.65 (s, 12H; β-CH_3), 3.3 (t, J = 12.4 Hz, 4H; CH_2COOH), 3.0 (t, J = 13.5 Hz, 4H; OCH_2), 2.98 (s, 24H; $N(CH_3)_4$), 2.42 (s, 6H; CH_3), 1.75, 1.39, 1.21 (m, 12H; CH_2), 0.75 (t, J = 12.7 Hz, 6H; CH_3), −0.48 ppm (s, 2H; NH); ^{13}C NMR (75 MHz, CD_3CN, 25 °C, TMS): δ = 210.86, 178.47 (2C; CO), 149.19, 148.67, 147.45, 146.77, 142.06, 141.08, 138.11, 118.2 (16C; C pyrrole), 100.17, 99.38, 98.29, 97.61 (4C; *meso*-C), 74.12, 73.85 (2C; O−CH), 60.67 (2C; OCH_2), 50.7 (8C; $N(CH_3)_4$), 30.8, 30.54 (2C; CH_2COOH), 29.37, 29.33, 25.68, 25.46 (6C; $-CH_2-$), 23.95, 23.71 (2C; CH_2CH_2COOH), 22.31, 23.05, 14.13, 14.1, 11.98, 11.92, 11.8, 11.65 ppm (8C; CH_3); ^{11}B NMR (96.3 MHz, CD_3CN, 25 °C, BF_3·Et_2O): δ = −14.39, −10.91, −9.58, −5.89 ppm; IR (KBr disc): $\tilde{\nu}$ = 3568 s, 3421 s (OH/NH), 3311 w (CH), 2500 s (BH), 1722, 1685 s (C=O), 1620 s (C=C), 1608 s (NH), 1386 s (CH_3), 1157 s (CN), 1080 s (B−B), 2986 m, 2864 m, 1471 m, 1440 m, 1400 m, 1185 m, 1093 s, 721 m cm^{-1} (δ, γ of CH_2 groups); UV/Vis (CH_3CN): λ_{max} = 414, 522, 538, 592, 635 nm; elemental analysis calcd (%) for $C_{52}H_{92}N_6B_{12}O_3S$ (1011.12): C 61.77, H 9.17, N 8.31; found: C 61.49, H 8.96, N 8.19.

Bis(sodium)bis(α-methyl-β-pentylethylether)protoporphyrin IX monothioester undecahydro-*closo*-dodecaborate (11): This compound was prepared from **10** (0.087 mmol, 88 mg) by the procedure described for **9**, to give **11** (29 mg, 37%) as a deep red solid; ^{1}H NMR (300 MHz, [D$_6$]DMSO, 25 °C, TMS): δ = 12.05 (s, 1H; COOH), 10.73, 10.64, 10.52, 10.24 (m, 4H; *meso*-H), 6.17 (m, 2H; α-CH), 4.32 (m, 4H; porphyrin-CH_2), 3.72, 3.66, 3.64, 3.62 (s, 12H; β-CH_3), 3.35 (t, J = 13.8 Hz, 4H; CH_2COOH), 2.97 (t, 4H; OCH_2), 2.35 (s, 6H; CH_3), 1.7, 1.35, 1.25 (m, 12H; CH_2), 0.7 (t, J = 12.5 Hz, 6H; CH_3), −3.91 ppm (s, 2H; NH); ^{13}C NMR (75 MHz, [D$_6$]DMSO, 25 °C, TMS): δ = 208.93, 177.47 (2C; CO), 148.15, 147.14, 146.21, 146.77, 142.06, 141.08, 138.11, 118.45 (16C; C pyrrole), 98.29, 97.61 (4C; *meso*-C), 73.78, 72.46 (2C; O−CH), 68.47 (2C; OCH_2), 30.82 (2C; CH_2COOH), 29.32, 29.27, 25.46, 25.19 (6C; $-CH_2-$), 22.98, 22.64 (2C; CH_2CH_2COOH), 22.05, 21.97, 14.17, 14.09, 11.96, 11.91, 11.76, 11.68 ppm (8C; CH_3); ^{11}B NMR (96.3 MHz, [D$_6$]DMSO, 25 °C, BF_3·Et_2O): δ = −14.39, −10.91, −9.58, −5.89 ppm; UV/Vis (H_2O): λ_{max} = 410, 517, 536, 585, 635 nm.

Bis(tetramethylammonium)bis(α-methyl-β-dodecanylethylether)protoporphyrin IX monothioester undecahydro-*closo*-dodecaborate (12): This compound was prepared from **7** (0.16 mmol, 150 mg) and $[(CH_3)_4N]_2B_{12}H_{11}SH$ (0.25 mmol, 80 mg) by the procedure described for **8**, to give **12** (110 mg, 57%) as a deep red solid; R_f = 0.39; ^{1}H NMR (300 MHz, CD_3CN, 25 °C, TMS): δ = 10.55, 10.42, 10.12, 10.0 (s, 4H; *meso*-H), 5.94 (m, 2H; α-CH), 4.25 (m, 4H; porphyrin-CH_2), 3.69, 3.67, 3.63, 3.6 (s, 12H; β-CH_3), 3.37 (m, 4H; CH_2COOH), 3.15 (s, 24H; $N(CH_3)_4$), 2.61 (m, 4H; OCH_2), 2.2 (d, J = 6.0 Hz, 6H; CH_3), 1.74–0.75 (m, 20H; CH_2), 0.71 (t, J = 13.2 Hz, 6H; CH_3), −0.69 ppm (s, 2H; NH); ^{13}C NMR (75 MHz, CD_3CN, 25 °C, TMS): δ = 213.41, 213.08 (2C; CO), 149.19, 148.60, 147.51, 146.76, 142.06, 141.95, 138.73, 138.19 (16C; C pyrrole), 99.78, 99.61, 98.36, 97.41 (4C; *meso*-C), 73.99, 69.61 (2C; O−CH), 50.73 (2C; OCH_2), 34.96, 32.33 (2C; CH_2COOH), 29.94–26.99 (20C; $-CH_2-$), 25.66, 24.26 (2C; CH_2CH_2COOH), 24.26, 23.11, 16.65, 14.21, 11.93, 11.65 ppm (8C; CH_3); ^{11}B NMR (96.3 MHz, CD_3CN, 25 °C, BF_3·Et_2O): δ = −15.35, −11.98, −9.75, −5.45 ppm; IR (KBr disc): $\tilde{\nu}$ = 3568 s, 3423 s (OH/NH), 3305 w (CH), 1735 s, 1689 (C=O), 1635 s (C=C), 1611 s (NH), 1458 s (CH_3), 1125 s (CN), 1080 s (B−B), 2995 m, 2854 m, 1475 s, 1458 s, 1410 m, 1282 m, 1165 m, 1058 s, 885 m, 721 m cm^{-1} (CH_2 groups); UV/Vis (CH_3CN): λ_{max} = 412, 520, 535, 591, 634 nm; MS (ESI, negative): *m/z* (%): 936 (100) $[M+2]^+$; elemental analysis calcd (%) for $C_{66}H_{120}N_6B_{12}O_3S$ (1207.49): C 65.65, H 10.02, N 6.96; found: C 65.34, H 9.83, N 6.7.

Bis(sodium)bis(α-methyl-β-dodecanylethylether)protoporphyrin-IX-monothioester undecahydro-*closo*-dodecaborate (13): This compound was prepared from **12** (0.091 mmol, 110 mg) by the procedure described for **9**, to give **13** (35 mg, 35%) as a deep red solid; ^{1}H NMR (300 MHz, [D$_6$]DMSO, 25 °C, TMS): δ = 10.57, 10.45, 10.21, 10.12 (s, 4H; *meso*-H), 6.11 (m, 2H; α-CH), 4.34 (m, 4H; porphyrin-CH_2), 3.68, 3.66, 3.64, 3.61 (s, 12H; β-CH_3), 3.35 (m, 4H; CH_2COOH), 2.85 (m, 4H; OCH_2), 2.18 (d, J = 6.0 Hz, 6H; CH_3), 1.85–0.81 (m, 20H; CH_2), 0.76 (t, J = 13.2 Hz, 6H; CH_3), −3.92 ppm (s, 2H; NH); ^{13}C NMR (75 MHz, [D$_6$]DMSO, 25 °C, TMS): δ = 207.41, 168.42 (2C; CO), 149.19, 148.60, 147.51, 146.76, 142.06, 141.95, 138.73, 118.25 (16C; C pyrrole), 98.56, 98.05, 96.85, 96.54 (4C; *meso*-C), 72.85, 71.65 (2C; O−CH), 52.65 (2C; OCH_2), 31.86, 28.89 (2C; CH_2COOH), 27.86–22.74 (20C; $-CH_2-$), 25.66, 24.26 (2C; CH_2CH_2COOH), 22.54, 21.19, 15.75, 12.41, 11.52 ppm (8C; CH_3);

^{11}B NMR (96.3 MHz, CD_3CN, 25 °C, $BF_3{\cdot}Et_2O$): $\delta = -15.40$, -11.95, -9.85, -5.42 ppm; UV/Vis(H_2O): $\lambda_{max} = 412$, 520, 535, 591, 634 nm.

Bis(methyltriphenylphosphenium)protoporphyrin IX monooxoester undecahydro-*closo*-dodecaborate (14): This compound was prepared from **1** (0.16 mmol, 90 mg) and $(MePh_3P)_2B_{12}H_{11}OH$ (0.25 mmol, 178 mg) by the procedure described for **8**, to give **14** (140 mg, 70 %) as a dark violet solid; $R_f = 0.31$; ^{1}H NMR (300 MHz, CD_3CN, 25 °C, TMS): $\delta = 9.48$, 9.26, 8.84 (s, 4H; *meso*-CH), 7.63 (m, 2H; $CH{=}CH_2$), 7.83–7.53 (m, 30H; Ph_3P), 6.1 (m, 4H; $CH{=}CH_2$), 4.12 (m, 4H; porphyrin-CH_2), 3.74, 3.65, 3.64, 3.61 (s, 12H; β-CH_3),3.35 (m, 4H; CH_2COOH), 3.1 (s, 6H; CH_3P), 0.4–1.69 (br s, 11H; $B_{12}H_{11}$), -2.05 ppm (s, 2H; NH); ^{13}C NMR (75 MHz, CD_3CN, 25 °C, TMS): $\delta = 177.26$, 175.08 (2C; CO), 148.33, 148.45, 140.9, 137.12, 136.52, 133.21, 133.07, 130.18 (16C; C pyrrole), 130.13, 129.96, 121.29, 121.23, 121.20, 119.24 (36C; Ph_3P), 97.92–97.14 (4C; *meso*-C), 54.78 (2C; $CH{=}CH_2$), 36.62 (2C; CH_3P), 31.35, 30.76 (2C; CH_2COOH), 23.15, 22.97 (2C; CH_2CH_2COOH), 13.05, 12.31, 12.01, 11.74 ppm (4C; CH_3); ^{11}B NMR (96.3 MHz, CD_3CN, 25 °C, $BF_3{\cdot}Et_2O$): $\delta = -23.46$, -17.55, -14.78, 6.41; IR (KBr disc): $\tilde{\nu} = 3567$ s, 3431 s (OH/NH), 2998 w (CH), 2484 s (BH), 1725 s, 1690 s (C=O), 1675 s (C=C), 1615 s (NH), 1377 s (CH_3), 1153 s (CN), 1065 s cm^{-1} (B–B); UV/Vis (CH_3CN): $\lambda_{max} =$ 415, 522, 536, 595, 639 nm; MS (ESI, negative): *m/z* (%): 358 (65) $[M]^-/2$; elemental analysis calcd (%) for $C_{72}H_{80}N_4B_{12}O_4P_2$ (1257.11): C 68.79, H 6.41, N 4.46; found: C 68.52, H 6.19, N 4.16.

Bis(sodium)protoporphyrin IX monooxoester undecahydro-*closo*-dodecaborate (15): This compound was prepared from **14** (0.11 mmol, 140 mg) by the procedure described for **9**, to give **15** (48 mg, 58 %) as a dark violet solid; ^{1}H NMR (300 MHz, CD_3CN, 25 °C, TMS): $\delta = 10.3$, 10.25, 10.19, 10.13 (s, 4H; *meso*-CH), 8.5 (m, 2H; $CH{=}CH_2$), 6.46 (d, $J =$ 16.4 Hz, 2H; $CH{=}CH_2$), 6.14 (d, $J = 12.2$ Hz, 2H; $CH{=}CH_2$), 4.34 (m, 4H; porphyrin-CH_2), 3.73–3.60 (s, 12H, β-CH_3), 3.21 (m, 4H; CH_2COOH), 0.21–1.55 (br s, 11H; $B_{12}H_{11}$), -3.81 ppm (s, 2H; NH); ^{13}C NMR (75 MHz, CD_3CN, 25 °C, TMS): $\delta = 176.43$, 176.69 (2C; CO), 145.39, 143.54, 142.37, 137.03, 136.85, 136.74, 130.61, 126.77 (16C; C pyrrole), 97.92–97.14 (4C; *meso*-C), 56.73, 56.6 (2C; $CH{=}CH_2$), 31.27, 30.56 (2C; CH_2COOH), 23.28, 22.67 (2C; CH_2CH_2COOH), 13.45, 12.57, 11.56, 11.28 ppm (4C; CH_3); ^{11}B NMR (96.3 MHz, CD_3CN, 25 °C, $BF_3{\cdot}Et_2O$): $\delta = -23.73$, -17.63, -14.9, 6.51 ppm; UV/Vis (H_2O): $\lambda_{max} = 415$, 525, 535, 595, 639 nm.

Synthesis of bis(tetramethylammonium)protoporphyrin IX monoamide undecahydro-*closo*-dodecaborate (16): Protoporphyrin IX (**1**, 0.16 mmol, 90 mg) was dissolved in anhydrous dichloromethane (10 mL) under argon in a 25 mL round-bottomed flask. Freshly distilled oxalyl chloride (8.2 mmol, 0.7 mL) was added, and the reaction mixture was stirred at room temperature for 1 h. The dichloromethane and the unreacted oxalyl chloride were removed under vacuum. The resulting green solid was dissolved in anhydrous DMF (10 mL). The tetramethylammonium salt of $B_{12}H_{11}NH_3$ (0.5 mmol, 110 mg) was dissolved in anhydrous DMF (10 mL) in a 30 mL round-bottomed flask and the solution was cooled to 0 °C in an ice bath. NaH (70 mg, 1 mmol, 60 % suspension in oil) was added and the mixture was stirred for 30 min. This reaction mixture was added dropwise to the porphyrin acid chloride solution over the course of 10 min. Anhydrous pyridine (3.7 mmol, 0.3 mL) was added and the reaction mixture was stirred for 72 h. The volatile components were removed under vacuum and the crude product was purified twice by preparative TLC with $MeOH/CH_2Cl_2$ (1:4) as eluent to give **16**. Yield (80 mg, 65 %) as a violet solid; $R_f = 0.33$; ^{1}H NMR (300 MHz, CD_3CN, 25 °C, TMS): $\delta =$ 9.59, 9.28, 10.12 (m, 4H; *meso*-H), 8.02 (m, 2H; $CH{=}CH_2$), 6.11 (m, 4H; $CH{=}CH_2$), 4.74 (S, 2H; NH_2), 4.28 (m, 4H; porphyrin-CH_2), 4.07, 3.88 (m, 12H; β-CH_3), 3.48, 3.27 (m, 4H; CH_2COOH), 2.88 (s, 12H; N-$(CH_3)_4$), 0.45–1.7 (br s, 11H; $B_{12}H_{11}$), -3.77 ppm (s, 2H; NH); ^{13}C NMR (75 MHz, CD_3CN, 25 °C, TMS): $\delta = 176.89$, 176.21 (2C; CO), 145.42, 143.93, 141.73, 140.34, 136.63, 136.33, 135.85, 130.14 (16C; C pyrrole), 97.46–97.04 (4C; *meso*-C), 54.35, 56.6 (2C; $CH{=}CH_2$), 54.31 (4C; N-$(CH_3)_4$), 33.0, 30.56 (2C; CH_2COOH), 23.28, 23.0 (2C; CH_2CH_2COOH), 13.45, 12.57, 11.56, 11.28 ppm (4C; CH_3); ^{11}B NMR (96.3 MHz, CD_3CN, 25 °C, $BF_3{\cdot}Et_2O$): $\delta = -15.37$, -11.97, -9.78, -5.49 ppm; IR (KBr disc): $\tilde{\nu} = 3565$ s, 3382 s, 3246 s (OH/NH), 2985 w (CH), 2493 s (BH), 1710 s, 1675 s (C=O), 1616 s (C=C), 1605 s (NH), 1406 s (CH_3), 1165 s (CN), 1065 s cm^{-1} (B–B); UV/Vis (CH_3CN): $\lambda_{max} = 415$, 524, 536, 595, 639 nm; MS (ESI, negative): *m/z* (%): 701.6 (100) $[M]^-$; elemental analysis calcd (%) for $C_{38}H_{56}N_6B_{12}O_3$ (776.64): C 58.77, H 7.53, N 10.82; found: C 58.47, H 7.26, N 10.67.

Sodium-protoporphyrin IX monoamide undecahydro-*closo*-dodecaborate (17): This compound was prepared from **16** (0.1 mmol, 80 mg) by the procedure described for **9**, to give **17** (36 mg, 49 %) as a violet solid; ^{1}H NMR (300 MHz, CD_3CN, 25 °C, TMS): $\delta = 10.39$, 10.3, 10.26, 10.22 (s, 4H; *meso*-H), 8.47 (m, 2H; $CH{=}CH_2$), 6.46 (d, $J = 13.2$ Hz, 2H; $CH{=}CH_2$), 6.22 (d, $J = 11.1$ Hz, 2H; $CH{=}CH_2$), 5.57 (s, 2H; NH_2), 4.28 (m, 4H; porphyrin-CH_2), 3.71–3.61 (s, 12H; β-CH_3), 2.93 (m, 4H; CH_2COOH), 0.27–1.89 (br s, 11H; $B_{12}H_{11}$), -3.82 ppm (s, 2H; NH); ^{13}C NMR (75 MHz, [D_6]DMSO, 25 °C, TMS): $\delta = 176.55$, 175.04 (2C; CO), 146.38, 145.41, 143.38, 140.12, 137.65, 136.96, 133.14 (16C; C pyrrole), 97.99–97.41 (4C; *meso*-C), 56.64, 56.23 (2C; $CH{=}CH_2$), 33.17, 30.87 (2C; CH_2COOH), 22.98, 22.05 (2C; CH_2CH_2COOH), 14.12, 13.57, 11.36, 11.05 ppm (4C; CH_3); ^{11}B NMR (96.3 MHz, CD_3CN, 25 °C, $BF_3{\cdot}Et_2O$): $\delta = -15.25$, -11.80, -9.95, -5.65 ppm; UV/Vis (H_2O): $\lambda_{max} =$ 415, 525, 535, 595, 639 nm; MS (ESI, negative): *m/z* (%): 701.6 (100) $[M]^-$.

Tetrakis(tetramethylammonium)protoporphyrin IX bisthioester undecahydro-*closo*-dodecaborate (18): Protoporphyrin IX (**1**, 0.16 mmol, 90 mg) was dissolved in anhydrous dichloromethane (10 mL) under argon in a 25 mL round-bottomed flask. Freshly distilled oxalyl chloride (17.5 mmol, 1.5 mL) was added, and the reaction mixture was stirred at room temperature for 1 h. The dichloromethane and unreacted oxalyl chloride were removed under vacuum. The resulting green solid of porphyrin acid chloride was dissolved in anhydrous acetonitrile (15 mL), and $[(CH_3)_4N]_2B_{12}H_{11}SH$ (0.5 mmol, 161 mg) and anhydrous pyridine (6.2 mmol, 0.5 mL) were added. The mixture was stirred for 72 h and the volatile components were removed under vacuum. The crude product was purified by column chromatography on silica gel with CH_2Cl_2/MeOH (7:3) to give **18**. Yield (139 mg, 74 %) as a violet solid; $R_f = 0.38$; ^{1}H NMR (300 MHz, CD_3CN, 25 °C, TMS): $\delta = 10.45$, 10.39, 10.26, 10.35 (m, 4H; *meso*-H), 8.59 (m, 2H; $CH{=}CH_2$), 6.39 (d, $J = 14.0$ Hz, 2H; $CH{=}CH_2$), 6.21 (d, $J = 9.0$ Hz, 2H; $CH{=}CH_2$), 4.35 (m, 4H; porphyrin-CH_2), 3.75, 3.70, 3.65, 3.60 (s, 12H; β-CH_3), 3.26 (m, 4H; CH_2COOH), 3.07 (s, 24H; $N(CH_3)_4$), 0.51–1.85 (br s, 11H; $B_{12}H_{11}$), -3.89 ppm (s, 2H; NH); ^{13}C NMR (75 MHz, CD_3CN, 25 °C, TMS): $\delta = 202.13$ (2C; CO), 146.56, 145.17, 143.25, 137.14, 136.92, 135.56, 131.66, 127.72 (16C; C pyrrole), 98.19–97.05 (4C; *meso*-C), 56.96, 56.62 (4C; $CH{=}CH_2$), 55.07 (8C; N-$(CH_3)_4$), 31.45, 29.99 (2C; CH_2COOH), 23.65, 23.02 (2C; CH_2CH_2COOH), 13.59, 12.59, 11.49, 11.74 ppm (4C; CH_3); ^{11}B NMR (96.3 MHz, CD_3CN, 25 °C, $BF_3{\cdot}Et_2O$): $\delta = -15.35$, -11.94, -9.71, -5.53 ppm; IR (KBr disc): $\tilde{\nu} = 3254$ s (NH), 3026 w (CH), 2499 s (BH), 1682 s (C=O), 1620 s (C=C), 1609 s (NH), 1416 s (CH_3), 1160 s (CN), 1053 s cm^{-1} (B–B); UV/Vis (CH_3CN): $\lambda_{max} = 415$, 523, 536, 595, 639 nm; MS (ESI, negative): *m/z* (%): 436.65 (100) $[M]^-/2$; elemental analysis calcd (%) for $C_{50}H_{102}N_8B_{24}O_2S_2$ (1170.99): C 51.28, H 8.78, N 9.57; found: C 51.12, H 8.75, N 9.38.

Tetrakis(sodium)protoporphyrin IX bis(thioester) undecahydro-*closo*-dodecaborate (19): This compound was prepared from **18** (0.12 mmol, 139 mg) by the procedure described for **9**, to give **19** (100 mg, 65 %) as a violet solid; ^{1}H NMR (300 MHz, [D_6]DMSO, 25 °C, TMS): $\delta = 10.37$, 10.27, 10.15, 10.01 (m, 4H; *meso*-H), 8.52 (m, 2H; $CH{=}CH_2$), 6.46 (d, $J =$ 18.0 Hz, 2H; $CH{=}CH_2$), 6.14 (d, $J = 18.0$ Hz, 2H; $CH{=}CH_2$), 4.34 (m, 4H; porphyrin-CH_2), 3.73, 3.71, 3.60, 3.57 (s, 12H; β-CH_3), 3.15 (m, 4H; CH_2COOH), 0.19–1.65 (br s, 11H; $B_{12}H_{11}$), -3.81 ppm (s, 2H; NH); ^{13}C NMR (75 MHz, [D_6]DMSO, 25 °C, TMS): $\delta = 179.79$ (2C; CO), 146.41, 144.64, 142.47, 136.98, 136.52, 136.12, 130.3, 127.07 (16C; C pyrrole), 97.95–97.33 (4C; *meso*-C), 56.79, 56.65 (4C; $CH{=}CH_2$), 32.25, 31.02 (2C; CH_2COOH), 23.19, 22.87 (2C; CH_2CH_2COOH), 14.05, 12.97, 11.59, 11.56 ppm (4C; CH_3); ^{11}B NMR (96.3 MHz, [D_6]DMSO, 25 °C, $BF_3{\cdot}Et_2O$): $\delta = -15.21$, -11.89, -10.05, -5.72; UV/Vis(H_2O): $\lambda_{max} = 415$, 522, 536, 591, 639 nm.

Biological studies

Cell viability (MTT) assay: Human cervical carcinoma HeLa cells, rat glioma C6 cells, mouse melanoma B16 cells, mouse colon cancer CT26

cells, human hepatocellular carcinoma HepG2 cells, and human colon cancer HCT15 and HCT116 cells were used for the cell viability assay. The cells (5×10^3 cells per well of a 96-well plate) were incubated at 37 °C for 72 h in RPMI-1640 medium (100 μL) containing various concentrations of the boronated porphyrins. After the incubation, 3′-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT, Sigma) in PBS (5 mg mL^{-1}, 10 μL) was added to each well, and the cells were further incubated at 37 °C for 4 h. After the removal of the medium, DMSO (100 μL) was added and the absorbance at 570 nm was determined with a microplate reader. The drug concentration required to reduce cell viability by 50 % (IC_{50}) was determined from semilogarithmic dose-response plots.

Boron accumulation study: HeLa cells (1×10^6 cells) were incubated at 37 °C for 3 h in medium containing each boronated porphyrin. After the incubation, the cells were washed three times with PBS and digested with perchloric acid/hydrogen peroxide (2 mL) at 70 °C for 6 h. Boron contents in the solution were determined by an inductively coupled plasma atomic emission spectroscopy (ICP-AES).

Fluorescence imaging: HeLa cells (1×10^3 cells) plated on cover slips in 35 mm dishes were incubated either with compound **17** (100 μM) or with BOPP (100 μM) for 3 h. After PBS washes, the cells were fixed for 10 min with paraformaldehyde (4 %) and stained for 10 min with DAPI (100 nM). The cells were observed and photographed with an Olympus IX71 microscope.

PDT study: HeLa cells (1×10^4 cells) were incubated for 3 h in medium containing each boronated porphyrin, and then the cells were irradiated with a xenon lamp [Ushio Inc., Japan, 2.4 mW cm^{-2} (average)] in the 400 to 800 nm range for 5 min. After incubation for 12 h, the ratios of viable cells were determined by MTT assay.

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