A Simple and Efficient Approach for the Synthesis of Fluorinated and Nonfluorinated Octaethylporphyrin-Based Benzochlorins with Variable Lipophilicity, Their in Vivo Tumor Uptake, and the Preliminary in Vitro Photosensitizing Efficacy†

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Starting from commercially available Ni(II)octaethylporphyrin (OEP), an efficient approach for the preparation of a series of fluorinated and nonfluorinated benzochlorins with variable lipophicity has been developed. Their spectroscopic properties, preliminary in vitro photosensitizing efficacy, and tumor selectivity were determined. Our methodology provides a facile approach for the preparation of the free-base and the related Zn(II) benzochlorins containing alkyl and alkyl ether side chains with variable carbon units. For the preparation of benzochlorins containing alkyl groups attached to the exocyclic phenyl ring, the Ni(II) *meso*-(2-formylvinyl)octaethyl porphyrin **2** was reacted with various reagents such as (trifluoromethyl)trimethylsilane (TMS-CF_3) or the Grignard reagents of various fluorinated or nonfluorinated alkyl halides. The corresponding intermediates **3**, **6a**−**6e**, and **8** obtained via intramolecular cyclization under acidic conditions afforded the related benzochlorins **5**, **7a**−**d**, and **9** in good yields except for **7e** which was obtained in poor yield (11.4%). The alcohol **10** obtained by reacting porphyrin **2** with ethynylmagnesium chloride did not produce the expected acetylenic benzochlorin; instead the corresponding acetyl derivative **11** was obtained as a major product, which under appropriate reaction conditions was converted into a series of alkyl ether derivatives **13a**−**13d**. To obtain a benzochlorin bearing an ester functionality (**15**), porphyrin **2** was first reacted with ethyl acetate/LDA and the intermediate alcohol **14** was then cyclized with sulfuric acid. Unlike most of the natural and synthetic chlorins, the Zn(II) complexes of the benzochlorin analogues exhibited a significant bathochromic shift (∼10 nm) in the electronic absorption spectra, and the long wavelength absorptions were observed in the range 671−677 nm (ϵ: 43270−50360). For investigating the in vitro efficacy of these analogues, Molt-4 cells were used. At a concentration of 2.5 μM, and a light dose of 4 J/cm^2, all benzochlorins produced significant photosensitizing efficacy. The tumor (RIF) and muscle uptake in C_3H mice of these photosensitizers was determined by in vivo reflectance spectroscopy. These results indicate that in this series increasing the length of the alkyl or alkyl ether carbon chains at the fused phenyl ring system produced a significant increase in tumor uptake.

Introduction

Benzochlorins are a class of chlorins that consists of a benzene ring fused to the tetrapyrrolic structure and were first prepared from octaethylporphyrin (OEP) by Arnold and co-workers.[1] Morgan et al.[2,3] followed this approach and showed the utility of this class of compounds as photosensitizers for photodynamic therapy (PDT). A very similar type of benzochlorin was also synthesized by Smith's group as a result of the cyclization of the product obtained after a Vilsmeier formylation reaction of Ni(II) or Cu(II)OEP using 3-(dimethylamino)acrolein and phosphorus oxychloride.[4] With a few exceptions,[4b] most of the benzochlorin derivatives prepared by Morgan's group are based on symmetrical porphyrins.

One of the major problems associated with benzochlorin preparation is the difficulty in the demetalation at the final step of the synthesis. Gunter et al. converted a

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series of Ni(II) 5,15-diphenylporphyrins into the corresponding benzochlorins, which upon acid treatment produced the corresponding free base analogues in excellent yield.[5] The X-ray analyses of Ni(II) 5,15-diarylbenzochlorin showed a remarkable distortion in the ring, which possibly helped in the removal of the central metal ion. This methodology was later followed by Osuka et al. for preparing related *meso*-substituted analogues.[6] Among the OEP-based benzochlorins, compared to the free base analogues, the corresponding Zn(II) complex was found to be a more effective PDT agent in mice.[7] Unfortunately, benzochlorins derived from OEP and the related *meso*-phenyl substituted porphyrins are difficult to dissolve in most of the desirable injecting solvents. To overcome the problem of solubility, Pandey and co-workers[8] reported an efficient regioselective synthesis of benzochlorins from Ni(II)methyl-9-deoxymesopyropheophorbide *a*. Among these analogues, the free base and the corresponding Zn(II) benzochlorins showed long wavelength absorptions at 711 and 753 nm and were soluble in 1% Tween 80/5% dextrose solution. However, these photosensitizers produced limited PDT efficacy.[9]

In our previous publications, we have shown the utility of Ruppert's reagent[10] for the synthesis of perfluorinated porphyrins, chlorins, and bacteriochlorins.[11] These compounds were prepared in order to determine their utility in investigating pharmacokinetic profiles by ^{19}F NMR studies as well as understanding the effects of fluoro analogues on photodynamic efficacy. Recently, we have shown the importance of this reagent for preparing fluorinated benzochlorins by first reacting the Ni(II)-*meso*-(2-formylvinyl) OEP with (trifluoromethyl)trimethylsilane (TMS-CF_3) and then treating the intermediate with sulfuric acid.[12] This approach produced the free base benzochlorin in 97% yield, and no sulfonated analogue was observed as previously reported for nonfluorinated OEP-based benzochlorin. Encouraged by these results, we decided to explore the utility of this methodology in preparing a series of Zn(II) fluorinated and nonfluorinated benzochlorin analogues with variable lipophilicity. Having developed the structure−activity relationship in certain chlorophyll *a* analogues,[13] we wanted to extend this approach to photosensitizers of different structures to determine whether generic requirements for effective photosensitizers could be found. The objective was to alter the overall lipophilicity of the benzochlorins by introducing a series of fluorinated and nonfluorinated substituents in the macrocycle and to investigate their effect on PDT efficacy.

Our previous studies with a variety of chlorin-based compounds indicate that lipophilicity is an important molecular descriptor that often has well-correlated efficacy.[14] Lipophilicity is often expressed as the logarithm of the partition coefficient, log *P*, which is the equilibrium partitioning of a molecule between a polar and a nonpolar phase, such as the *n*-octanol/water system.[15] In recent years, numerous theoretical methods have been developed to predict lipophilicity by calculating the log *P* value.[16] Although values vary for a given functional group depending on its electronic environment, this variation is generally small. In a homologous series of the alkyl ether analogues of pyropheophorbide *a*,[17] *N*-alkyl purpurinimides[18] and benzoporphyrin derivatives,[19] the PALLAS program was found to be useful in predicting the log *P* values. This program was successfully used for calculating the log *P* values of the free-base benzochlorins but had limitations in calculating the lipophilicity of the corresponding Zn(II) derivatives.

Results and Discussion

Chemistry. The commercially available octaethylporphyrin **1** was converted into the 10-(2-formylvinyl) octaethylporphyrin **2** in 85% yield by following the methodology developed by Vicente and Smith[4] and was used as a starting material for the syntheses of a variety of fluorinated and nonfluorinated benzochlorin analogues.

Reaction of porphyrin **2** with (trifluoromethyl)trimethylsilane (Ruppert's reagent)[10] in the presence of tetrabutylammonium fluoride under Prakash and Olah[20] reaction conditions produced the intermediate trimethylsilyl ether analogue **3** in 92% yield, which on reaction with trifluoroacetic acid (TFA) gave the corresponding alcohol **4** in quantitative yield. Porphyrin **4** on treatment with neat sulfuric acid afforded the free base 3[1]-trifluoromethylbenzochlorin **5** in quantitative yield. Under similar reaction conditions, the desired benzochlorin **5** could also be obtained directly from porphyrin **3** in excellent yield (97%), and no sulfonated analogue as reported previously by Morgan and co-workers[21] was isolated (Scheme 1). Encouraged by these results, we thought it worthwhile to extend this approach to the preparation of benzochlorins containing a series of alkyl groups with variable carbon units. Thus, in our initial approach methylmagnesium bromide was reacted with porphyrin **2** at −30 °C. The intermediate alcohol **6a** isolated in 85% yield was cyclized under acid conditions to afford the 3′-methylbenzochlorin in 72% yield. By following a similar meth-

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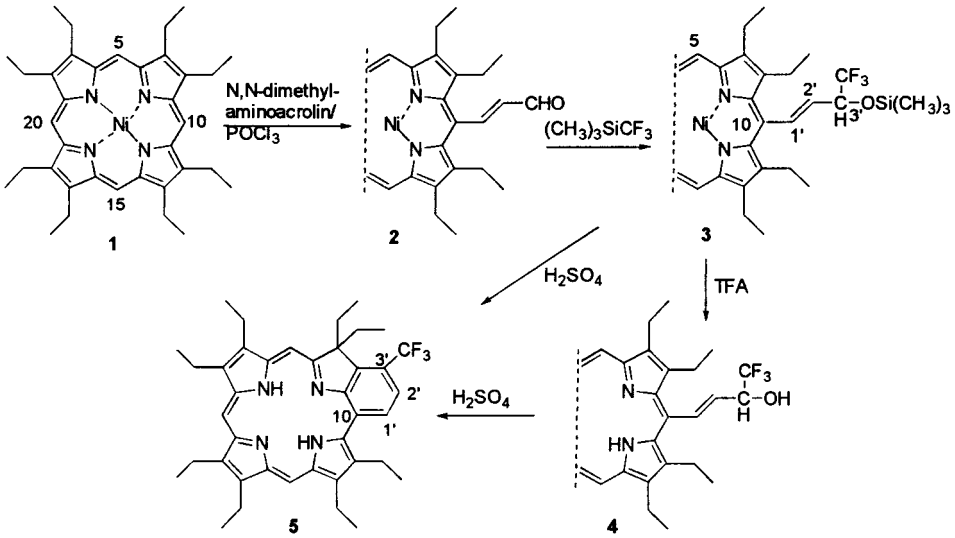
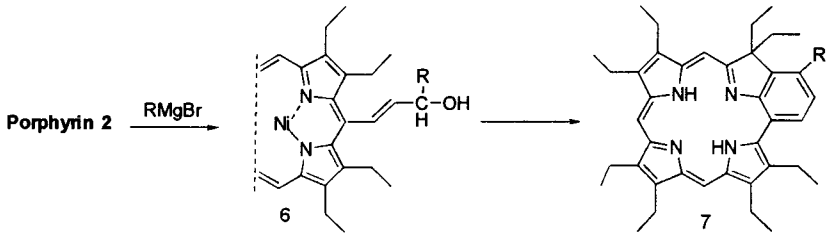
Scheme 1. A Typical Method for the Preparation of Benzochlorins

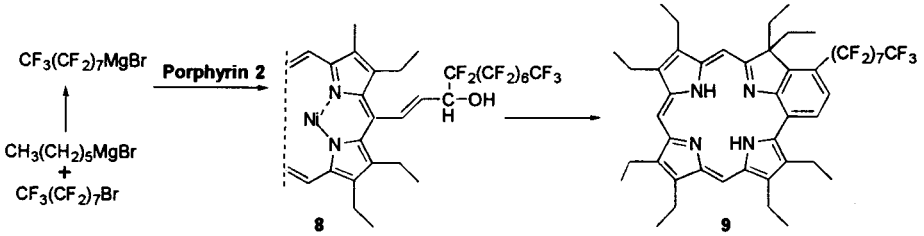


Scheme 2. Preparation of Benzochlorins Containing Alkyl Groups Attached to the Fused Six-Membered Exocyclic Ring



a. R = Methyl, b. R = Hexyl, c. R = Decyl, d. R = Octadecyl and e. R = Cyclopentyl

Scheme 3. Synthesis of Fluorinated Benzochlorins

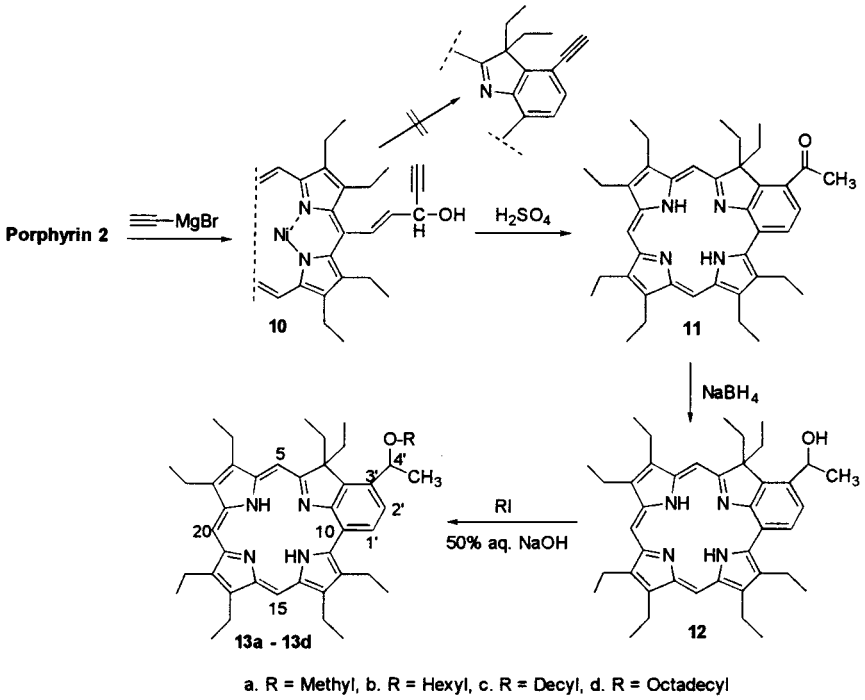


odology, a series of other alkyl benzochlorin analogues (**7b**−**7e**) were synthesized by using the proper alkyl Grignard reagents, which in turn were prepared from the corresponding alkyl bromides (Scheme 2). For the synthesis of the long carbon chain fluorinated benzochlorin **9**, perfluorooctyl bromide was first treated with hexylmagnesium bromide and the perfluorooctylmagnesium bromide so obtained was reacted in situ with porphyrin **2** at −60 °C to produce the intermediate **8** in 81% yield. Treatment of **8** with concentrated sulfuric acid afforded benzochlorin **9** as the sole product in 98% yield (Scheme 3).

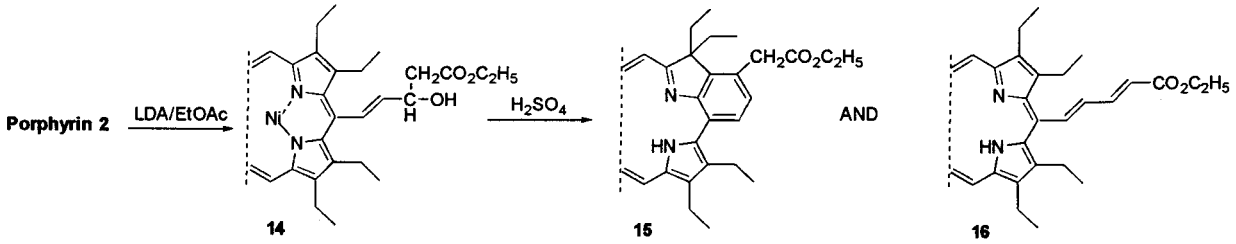
In our attempt to introduce the acetylene functionality in the exocyclic ring system, formylvinylporphyrin **2** was reacted with ethynylmagnesium chloride and intermediate alcohol **10** was obtained in 84% yield. Interestingly, the intramolecular cyclization of the intermediate under acidic conditions did not produce the expected acetylene analogue; instead the corresponding acetyl derivative **11** was obtained in 20% yield. This result prompted us to prepare a series of alkyl ether analogues by following a standard methodology as depicted in Scheme 4. In our previous studies, such functionalities in other series of photosensitizers were found to be valuable in understanding structure/activity relationships and resulted in enhancement photosensitizing efficacy. For preparing benzochlorins with ester functionality, the intermediate alcohol **14** was obtained in 97% by reacting porphyrin **2** with EtOAc/LDA at −78 °C. Subsequent reaction under acidic conditions produced the dehydration product **16** as a major compound (50%) and the expected benzochlorin **15** in 31% yield (Scheme 5).

All new compounds were characterized by NMR and mass spectrometry analyses. Initially, the ^{1}H NMR resonances for benzochlorin analogue **7b** were assigned by COSY and ROESY experiments and were then used to confirm the structures of other benzochlorin analogues. For example, in the NMR spectrum of the intermediate alcohol **6b**, the vinyl protons were observed at δ 9.01 (1H, dd, J = 15.4, 1.6 Hz) and 4.88 ppm (1H, dd, J = 15.4, 5.2 Hz). The C*H*(hexyl)OH proton appeared at 4.48 ppm (1H, td, J = 5.2 Hz). As expected, the NMR spectrum of the corresponding benzochlorin **7b** showed a significant upfield shift of the 7-ethyl protons which appeared as a

Scheme 4. Preparation of Benzochlorins with Alkyl Ether Side Chains



Scheme 5. Benzochlorin with Ethoxycarbonyl Methyl Functionality



triplet at δ 0.03 ppm (t, 6H, J = 7.5 Hz). The phenyl protons at 1′ and 2′ appeared at δ 9.50 and 7.94 ppm, respectively (each 1H, d, J = 8.3 Hz). The NH protons of the chlorin core were observed at δ 2.30 and 1.92 ppm, respectively.

In the ^{19}F NMR of benzochlorin **5**, the trifluoromethyl resonances appeared at −54.47 ppm. Benzochlorin **9** produced perfluorooctyl resonances at −81.19, −100.68, −118.31, −121.45, −121.97, −122.17, −123.03, and −126.47 ppm.

The absorption and fluorescence characteristics of these benzochlorins were measured in dichloromethane. The typical UV/visible spectra of the free base benzochlorin and its corresponding Zn(II) complex are shown in Figure 1. Compared to the free base analogue **7a** which exhibits long wavelength absorption near 664 nm, the related Zn(II) complex **17b** produced a significant bathochromic shift of about 13 nm and the absorption band was observed at 677 nm. Both the free base and the metalated analogues showed strong fluorescence at 670 and 672 nm with a small shift between the absorption and emission bands.

In previous studies with benzochlorins derived from OEP and chlorophyll *a* analogues, the zinc derivatives were found to have better PDT efficacy than the related free-base analogues. Thus, the fluorinated and nonfluorinated benzochlorins were converted into the corresponding zinc analogues **17a**−**17j** in quantitative yields (Scheme 6) and were evaluated for in vivo tumor uptake and in vitro photosensitizing efficacy. The partition coefficient values (log P) of the free-base benzochlorins

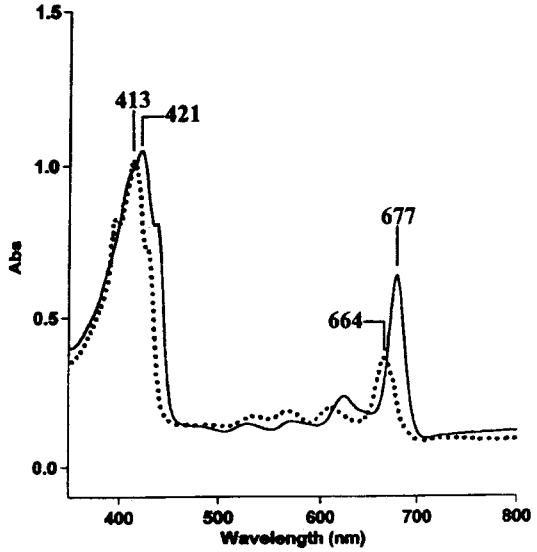


Figure 1. Electronic absorption spectra (in CH_2Cl_2) of benzochlorin **7a** (- - -) and the corresponding Zn(II) complex **17a** (—) at 2.0 × 10^5 M.

Scheme 6. Benzochlorins Investigated for Photosensitizing Efficacy

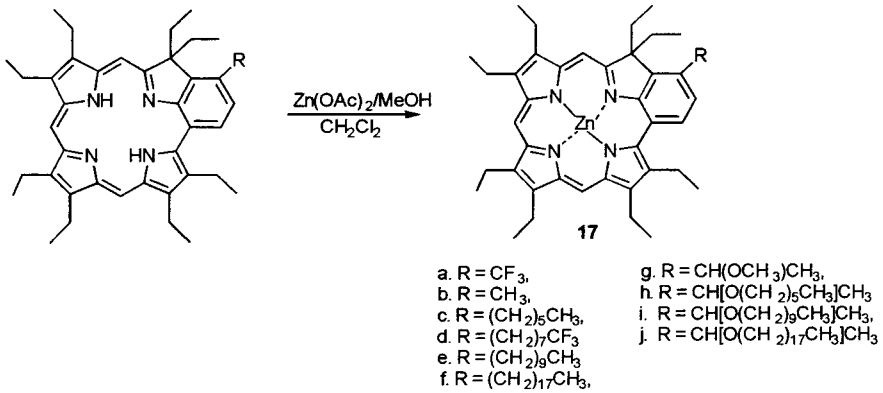
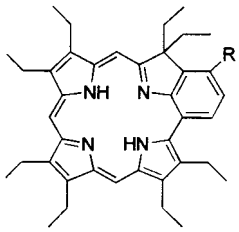


Table 1. Calculated Partition Coefficient Values (log *P*) of the Free-Base Benzochlorins



compound no.	R	log *P* value	compound no.	R	log *P* value
7a	CH_3	13.17	**7b**	$(CH_2)_5CH_3$	15.75
13a	$CH(OCH_3)CH_3$	13.00	**13b**	$CH[O(CH_2)_5CH_3]CH_3$	15.50
5	CF_3	13.88			
13c	$CH[O(CH_2)_9CH_3]CH_3$	18.06	**13d**	$CH[O(CH_2)_{17}CH_3]CH_3$	21.62
7c	$(CH_2)_9CH_3$	18.30	**7d**	$(CH_2)_{17}CH_3$	21.86
9	$(CF_2)_7CF_3$	19.16			

were calculated by the PALLAS program and were in the range 13.00−21.86 (Table 1).

Determination of Tumor Uptake by in Vivo Reflectance Spectroscopy. Most of the benzochlorins were insoluble in water and for the biological studies were dissolved in a 1% Tween 80 and 5% dextrose solution. The concentration of the photosensitizers in the solutions was calculated on the basis of their extinction coefficient values, using the Beer−Lambert law.[22]

We have previously shown that the absorption spectrum of a compound in living tissue can be obtained by in vivo reflectance spectroscopy.[23] In brief, the experiment measures the light scattered by the tissue. For these experiments, the mice were first anesthetized using ketamine xylazine intraperitoneally. The optical power as a function of wavelength was recorded before the i.v. injection of the photosensitizer. The drug was then injected and the spectrum again recorded. The in vivo drug absorption spectrum is best displayed by determining the ratio of the postinjection spectrum to the preinjection spectrum. This ratio offers the same advantages as a double-beam absorption spectrophotometer. The preinjection mouse data can be thought of as the reference beam sample (typically a cuvette and solvents) and the postinjection data as the sample beam containing everything in the reference beam plus the experimental drug.

Table 2. Tumor, Skin Uptake in C_3H Mice Implanted with RIF Tumors and the Long Wavelength Absorptions (in Vitro and in Vivo) of Various Benzochlorins[a]

compound no.	λ_{max} (nm) (in vitro)	λ_{max} (nm) (in vivo)	tumor/skin ratio at 24 h	tumor uptake (μmol/kg), 24 h
17a	674	684	2.0	4.2
17b	677	686	1.22	3.4
17c	674	682	3.5	7.5
17d	674	683	2.2	4.6
17e	674	683	3.9	7.9
17f	674	683	1.5[b]	6.0[b]
17g	671	682	1.2	1.64
17h	671	680	3.0	3.9
17i	671	680	3.3	4.5
17j	671	680	2.8	6.0

[a] The in vivo uptake and the in vivo absorptions were determined by in vivo reflectance spectroscopy at a dose of 5.0 μmol/kg. [b] At 95 h.

For measuring the tumor uptake, the benzochlorins were injected into mice implanted with RIF tumors at a dose of 5.0 μmol/kg. As shown in Table 2, most of the benzochlorins produced high tumor uptake and some of them showed considerable difference in tumor to skin uptake at 24 h postinjection, indicating enhanced tissue selectivity, an advantage for all photosensitizers in achieving high therapeutic ratio. These data indicate that in the benzochlorin series increasing the length of the alkyl or alkyl ether carbon chains at the fused phenyl ring system resulted a significant increase in tumor uptake. The in vivo absorption spectra, representing the tumor to skin uptake of one of the benzochlorins (**17e**), is shown in Figure 2. The maximum red shifts from 674 nm in vitro to 683 nm in vivo, apparently reflecting binding to various tissue components.

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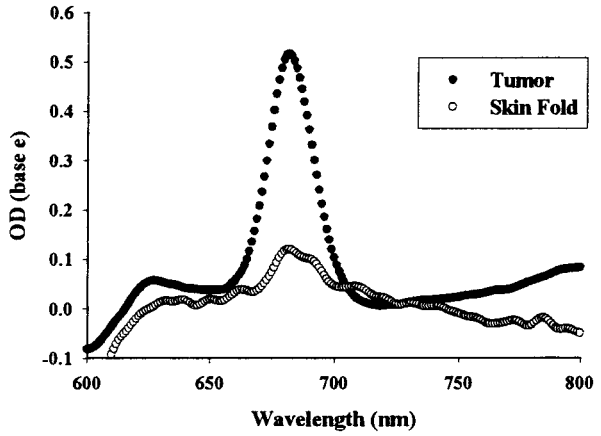

Figure 2. The tumor and skin uptake of benzochlorin **17e** in the mice implanted with RIF tumors (C_3H mice) as determined by in vivo reflectance spectroscopy. The spectra were taken at 24 h postinjection (i.v.) at a drug dose of 5.0 μmol/kg.

In Vitro Photosensitizing Efficacy.[24,25] For determining the in vitro photosensitizing efficacy, Molt-4 cells were grown in RPMI1640 5%, FCS (fetal calf serum) in 100% humidity with 5% CO_2. In a typical experiment, cells were transferred to phenol red free (prf) RPMI 1640 media with 1% FCS and plated at 2.5×10^5 cells/mL in 96-well plates. After a 3 h drug incubation in the dark, cells were washed once with PBS and resuspended in prf RPMI 1640 with 1% FCS. Cells were illuminated with a 1000 W quartz halogen lamp with IR and band-pass dichroic filters 400 nm−700 nm, at a dose rate of 16 mW/cm^2 at 675 nm. After the light treatment, the cells were resuspended in fresh media and placed back in the incubator for 48 h. After 48 h, 0.4 mg of MTT (3-[4,5-dimethylthiazol-2-yl]-2,5-diphenylyetrazolium bromide), dissolved in 10 μL of PBS phosphate-buffered saline (Sigma, St. Louis, MO), was added to the cells which then were incubated for 4 h. Then, 100 μL of dimethyl sulfoxide (DMSO) was added to each well to dissolve the formazin crystals. The plates were read on a 96-well plate reader (Miles Inc. Titertek Multiskan Plus MK II) at an absorbance of 560 nm. The data are in replicates of 6 wells and are normalized to control cells (light, no drug).

For determining the optimum drug dose, one of the benzochlorins, **17e**, was initially tested at three different concentrations (1.0, 2.0, and 2.5 μM). Compared to lower drug doses, the drug concentration of 2.5 μL, together with a light dose of 4.0 J/cm^2, produced the highest photocytotoxicity without any dark toxicity. Other photosensitizers were then evaluated under similar drug/light doses to **17e** and demonstrated similar phototoxicity (Figures 3−5). The in vivo uptake data as measured by in vivo reflectance spectroscopy (Table 2) indicated that in the benzochlorin series increasing the length of the alkyl or alkyl ether carbon chains produced a significant increase in tumor uptake. Taken together, these results suggest that variation of lipophilicity could result in a significant difference in their pharmacokinetic profiles and produce significant differences in in vivo PDT efficacy. The detailed in vivo studies with these compounds are currently in progress and will be reported elsewhere.

(24) Morgan, J.; Potter, W. R.; Oseroff, A. R. *Photochem. Photobiol.* **2000**, *71*, 747.
(25) Kessel, D.; Luo, Y. *Photochem. Photobiol.* **1996**, *64*, 601.

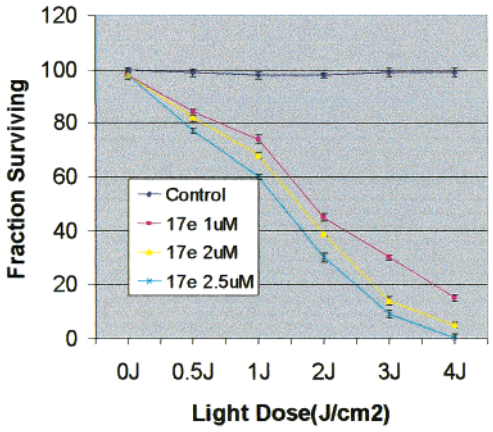

Figure 3. In vitro photosensitizing activity of benzochlorin **17e** at variable concentrations in Molt-4 cells. Control: without photosensitizer.

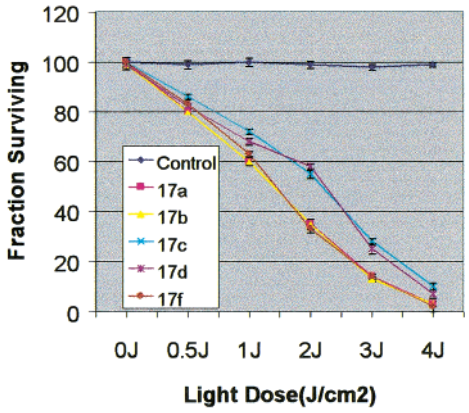

Figure 4. In vitro photosensitizing activity of benzochlorins containing alkyl side chains (2.5 μM) with variable carbon unit (2.5 μM) in Molt-4 cells. Control: without photosensitizer.

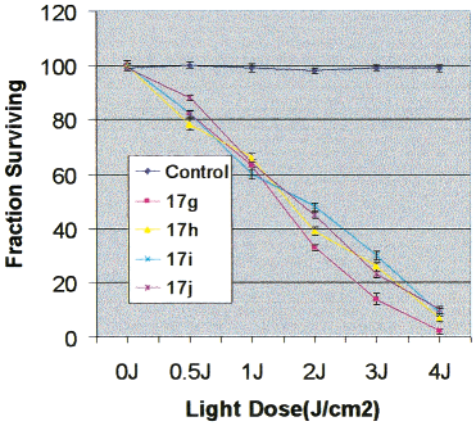

Figure 5. In vitro photosensitizing activity of benzochlorins containing alkyl ether side chains with variable carbon unit (2.5 μM) in Molt-4 cells. Control: without photosensitizer.

Experimental Section

Melting points are uncorrected. ^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded in $CDCl_3$ solutions at 400.1, 100.6, and 376.5 MHz, respectively. Chemical shifts are reported in ppm with $CDCl_3$ as internal standard (for ^{1}H, 7.26 ppm; and ^{13}C, 77.23 ppm) and $CFCl_3$ as external standard (for ^{19}F, 0.00 ppm). Column chromatographic separations were performed over

neutral alumina (Brockmann grade III). Preparative TLC was performed on 20 × 20 cm TLC plates (Analtech).

Ni(II) *meso*-(3-Trimethylsiloxy-3-trifuoromethyl-propenyl)octaethylporphyrin (3). To a solution of *meso*-vinylformyl-octaethylporphyrin (**2**) (322 mg, 0.5 mmol) in dry THF (10 mL) at 0 °C under nitrogen atmosphere was added (trifluoromethyl)trimethylsilane (142 mg, 1.0 mmol). Tetrabutylammonium fluoride (40 μL, 1.0 M solution in THF) was then added to the above solution successively. The mixture was stirred at this temperature for 30 min. The reaction was quenched with water, diluted with CH_2Cl_2, washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Purification by alumina (Brockmann grade III) column chromatography (hexanes/CH_2Cl_2, 3:1) gave **3** (351 mg, 92%) as deep red needles. Mp 235−236 °C. ^{1}H NMR: δ 9.43 (2H, s, *meso* H), 9.42 (1H, s, *meso* H), 9.20 (1H, dd, J = 15.5, 1.6 Hz, H-1′), 4.84 (1H, dd, J = 15.5, 3.6 Hz, H-2′), 4.73 (1H, m, H-3′), 3.93−3.72 (16H, m, CH_3CH_2-2,3,7,8,12,13,17,18), 1.87−1.66 (24H, m, CH_3CH_2-2,3,7,8,12,13,17,18), 0.39 (9H, s, Me_3SiO-3′). ^{19}F NMR δ −78.09 (3F, s, CF_3-3′). MS (FAB) m/z 787 (MH^+, 100). Anal. Calcd for $C_{43}H_{55}F_3N_4NiOSi$: C, 65.57; H, 7.04; N, 7.11. Found: C, 65.44; H, 6.93; N, 7.09.

***meso*-(3-Hydroxy-3-trifluoromethyl-propenyl)octaethylporphyrin (4).** Porphyrin **3** (54 mg) was dissolved in TFA (10 mL), and the solution was stirred at room temperature for 2 h under a N_2 atmosphere. The reaction mixture was then diluted with CH_2Cl_2, washed with brine and 5% $NaHCO_3$, dried over Na_2SO_4, and concentrated in vacuo to give compound **4** (45 mg, 100%) as brown plates. Mp 191−193 °C. ^{1}H NMR: δ 10.12 (2H, s, *meso* H), 9.94 (1H, s, *meso* H), 9.59 (1H, dd, J = 15.0, 1.6 Hz, H-1′), 5.85 (1H, dd, J = 15.0, 5.2 Hz, H-2′), 5.08 (1H, m, H-3′), 4.20−3.85 (16H, m, CH_3CH_2-2,3,7,8,-12,13,17,18), 1.93, 1.92, 1.86, 1.67 (each 6H, t, J = 7.6, 7.4, 7.9, 7.6 Hz, CH_3CH_2-2,3,7,8,12,13,17,18). ^{19}F NMR δ −78.41 (3F, s, CF_3-3′). MS (FAB) m/z 659 (MH^+, 100).

General Procedure for Grignard Reagent Reactions. A solution of porphyrin **2** in dry THF (10−20 mL) was degassed with high vacuum and cooled to −30 °C with a dry ice−acetone bath. Grignard reagent (0.5−3.0 M solution in diethyl ether or THF) was added dropwise to the above solution. The mixture was stirred at this temperature for 1−30 min and monitored by TLC. A 10% NH_4Cl solution was added to quench the reaction. The reaction mixture was extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried over Na_2SO_4, and evaporated. Purification was performed on neutral alumina (Brockmann grade III) columns or preparative TLC plates.

Ni(II) *meso*-(3-Hydroxy-3-methyl-propenyl)octaethylporphyrin (6a). As described in the general procedure, reaction of porphyrin **2** (35 mg) with methylmagnesium bromide (40 μL, 3M in diethyl ether) in THF (10 mL) for 1 min afforded, after purification with silica gel plates (hexanes/CH_2Cl_2, 1:6), **6a** (30 mg, 85%) as deep red needles. Mp 215−216 °C. ^{1}H NMR: δ 9.50 (2H, s, *meso* H), 9.49 (1H, s, *meso* H), 9.03 (1H, dd, J = 15.3, 1.6 Hz, H-1′), 4.95 (1H, dd, J = 15.3, 5.2 Hz, H-2′), 4.70 (1H, qd, J = 6.8, 5.2 Hz, H-3′), 3.98−3.83 (16H, m, CH_3CH_2-2,3,7,8,12,13,17,18), 1.94−1.72 (24H, m, CH_3CH_2-2,3,7,8,12,13,17,18), 1.41 (3H, d, J = 6.8 Hz, CH_3-3′). MS (FAB) m/z 660 (M^+, 100). Anal. Calcd for $C_{40}H_{50}N_4NiO$: C, 72.62; H, 7.62; N, 8.47. Found: C, 72.85; H, 7.80; N, 8.60.

Ni(II) *meso*-(3-Hydroxy-3-hexyl-propenyl)octaethylporphyrin (6b). As described in the general procedure, reaction of porphyrin **2** (102 mg) with hexylmagnesium bromide (300 μL, 2.0 M in diethyl ether) in THF (10 mL) for 10 min afforded, after purification with silica gel plates (hexanes/CH_2Cl_2, 1:4), **6b** (88 mg, 76%) as deep red needles. Mp 141−142 °C. ^{1}H NMR: δ 9.46 (2H, s, *meso* H), 9.45 (1H, s, *meso* H), 9.01 (1H, dd, J = 15.4, 1.6 Hz, H-1′), 4.88 (1H, dd, J = 15.4, 5.2 Hz, H-2′), 4.48 (1H, td, J = 5.2, 5.2 Hz, H-3′), 3.98−3.77 (16H, m, CH_3CH_2-2,3,7,8,12,13,17,18), 1.87−1.70 (24H, m, CH_3CH_2-2,3,7,8,12,13,17,18), 1.56 [2H, m, $CH_3(CH_2)_4CH_2$-3′], 1.23 [8H, m, $CH_3(CH_2)_4CH_2$-3′], 0.85 [3H, t, J = 7.1 Hz, $CH_3(CH_2)_4CH_2$-3′]. MS (FAB) m/z 731 (MH^+, 100). Anal. Calcd for $C_{45}H_{60}N_4NiO$: C, 73.87; H, 8.27; N, 7.66. Found: C, 73.88; H, 8.22; N, 7.70.

Ni(II) *meso*-(3-Hydroxy-3-decyl-propenyl)octaethylporphyrin (6c). Porphyrin **2** (180 mg) with decylmagnesium bromide (0.75 mL, 1.0 M in diethyl ether) in THF (20 mL) for 30 min afforded, after purification with a neutral alumina (Brockmann grade III) column (hexanes/CH_2Cl_2, 1:1), **6c** (163 mg, 72%) as a deep red powder. Mp 116−118 °C. ^{1}H NMR: δ 9.43 (2H, s, *meso* H), 9.42 (1H, s, *meso* H), 8.98 (1H, d, J = 15.6 Hz, H-1′), 4.85 (1H, dd, J = 15.6, 4.8 Hz, H-2′), 4.45 (1H, m, H-3′), 3.95−3.75 (16H, m, CH_3CH_2-2,3,7,8,12,13,17,18), 1.86−1.67 (24H, m, CH_3CH_2-2,3,7,8,12,13,17,18), 1.53 [2H, m, $CH_3(CH_2)_8CH_2$-3′], 1.42−1.15 [16H, m, $CH_3(CH_2)_8CH_2$-3′], 0.85 [3H, t, J = 6.6 Hz, $CH_3(CH_2)_8CH_2$-3′]. MS (FAB) m/z 786 (M^+, 100).

Ni(II) *meso*-(3-Hydroxy-3-octadecyl-propenyl)octaethylporphyrin (6d). Following the general procedure, reaction of porphyrin **2** (100 mg) with octadecylmagnesium chloride (1.0 mL, 0.5 M in THF) in THF (20 mL) for 30 min afforded, after purification with silica gel plates (hexanes/CH_2Cl_2, 1:2), **6d** (93 mg, 67%) as deep red needles. Mp 109−110 °C. ^{1}H NMR: δ 9.44 (2H, s, *meso* H), 9.43 (1H, s, *meso* H), 8.99 (1H, dd, J = 15.6, 2.1 Hz, H-1′), 4.87 (1H, dd, J = 15.6, 5.1 Hz, H-2′), 4.46 (1H, td, J = 5.1, 5.1 Hz, H-3′), 3.97−3.76 (16H, m, CH_3CH_2-2,3,7,8,12,13,17,18), 1.88−1.68 (24H, m, CH_3CH_2-2,3,7,8,12,-13,17,18), 1.55 [2H, m, $CH_3(CH_2)_{16}CH_2$-3′], 1.39−1.16 [32H, m, $CH_3(CH_2)_{16}CH_2$-3′], 0.90 (3H, t, J = 6.3 Hz, $CH_3(CH_2)_{16}CH_2$-3′]. MS (FAB) m/z 899 (M^+, 100). Anal. Calcd for $C_{57}H_{84}N_4$-NiO: C, 76.07; H, 9.41; N, 6.23. Found: C, 76.11; H, 9.44; N, 6.21.

Ni(II) *meso*-(3-Hydroxy-3-cyclopentyl-propenyl)octaethylporphyrin (6e). Following a similar approach, porphyrin **2** (144 mg) was reacted with cyclopentylmagnesium chloride (0.3 mL, 2.0 M in diethyl ether) in THF (20 mL) for 10 min to afford, after purification with silica gel plates (CH_2-Cl_2), **6e** (150 mg, 94%) as deep red needles. Mp 228−229 °C. ^{1}H NMR: δ 9.44 (2H, s, *meso* H), 9.42 (1H, s, *meso* H), 9.01 (1H, d, J = 15.5 Hz, H-1′), 4.87 (1H, dd, J = 15.5, 5.0 Hz, H-2′), 4.26 (1H, dd, J = 5.0, 5.0 Hz, H-3′), 3.99−3.75 (16H, m, CH_3CH_2-2,3,7,8,12,13,17,18), 1.91 (1H, m, CH of cyclopentyl), 1.88−1.65 (24H, m, CH_3CH_2-2,3,7,8,12,13,17,18), 1.62−1.26 (8H, m, CH_2 of cyclopentyl). MS (FAB) m/z 715 (MH^+, 90). Anal. Calcd for $C_{44}H_{56}N_4NiO$: C, 73.85; H, 7.89; N, 7.83. Found: C, 73.93; H, 8.01; N, 7.91.

Ni(II) *meso*-(3-Hydroxy-3-perfluorooctyl-propenyl)octaethylporphyrin (8). A solution of perfluorooctyl bromide (200 μL) in 20 mL of dry THF was degassed with a high vacuum and cooled to −70 °C with a dry ice−acetone bath. Hexylmagnesium bromide (400 μL, 2.0 M solution in diethyl ether) was added dropwise to the above solution. The resultant mixture was kept at −60 °C for 30 min. A solution of porphyrin **2** (160 mg) in THF (10 mL) was then added dropwise, and the reaction mixture was maintained at −60 °C for 10 min. Distilled water was added to quench the reaction, and the mixture was extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried over Na_2SO_4, and evaporated. The residue was purified on preparative TLC plates (hexanes/CH_2Cl_2, 2:3) to afford **8** (214 mg, 81%) as deep red needles. Mp 254−255 °C. ^{1}H NMR: δ 9.49 (2H, s, *meso* H), 9.48 (1H, s, *meso* H), 9.33 (1H, dd, J = 15.5, 1.5 Hz, H-1′), 5.03 (1H, m, H-3′), 4.94 (1H, dd, J = 15.5, 4.7 Hz, H-2′), 3.98−3.75 (16H, m, CH_3CH_2-2,3,7,8,12,13,17,18), 2.40 (1H, d, J = 8.2 Hz, HO-3′), 1.90−1.71 (24H, m, CH_3CH_2-2,3,7,8,12,13,17,-18). MS (FAB) m/z 1065 (MH^+, 100). Anal. Calcd for $C_{47}H_{47}$-$F_{17}N_4NiO$: C, 52.98; H, 4.45; N, 5.26; F, 30.31. Found: C, 53.08; H, 4.47; N, 5.24; F, 30.27.

***meso*-(3-Hydroxy-3-ethynyl-propenyl)octaethylporphyrin (10).** Porphyrin **2** (230 mg) was reacted with ethynylmagnesium chloride (1.5 mL, 0.5 M in THF) in THF (15 mL) for 30 min to afford, after purification over a neutral alumina (Brockmann grade III) column (hexanes/CH_2Cl_2, 2:3 as eluent), **10** (201 mg, 84%) as deep red needles. Mp 230−231 °C. ^{1}H NMR: δ 9.48 (2H, s, *meso* H), 9.47 (1H, s, *meso* H), 9.32 (1H, d, J = 15.9 Hz, H-1′), 5.20 (1H, m, H-3′), 5.04 (1H, dd, J = 15.9, 4.9 Hz, H-2′), 3.98−3.75 (16H, m, CH_3CH_2-2,3,7,8,12,13,17,18), 2.80 (1H, d, J = 2.1 Hz, acetylene H), 2.00 (1H, d, J = 7.0 Hz, HO-3′ or acetylene H), 1.94−1.64 (24H, m,

CH_3CH_2-2,3,7,8,12,13,17,18). MS (FAB) *m*/*z* 670 (M^+, 100). Anal. Calcd for $C_{41}H_{48}N_4NiO$: C, 73.33; H, 7.20; N, 8.34. Found:C, 73.05; H, 7.26; N, 8.30.

Ni(II) *meso*-(4-Ethoxycarbonyl-3-hydroxy-1-butenyl)-octaethylporphyrin (14). To a solution of diisopropylamine (200 μL) in dry THF (15 mL) at 0 °C was added *n*-butyllithium (570 μL, 2.5 M in hexane) dropwise. The solution was stirred at this temperature for 20 min and then was cooled to −78 °C with a dry ice−acetone bath. Ethyl acetate (140 μL) was added to above solution slowly. The mixture was maintained at −78 °C for 20 min. A solution of porphyrin **2** (125 mg) in THF (3 mL) was added dropwise. The resultant solution was stirred at −78 °C for 1 min. A 10% NH_4Cl solution was added to quench the reaction. The reaction mixture was extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried over Na_2SO_4, and evaporated. Purification was performed on preparative TLC plates (1% MeOH/CH_2Cl_2) to give **14** (137 mg, 97%) as deep red plates. Mp 222−223 °C. ^{1}H NMR: δ 9.46 (2H, s, *meso* H), 9.44 (1H, s, *meso* H), 9.13 (1H, d, J = 15.9 Hz, H-1′), 4.88 (1H, m, H-3′), 4.83 (1H, dd, J = 15.7, 4.2 Hz, H-2′), 4.15 (2H, q, J = 7.1 Hz, $CH_3CH_2OOCCH_2$-3′), 3.98−3.77 (16H, m, CH_3CH_2-2,3,7,8,12,13,17,18), 3.34 (1H, s, HO-3′), 2.53 (2H, m, $CH_3CH_2OOCCH_2$-3′), 1.88−1.67 (24H, m, CH_3CH_2-2,3,7,8,12,13,17,18), 1.22 (2H, t, J = 7.0 Hz, $CH_3CH_2OOCCH_2$-3′). MS (FAB) *m*/*z* 733 (MH^+, 100). Anal. Calcd for $C_{43}H_{54}N_4NiO_3$: C, 70.40; H, 7.42; N, 7.64. Found: C, 70.24; H, 7.54; N, 7.58.

General Procedure for the Preparation of Benzochlorins. Porphyrin (**3**, **4**, **6a**, **6b**, **6c**, **6d**, **6e**, **8**, **10**, or **14**) was dissolved in 10 mL of concentrated sulfuric acid (95−98%). The resultant green solution was stirred at room temperature for 10 min − 2 h and then poured into ice. The mixture was extracted with CH_2Cl_2. The combined organic extracts were washed with brine and 5% $NaHCO_3$, dried over Na_2SO_4, and evaporated. Purification was performed on neutral alumina (Brockmann grade III) columns or preparative TLC plates.

Benzochlorin 5. Following the general procedure, as described above, porphyrin **3** or **4** (120 mg for **3**, 30 mg for **4**) was dissolved in 10 mL of concentrated sulfuric acid (95−98%). The resultant green solution was stirred at room temperature for 2 h. Purification was performed on neutral alumina (Brockmann grade III) column (hexanes/CH_2Cl_2, 2:1) to give **5** (95 mg from **3**, 29 mg from **4**) as dark gray blue plates in 97% yield from **3** and in 100% yield from **4**. Mp 265−266 °C. Vis in CH_2Cl_2 [λ_{max} (ϵ)]: 409 (95570), 527 (5870), 562 (7570), 598 (8480), 650 (21230). ^{1}H NMR: δ 9.66 (1H, d, J = 8.7 Hz, H-1′), 9.23 (1H, s, H-15), 8.56 (1H, s, H-20), 8.38 (1H, d, J = 8.7 Hz, H-2′), 8.10 (1H, s, H-5), 3.90 (2H, q, J = 7.2 Hz, CH_3CH_2-12), 3.80 (2H, q, J = 7.6 Hz, CH_3CH_2-13), 3.62 (6H, m, CH_3CH_2-3,17,18), 3.54 (2H, q, J = 7.7 Hz, CH_3CH_2-2), 3.08 (2H, m, CH_3CH_2-7), 2.78 (2H, m, CH_3CH_2-7), 2.50 (1H, br, -NH), 2.10 (1H, br, -NH), 1.86 (3H, t, J = 7.2 Hz, CH_3CH_2-12), 1.80−1.63 (15H, m, CH_3CH_2-2,3,13,17,18), −0.01 (6H, t, J = 7.3 Hz, CH_3CH_2-7). ^{19}F NMR: δ −54.47 (3F, s, CF_3-3′). ^{13}C NMR: δ 177.0, 158.6, 152.9, 147.7, 146.0, 143.3, 140.9, 140.8, 140.5, 138.9, 138.8, 133.2, 129.9, 127.8, 126.1, 121.5 (q, -CF_3), 118.9, 118.8, 117.6, 107.5, 95.2, 87.4, 32.6, 32.6, 19.6, 19.4, 19.3, 19.2, 19.1, 18.5, 18.4, 17.9, 17.4, 15.9, 8.4. MS (FAB) *m*/*z* 641 (MH^+, 100). Anal. Calcd for $C_{40}H_{47}F_3N_4\cdot 1/2H_2O$: C, 73.93; H, 7.45; N, 8.62; F, 8.77. Found: C, 73.85; H, 7.62; N, 8.57; F, 8.97.

Benzochlorin 7a. Porphyrin **6a** (80 mg) was dissolved in 10 mL of concentrated sulfuric acid (95−98%). The resultant green solution was stirred at room temperature for 1 h. Purification was performed on a neutral alumina (Brockmann grade III) column (hexanes/CH_2Cl_2, 5:1) to give **7a** (51 mg, 72%) as dark gray blue plates. Mp 292−293 °C. Vis in CH_2Cl_2 [λ_{max} (ϵ)]: 413 (10180), 530 (6720), 564 (8200), 609 (10180), 664 (28660). ^{1}H NMR: δ 9.42 (1H, d, J = 8.6 Hz, H-1′), 9.16 (1H, s, H-15), 8.51 (1H, s, H-20), 7.95 (1H, s, H-5), 7.82 (1H, d, J = 8.6 Hz, H-2′), 3.87 (2H, q, J = 7.1 Hz, CH_3CH_2-12), 3.77 (2H, q, J = 7.6 Hz, CH_3CH_2-13), 3.58 (6H, m, CH_3CH_2-3, 17, 18), 3.51 (2H, q, J = 7.6 Hz, CH_3CH_2-2), 3.09 (3H, s, CH_3-3′), 2.99 (2H, m, CH_3CH_2-7), 2.63 (2H, m, CH_3CH_2-7), 2.44 (1H, br, -NH), 2.06 (1H, br, -NH), 1.82 (3H, t, J = 7.1 Hz, CH_3CH_2-12), 1.75−1.60 (15H, m, CH_3CH_2-2,3,13,17,18), 0.05 (6H, t, J = 7.3 Hz, CH_3CH_2-7). MS (FAB) *m*/*z* 587 (MH^+, 100). Anal. Calcd for $C_{40}H_{50}N_4\cdot 1/2H_2O$: C, 79.43; H, 8.67; N, 9.26. Found: C, 79.13; H, 8.66; N, 8.82.

Benzochlorin 7b. As described in the general procedure, porphyrin **6b** (30 mg) was dissolved in 10 mL of concentrated sulfuric acid (95−98%). The resultant green solution was stirred at room temperature for 1.5 h. Purification was performed on a neutral alumina (Brockmann grade III) column (hexanes/CH_2Cl_2, 5:1) to give **7b** (25 mg, 92%) as dark gray blue plates. Mp 131−132 °C. Vis in CH_2Cl_2 [λ_{max} (ϵ)]: 412 (101170), 530 (6700), 564 (8260), 609 (10160), 663 (28610). ^{1}H NMR: δ 9.50 (1H, d, J = 8.3 Hz, H-1′), 9.22 (1H, s, H-15), 8.56 (1H, s, H-20), 8.00 (1H, s, H-5), 7.94 (1H, d, J = 8.3 Hz, H-2′), 3.90 (2H, q, J = 7.2 Hz, CH_3CH_2-12), 3.80 (2H, q, J = 7.6 Hz, CH_3CH_2-13), 3.61 (6H, m, CH_3CH_2-3,17,18), 3.53 (2H, q, J = 7.6 Hz, CH_3CH_2-2), 3.43 [2H, t, J = 8.0 Hz, $CH_3(CH_2)_4CH_2$-3′], 2.93 (2H, m, CH_3CH_2-7), 2.69 (2H, m, CH_3CH_2-7), 2.30 (1H, br, -NH), 2.02 [2H, m, $CH_3(CH_2)_3CH_2CH_2$-3′], 1.92 (1H, br, -NH), 1.85 (3H, t, J = 7.2 Hz, CH_3CH_2-12), 1.77−1.63 (15H, m, CH_3CH_2-2,3,13,17,18), 1.60−1.40 [6H, m, $CH_3(CH_2)_3CH_2CH_2$-3′], 1.01 [3H, t, J = 6.9 Hz, $CH_3(CH_2)_4CH_2$-3′], 0.03 (6H, t, J = 7.5 Hz, CH_3CH_2-7). MS (FAB) *m*/*z* 657 (MH^+, 100). Anal. Calcd for $C_{45}H_{60}N_4$: C, 82.27; H, 9.21; N, 8.53. Found: C, 82.39; H, 9.35; N, 8.39.

Benzochlorin 7c. As discussed for the foregoing compound, porphyrin **6c** (60 mg) was dissolved in 10 mL of concentrated sulfuric acid (95−98%). The resultant green solution was stirred at room temperature for 1.0 h. Purification was performed on a neutral alumina (Brockmann grade III) column (hexanes/CH_2Cl_2, 6:1) to give **7c** (44 mg, 81%) as dark gray blue plates. Mp 157−158 °C. Vis in CH_2Cl_2 [λ_{max} (ϵ)]: 413 (101120), 530 (6640), 564 (8210), 609 (10100), 663 (28570). ^{1}H NMR: δ 9.49 (1H, d, J = 8.8 Hz, H-1′), 9.20 (1H, s, H-15), 8.54 (1H, s, H-20), 7.99 (1H, s, H-5), 7.92 (1H, d, J = 8.8 Hz, H-2′), 3.89 (2H, q, J = 7.7 Hz, CH_3CH_2-12), 3.79 (2H, q, J = 7.6 Hz, CH_3CH_2-13), 3.60 (6H, m, CH_3CH_2-3,17,18), 3.52 (2H, q, J = 7.6 Hz, CH_3CH_2-2), 3.41 [2H, t, J = 8.1 Hz, $CH_3(CH_2)_8CH_2$-3′], 2.92 (2H, m, CH_3CH_2-7), 2.68 (2H, m, CH_3CH_2-7), 2.28 (1H, br, -NH), 2.01 [2H, m, $CH_3(CH_2)_7CH_2CH_2$-3′], 1.90 (1H, br, -NH), 1.84 (3H, t, J = 7.7 Hz, CH_3CH_2-12), 1.77−1.61 (15H, m, CH_3CH_2-2,3,13,17,18), 1.53 [2H, m, $CH_3(CH_2)_6CH_2CH_2CH_2$-3′], 1.47−1.26 [16H, m, $CH_3(CH_2)_6CH_2CH_2CH_2$-3′], 0.92 [3H, t, J = 7.1 Hz, $CH_3(CH_2)_8CH_2$-3′], 0.01 (6H, t, J = 7.5 Hz, CH_3CH_2-7). MS (FAB) *m*/*z* 712 (M^+, 100). Anal. Calcd for $C_{51}H_{72}N_4$: C, 82.65; H, 9.79; N, 7.56. Found: C, 82.42; H, 9.79; N, 7.42.

Benzochlorin 7d. Porphyrin **6d** (24 mg) was dissolved in 10 mL of concentrated sulfuric acid (95−98%). The resultant green solution was stirred at room temperature for 1.0 h. Purification was performed on a neutral alumina (Brockmann grade III) column (hexanes/CH_2Cl_2, 6:1) to give **7d** (16 mg, 72%) as dark gray blue powder. Mp 116−118 °C. Vis in CH_2Cl_2 [λ_{max} (ϵ)]: 413 (101130), 530 (6650), 564 (8110), 610 (10070), 664 (28510). ^{1}H NMR: δ 9.48 (1H, d, J = 8.1 Hz, H-1′), 9.20 (1H, s, H-15), 8.54 (1H, s, H-20), 7.99 (1H, s, H-5), 7.92 (1H, d, J = 8.1 Hz, H-2′), 3.88 (2H, q, J = 7.8 Hz, CH_3CH_2-12), 3.79 (2H, q, J = 7.6 Hz, CH_3CH_2-13), 3.60 (6H, m, CH_3CH_2-3, 17, 18), 3.52 (2H, q, J = 7.6 Hz, CH_3CH_2-2), 3.41 [2H, t, J = 8.0 Hz, $CH_3(CH_2)_{16}CH_2$-3′], 2.92 (2H, m, CH_3CH_2-7), 2.68 (2H, m, CH_3CH_2-7), 2.27 (1H, br, -NH), 2.00 [2H, m, $CH_3(CH_2)_{15}CH_2CH_2$-3′], 1.90 (1H, br, -NH), 1.84 (3H, t, J = 7.8 Hz, CH_3CH_2-12), 1.75−1.61 (15H, m, CH_3CH_2-2,3,13,17,18), 1.51 [2H, m, $CH_3(CH_2)_{14}CH_2CH_2CH_2$-3′], 1.47−1.24 [28H, m, $CH_3(CH_2)_{14}CH_2CH_2CH_2$-3′], 0.89 [3H, t, J = 6.6 Hz, $CH_3(CH_2)_{16}CH_2$-3′], 0.01 (6H, t, J = 7.2 Hz, CH_3CH_2-7). MS (FAB) *m*/*z* 825 (MH^+, 100). Anal. Calcd for $C_{57}H_{84}N_4$: C, 82. 95; H, 10.26; N, 6.79. Found: C, 82.86; H, 10.37; N, 6.80.

Benzochlorin 7e. Porphyrin **6e** (51 mg) was dissolved in 10 mL of concentrated sulfuric acid (95−98%). The resultant green solution was stirred at room temperature for 1.0 h. Purification was performed on a neutral alumina (Brockmann grade III) column (hexanes/CH_2Cl_2, 5:1) to give **7e** (5.2 mg, 11.4%) as a dark gray blue powder. Mp 254−257 °C. Vis in CH_2Cl_2 [λ_{max} (ϵ)]: 414 (101140), 531 (6660), 565 (8150), 608

(10110), 663 (28560). ^{1}H NMR: δ 9.52 (1H, d, J = 8.8 Hz, H-1′), 9.21 (1H, s, H-15), 8.55 (1H, s, H-20), 8.01 (1H, d, J = 8.8 Hz, H-2′), 8.00 (1H, s, H-5), 4.08 (1H, m, CH of cyclopentyl), 3.87 (2H, q, J = 7.4 Hz, CH_3CH_2-12), 3.78 (2H, q, J = 7.6 Hz, CH_3CH_2-13), 3.59 (6H, m, CH_3CH_2-3, 17, 18), 3.51 (2H, q, J = 7.6 Hz, CH_3CH_2-2), 2.87 (2H, m, CH_3CH_2-7), 2.70 (2H, m, CH_3CH_2-7), 2.33 (2H, m, CH_2 of cyclopentyl), 2.11 (4H, m, CH_2 of cyclopentyl), 1.95 (2H, m, CH_2 of cyclopentyl), 1.83 (3H, t, J = 7.4 Hz, CH_3CH_2-12), 1.75−1.59 (15H, m, CH_3CH_2-2,3,13,-17,18), −0.01 (6H, t, J = 7.5 Hz, CH_3CH_2-7). MS (FAB) m/z 731 (MH^+, 100).

Benzochlorin 9. Porphyrin **8** (77 mg) was dissolved in 10 mL of concentrated sulfuric acid (95−98%). The resultant green solution was stirred at room temperature for 1.0 h. Purification was performed on a neutral alumina (Brockmann grade III) column (hexanes/CH_2Cl_2, 3:1) to give **9** (70 mg, 98%) as dark gray blue plates. Mp 220−221 °C. Vis in CH_2Cl_2 [λ_{max} (ϵ)]: 409 (119140), 527 (7200), 563 (9170), 596 (10290), 649 (25090). ^{1}H NMR: δ 9.64 (1H, d, J = 8.5 Hz, H-1′), 9.20 (1H, s, H-15), 8.53 (1H, s, H-20), 8.22 (1H, d, J = 8.5 Hz, H-2′), 8.07 (1H, s, H-5), 3.87 (2H, q, J = 7.7 Hz, CH_3CH_2-12), 3.78 (2H, q, J = 7.6 Hz, CH_3CH_2-13), 3.59 (6H, m, CH_3CH_2-3, 17, 18), 3.50 (2H, q, J = 7.6 Hz, CH_3CH_2-2), 3.00 (2H, m, CH_3CH_2-7), 2.73 (2H, m, CH_3CH_2-7), 2.36 (1H, br, -NH), 1.97 (1H, br, -NH), 1.85 (3H, t, J = 7.7 Hz, CH_3CH_2-12), 1.76−1.60 (15H, m, CH_3CH_2-2, 3, 13, 17, 18), −0.09 (6H, t, J = 7.2 Hz, CH_3-CH_2-7). ^{19}F NMR: δ −81.19 (3F, t, J = 10.1 Hz), −100.68 (2F, t, J = 13.3 Hz), −118.31 (2F, s), −121.45 (2F, s), −121.97 (2F, s), −122.17 (2F, s), −123.03 (2F, s), −126.47 (2F, s). MS (FAB) m/z 991 (MH^+, 100). Anal. Calcd for $C_{47}H_{47}F_{17}N_4$: C, 56.97; H, 4.78; N, 5.65; F, 32.59. Found: C, 57.08; H, 4.80; N, 5.62; F, 32.48.

Benzochlorin 11. As described in the general procedure, porphyrin **10** (125 mg) was dissolved in 150 mL of concentrated sulfuric acid (95−98%). The resultant green solution was stirred at room temperature for 10 min. Purification was performed on a neutral alumina (Brockmann grade III) column (hexanes/CH_2Cl_2, 1:1) and then on silica gel plates (hexanes/CH_2Cl_2/EtOAc, 20:6:1) to give **11** (23 mg, 20%) as dark gray blue plates. Mp 231−232 °C. Vis in CH_2Cl_2 [λ_{max} (ϵ)]: 414 (111100), 425 (105250), 536 (6580), 568 (7640), 602 (10930), 656 (25290). ^{1}H NMR: δ 9.54 (1H, d, J = 8.7 Hz, H-1′), 9.12 (1H, s, H-15), 8.45 (1H, s, H-20), 8.39 (1H, d, J = 8.7 Hz, H-2′), 8.02 (1H, s, H-5), 3.87 (2H, q, J = 7.3 Hz, CH_3CH_2-12), 3.76 (2H, q, J = 7.6 Hz, CH_3CH_2-13), 3.56 (6H, m, CH_3CH_2-3, 17, 18), 3.47 (2H, q, J = 7.6 Hz, CH_3CH_2-2), 3.35 (2H, m, CH_3CH_2-7), 2.99 (3H, s, CH_3CO-5′), 2.66 (1H, br, -NH), 2.62 (2H, m, CH_3CH_2-7), 2.20 (1H, br, -NH), 1.83 (3H, t, J = 7.3 Hz, CH_3-CH_2-12), 1.74−1.59 (15H, m, CH_3CH_2-2,3,13,17,18), −0.07 (6H, t, J = 7.3 Hz, CH_3CH_2-7). MS (FAB) m/z 615 (MH^+, 100). Anal. Calcd for $C_{41}H_{50}N_4O$: C, 80.09; H, 8.20; N, 9.11. Found: C, 79.71; H, 8.51; N, 9.00.

Benzochlorin 15. As discussed for the foregoing compound, porphyrin **14** (137 mg) was dissolved in 10 mL of concentrated sulfuric acid (95−98%). The resultant green solution was stirred at room temperature for 30 min. Purification was performed on a neutral alumina (Brockmann grade III) column (hexanes/CH_2Cl_2, 3:2) to give **15** (38 mg, 31%, dark gray blue plates) and the dehydration product **16** (62 mg, 50%, brown powder). Data of **15**: mp 256−257 °C. Vis in CH_2Cl_2 [λ_{max} (ϵ)]: 412 (101200), 531 (6700), 563 (8240), 605 (10180), 660 (28660). ^{1}H NMR: δ 9.53 (1H, d, J = 8.5 Hz, H-1′), 9.22 (1H, s, H-15), 8.56 (1H, s, H-20), 8.01 (1H, d, J = 8.5 Hz, H-2′), 8.00 (1H, s, H-5), 4.45 (2H, s, $CH_3CH_2OOCCH_2$-3′), 4.29 (2H, q, J = 7.1 Hz, $CH_3CH_2OOCCH_2$-3′), 3.89 (2H, q, J = 7.8 Hz, CH_3CH_2-12), 3.79 (2H, q, J = 7.3 Hz, CH_3CH_2-13), 3.60 (6H, m, CH_3CH_2-3, 17, 18), 3.52 (2H, q, J = 7.6 Hz, CH_3CH_2-2), 2.90 (2H, m, CH_3CH_2-7), 2.72 (2H, m, CH_3CH_2-7), 2.23 (1H, br, −NH), 1.94 (1H, br, −NH), 1.84 (3H, t, J = 7.1 Hz, CH_3CH_2-12), 1.77−1.60 (15H, m, CH_3CH_2-2, 3, 13, 17, 18), 1.31 (3H, t, J = 7.1 Hz, $CH_3CH_2OOCCH_2$-3′), 0.00 (6H, t, J = 7.2 Hz, CH_3CH_2-7). MS (FAB) m/z 659 (MH^+, 100). Anal. Calcd for $C_{43}H_{54}N_4O_2 \cdot {}^1/_2H_2O$: C, 77.32; H, 8.30; N, 8.39. Found: C, 77.76; H, 8.45; N, 8.24. Data of **16**: mp 199−202 °C. ^{1}H NMR: δ 10.15 (2H, s, *meso* H), 9.98 (1H, s, *meso* H), 9.68 (1H, d, J = 15.8 Hz), 8.11 (1H, dd, J = 15.5, 11.2 Hz), 6.59 (1H, dd, J = 15.5, 10.9 Hz), 6.10 (1H, d, J = 15.3 Hz), 4.40 (2H, q, J = 7.3 Hz), 4.12 (12H, m), 4.01 (4H, q, J = 7.3 Hz), 1.97 (18H, m), 1.91 (3H, t, J = 7.5 Hz), 1.73 (3H, t, J = 7.5 Hz), 1.45 (3H, t, J = 7.5 Hz). MS (FAB) m/z 659 (MH^+, 100).

Benzochlorin 12. To a solution of benzochlorin **11** (45 mg) in CH_2Cl_2/MeOH (20 mL, 1:3) was added $NaBH_4$ (200 mg) in portions. The reaction mixture was stirred at room temperature for 30 min. Water was then introduced slowly to discompose the excess $NaBH_4$. The mixture was extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried over Na_2SO_4, and evaporated. The residue was purified on an alumina (Brockmann grade III) column (hexanes/CH_2Cl_2, 1:1) to afford **12** (43 mg, 95%) as dark gray blue plates. Mp 297−299 °C. Vis in CH_2Cl_2 [λ_{max} (ϵ)]: 412 (106790), 529 (6890), 563 (8850), 605 (10300), 659 (29120). ^{1}H NMR: δ 9.62 (1H, d, J = 8.8 Hz, H-1′), 9.23 (1H, s, H-15), 8.58 (1H, s, H-20), 8.29 (1H, d, J = 8.8 Hz, H-2′), 8.02 (1H, s, H-5), 6.07 (1H, q, J = 6.0 Hz, H-4′), 3.89 (2H, q, J = 7.5 Hz, CH_3CH_2-12), 3.79 (2H, q, J = 7.6 Hz, CH_3CH_2-13), 3.60 (6H, m, CH_3CH_2-3, 17, 18), 3.52 (2H, q, J = 7.6 Hz, CH_3CH_2-2), 2.96 (1H, m, CH_3CH_2-7), 2.87−2.65 (3H, m, CH_3CH_2-7), 2.14 (1H, br, -NH), 2.05 (1H, br, -NH), 1.88 (3H, d, J = 6.0 Hz, H-5′), 1.84 (3H, t, J = 7.5 Hz, CH_3CH_2-12), 1.75−1.60 (15H, m, CH_3CH_2-2,3,13,-17,18), 0.00 (3H, t, J = 7.0 Hz, CH_3CH_2-7), −0.03 (3H, t, J = 7.5 Hz, CH_3CH_2-7). MS (FAB) m/z 617 (MH^+, 100).

General Procedure for O-Alkylation. To a solution of benzochlorin **12** (50 mg) in DMSO (15 mL) were added aqueous NaOH (50%, 1.5 mL) and alkyl iodide (3 mmol). The mixture was stirred at room temperature for 30 min to 6 h and then poured into ice. The mixture was neutralized with acetic acid and then extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried over Na_2SO_4, and evaporated. Purification was performed on neutral alumina (Brockmann grade III) columns.

Benzochlorin 13a. As described above, the reaction mixture was stirred at room temperature for 30 min. Purification was performed on a neutral alumina (Brockmann grade III) column (hexanes/CH_2Cl_2, 10:3) to give **13a** (27 mg, 53%) as dark gray blue plates. Mp 236−237 °C. Vis in CH_2Cl_2 [λ_{max} (ϵ)]: 413 (108710), 529 (7240), 563 (9080), 605 (10600), 660 (30110). ^{1}H NMR: δ 9.62 (1H, d, J = 8.8 Hz, H-1′), 9.25 (1H, s, H-15), 8.60 (1H, s, H-20), 8.23 (1H, d, J = 8.8 Hz, H-2′), 8.02 (1H, s, H-5), 5.58 (1H, q, J = 6.5 Hz, H-4′), 3.92 (2H, q, J = 7.2 Hz, CH_3CH_2-12), 3.81 (2H, q, J = 7.6 Hz, CH_3CH_2-13), 3.62 (6H, m, CH_3CH_2-3,17,18), 3.54 (2H, q, J = 7.6 Hz, CH_3CH_2-2), 3.46 (3H, s, CH_3O-4′), 3.07 (1H, m, CH_3CH_2-7), 2.81 (1H, m, CH_3CH_2-7), 2.70 (2H, m, CH_3CH_2-7), 2.13 (1H, br, -NH), 1.87 (3H, t, J = 7.2 Hz, CH_3CH_2-12), 1.79 (3H, d, J = 6.5 Hz, H-5′), 1.76−1.61 (15H, m, CH_3CH_2-2,3,13,17,18), 0.02 (3H, t, J = 6.5 Hz, CH_3CH_2-7), −0.01 (3H, t, J = 7.0 Hz, CH_3-CH_2-7). MS (FAB) m/z 631 (MH^+, 100). Anal. Calcd for $C_{42}H_{54}N_4O$: C, 79.96; H, 8.63; N, 8.88. Found: C, 79.82; H, 8.78; N, 8.57.

Benzochlorin 13b. As described for the foregoing benzochlorin, the reaction mixture was stirred at room temperature for 50 min. Purification was performed on a neutral alumina (Brockmann grade III) column (hexanes/CH_2Cl_2, 5:1) to give **13b** (48 mg, 84%) as dark gray blue plates. Mp 169−170 °C. Vis in CH_2Cl_2 [λ_{max} (ϵ)]: 413 (108680), 529 (7200), 563 (9100), 605 (10630), 660 (30120). ^{1}H NMR: δ 9.60 (1H, d, J = 8.8 Hz, H-1′), 9.24 (1H, s, H-15), 8.59 (1H, s, H-20), 8.24 (1H, d, J = 8.8 Hz, H-2′), 8.01 (1H, s, H-5), 5.64 (1H, q, J = 6.4 Hz, H-4′), 3.91 (2H, q, J = 7.5 Hz, CH_3CH_2-12), 3.80 (2H, q, J = 7.6 Hz, CH_3CH_2-13), 3.61 (6H, m, CH_3CH_2-3,17,18), 3.52 [4H, m, CH_3CH_2-2 and $CH_3(CH_2)_4CH_2$O-4′], 3.06 (1H, m, CH_3CH_2-7),), 2.79 (1H, m, CH_3CH_2-7), 2.70 (2H, m, CH_3CH_2-7), 2.12 (1H, br, -NH), 1.86 (3H, t, J = 7.5 Hz, CH_3CH_2-12), 1.77 (3H, d, J = 6.4 Hz, H-5′), 1.75−1.61 (15H, m, CH_3CH_2-2,3,13,17,-18), 1.42 [2H, m, $CH_3(CH_2)_3CH_2CH_2$O-4′], 1.31 (6H, m, $CH_3(CH_2)_3CH_2CH_2$O-4′), 0.88 (3H, t, J = 7.2 Hz, $CH_3(CH_2)_4$-CH_2O-4′), 0.01 (3H, t, J = 7.3 Hz, CH_3CH_2-7), −0.03 (3H, t, J = 7.3 Hz, CH_3CH_2-7). MS (FAB) m/z 700 (M^+, 100). Anal. Calcd for $C_{47}H_{64}N_4O$: C, 80.52; H, 9.20; N, 7.99. Found: C, 80.26; H, 9.30; N, 7.76.

Benzochlorin 13c. Following the general procedure, the reaction mixture was stirred at room temperature for 4 h. Purification was performed on a neutral alumina (Brockmann grade III) column (hexanes/CH_2Cl_2, 6:1) to give **13c** (58 mg, 91%) as dark gray blue plates. Mp 140−141 °C. Vis in CH_2Cl_2 [λ_{max} (ϵ)]: 413 (108700), 529 (7230), 563 (9120), 605 (10670), 660 (30160). ^{1}H NMR: δ 9.60 (1H, d, J = 8.8 Hz, H-1′), 9.24 (1H, s, H-15), 8.59 (1H, s, H-20), 8.24 (1H, d, J = 8.8 Hz, H-2′), 8.01 (1H, s, H-5), 5.64 (1H, q, J = 6.4 Hz, H-4′), 3.90 (2H, q, J = 7.4 Hz, CH_3CH_2-12), 3.80 (2H, q, J = 7.6 Hz, CH_3CH_2-13), 3.61 (6H, m, CH_3CH_2-3,17,18), 3.52 [4H, m, CH_3CH_2-2 and $CH_3(CH_2)_8CH_2$O-4′], 3.05 (1H, m, CH_3CH_2-7),), 2.79 (1H, m, CH_3CH_2-7), 2.69 (2H, m, CH_3CH_2-7), 2.08 (1H, br, -NH), 1.86 (3H, t, J = 7.4 Hz, CH_3CH_2-12), 1.77 (3H, d, J = 6.4 Hz, H-5′), 1.75−1.60 (15H, m, CH_3CH_2-2,3,13,17,18), 1.40 [2H, m, $CH_3(CH_2)_7CH_2CH_2$O-4′], 1.25 [18H, m, $CH_3(CH_2)_7CH_2CH_2$O-4′], 0.85 [3H, t, J = 6.8 Hz, $CH_3(CH_2)_8CH_2$O-4′], 0.00 (3H, t, J = 7.5 Hz, CH_3CH_2-7), −0.05 (3H, t, J = 7.4 Hz, CH_3CH_2-7). MS (FAB) m/z 756 (M^+, 100). Anal. Calcd for $C_{53}H_{76}N_4O$: C, 81.07; H, 9.76; N, 7.14. Found: C, 80.96; H, 9.95; N, 7.31.

Benzochlorin 13d. To a solution of benzochlorin **12** (50 mg) in DMSO (15 mL) were added aqueous NaOH (50%, 1.5 mL) and a solution of octadecyl iodide (1.14 g) in THF (3 mL). The mixture was stirred at room temperature for 6 h. Purification was performed on a neutral alumina (Brockmann grade III) column (hexanes/CH_2Cl_2, 6:1) to give **13d** (22 mg, 31%) as dark gray blue plates. The unreacted starting material benzochlorin **12** (30 mg) was recovered from the column (hexanes/CH_2Cl_2, 3:1). Mp 110−111 °C. Vis in CH_2Cl_2 [λ_{max} (ϵ)]: 414 (108650), 530 (7210), 564 (9080), 606 (10670), 661 (30130). ^{1}H NMR: δ 9.60 (1H, d, J = 8.8 Hz, H-1′), 9.24 (1H, s, H-15), 8.59 (1H, s, H-20), 8.24 (1H, d, J = 8.8 Hz, H-2′), 8.00 (1H, s, H-5), 5.64 (1H, q, J = 6.4 Hz, H-4′), 3.90 (2H, q, J = 7.2 Hz, CH_3CH_2-12), 3.80 (2H, q, J = 7.6 Hz, CH_3CH_2-13), 3.60 (6H, m, CH_3CH_2-3,17,18), 3.53 [4H, m, CH_3CH_2-2 and $CH_3(CH_2)_{16}CH_2$O-4′], 3.05 (1H, m, CH_3CH_2-7),), 2.79 (1H, m, CH_3CH_2-7), 2.69 (2H, m, CH_3CH_2-7), 2.11 (1H, br, −NH), 1.86 (3H, t, J = 7.2 Hz, CH_3CH_2-12), 1.77 (3H, d, J = 6.1 Hz, H-5′), 1.75−1.60 (15H, m, CH_3CH_2-2, 3, 13, 17, 18), 1.39 [2H, m, $CH_3(CH_2)_{15}CH_2CH_2$O-4′], 1.36−1.19 [30H, m, $CH_3(CH_2)_{15}CH_2CH_2$O-4′], 0.87 [3H, t, J = 6.4 Hz, $CH_3(CH_2)_{16}CH_2$O-4′], 0.01 (3H, t, J = 7.3 Hz, CH_3CH_2-7), −0.04 (3H, t, J = 7.4 Hz, CH_3CH_2-7). MS (FAB) m/z 869 (MH^+, 100). Anal. Calcd for $C_{59}H_{88}N_4O$: C, 81.51; H, 10.20; N, 6.44. Found: C, 81.61; H, 10.44; N, 6.40.

General Procedure for Preparing Zinc Complexes of Benzochlorins (17a−j) for in Vitro and in Vivo Studies. To a solution of benzochlorin (∼10 mg) in CH_2Cl_2 (25 mL) was added a solution of $Zn(OAc)_2 \cdot 2H_2O$ (100 mg) in methanol (15 mL). The mixture was stirred at room temperature for 1.5 h and then washed with brine, dried over Na_2SO_4, and evaporated. The residue was passed through an alumina (Brockmann grade III) column (CH_2Cl_2 as eluant) to afford zinc complexes of benzochlorin in quantitative yield.

The solutions for biological studies were prepared by grinding individually the dry zinc complexes of the benzochlorins with 0.1 mL of Tween 80. The sticky paste was then kept in dark overnight before diluting it with 10 mL of 5% dextrose in water. The resultant solution was filtered with a syringe filter (0.22 μm). The concentrations were calculated on the basis of their molecular weight and extinction coefficient values by using the Beer−Lambert law.

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Supporting Information Available: Set of ^{1}H and ^{19}F spectra of all the new products. This material is available free of charge via the Internet at http://pubs.acs.org.

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