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Core-modified porphyrins. Part 5: Electronic effects on photophysical and biological properties in vitro

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Abstract—21,23-Dithiaporphyrins **2**–**11** were prepared as analogues of 5,20-diphenyl-10,15-bis(4-carboxylatomethoxy)phenyl-21,23-dithiaporphyrin **1** to examine the impact of electronic properties at the 5- and 20-*meso*-positions. The effects of the electronic properties at the *meso*-rings were not significant with respect to absorption spectra, quantum yields for the generation of singlet oxygen and for fluorescence. While some differences were noted in the *n*-octanol/pH 7.4 buffer partition coefficient, log $D_{7.4}$, among the compounds, log $D_{7.4}$ did not critically influence the cellular uptake or phototoxicity. None of the dithiaporphyrins **1**–**11** displayed dark toxicity at concentrations up to 1×10^{-5} M. Once irradiated with 5 J cm^{-2} of 350–750 nm light, five porphyrins **2**, **3**, **5**, **6**, and **8** killed over 80% of R3230AC rat mammary adenocarcinoma cells at 5×10^{-7} M photosensitizer. Among these five, compound **3** bearing 5-phenyl and 20-(4-fluorophenyl) substituents was the most potent photosensitizer toward R3230AC cells showing 67% cell kill at 1×10^{-7} M **3**. Bulky substituents at the 5- and 20-positions gave photosensitizers with minimal phototoxicity.

1. Introduction

Photodynamic therapy (PDT) is a promising new treatment regimen for cancer that uses three components to destroy the tumor: a photosensitizer, light, and oxygen.[1–9] The photosensitizer generates cytotoxic singlet oxygen following absorption of a photon of appropriate wavelength. Photofrin has gained regulatory approval in many countries but it has several drawbacks, such as long-term skin phototoxicity, chemical complexity, and weak absorption at shorter wavelengths (~630 nm).[10] Therefore, the development of more ''ideal'' photosensitizers is a major emphasis in research on photodynamic therapy, which should be chemically pure, generate singlet oxygen efficiently, accumulate selectively in the tumor, and observe longer wavelength light (650–800 nm). Currently, several new photosensitizers are approved or are under clinical study.[11]

Dithiaporphyrins have been extensively studied in our laboratory as second-generation photosensitizers due to several advantages. The various dithiaporphyrins can be prepared in high purity through established synthetic schemes, can absorb longer wavelengths of light (690–710 nm) than natural tetra nitrogenic porphyrins (~630 nm), and are more photostable than Photofrin upon irradiation.[12] Dithiaporphyrins with two carboxylic acids exhibited a higher phototoxic activity toward R3230AC rat mammary adenocarcinoma cells than derivatives with one, three, or four acid groups.[13] Bulky substituents at the *meso*-positions reduced phototoxicity, while effects on physicochemical properties, such as absorption spectra and quantum yields for the generation of singlet oxygen and fluorescence, were minimal.[14] Of the dithiaporphyrins prepared in our previous study, 5-phenyl-20-(2-thienyl)-10,15-bis-(4-carboxylatomethoxyphenyl)-21,23-dithiaporphyrin (**IY69**) showed the most potent phototoxic activity and irradiation of cells treated with **IY69** induced apoptotic cell death along with the damage to mitochondrial function.[14]

The phototoxicity of **IY69** prompted us to develop a more extensive study of substituent effects in the dithiaporphyrin diacids. The structures of compounds in this

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work were designed to investigate the electronic effects of substituents at the *para*-positions of *meso*-phenyl rings on physicochemical and biological outcomes. Cellular uptake and photo- and dark toxicity of the various dithiaporphyrins were evaluated along with the important physicochemical properties for a photosensitizer, such as absorption spectra, quantum yields for the generation of singlet oxygen and for fluorescence, and the *n*-octanol/water partition coefficient at pH 7.4, log $D_{7.4}$.

2. Results and discussion

2.1. Chemistry

2.1.1. Synthesis of symmetrical 21,23-dithiaporphyrins 4, 5, and 7–11. The synthesis of symmetric core-modified porphyrins **4**, **5**, **8**, **10**, and **11** (Fig. 1) followed our previous method.[12–14] As shown in Scheme 1, 2,5-bis[1-(4-substituted-phenyl)-1-hydroxymethyl]thiophene diols **12**, **13**, and **15**–**17** were synthesized from thiophene and the corresponding aldehydes in 70–75% isolated yields. The diols were condensed with 2,5-bis[1-(4-methoxyphenyl)-1-pyrrolomethyl]-thiophene **22** and oxidized in the presence of 2,3,5,6-tetrachlorobenzoquinone (TCBQ) and *p*-toluenesulfonic acid monohydrate ($TsOH{\cdot}H_2O$) or boron trifluoride etherate ($BF_3{\cdot}OEt_2$) in CH_2Cl_2 giving dimethoxy dithiaporphyrins **24**–**28** in 3–18% isolated yields (Scheme 2). Demethylation with boron tribromide (BBr_3) in CH_2Cl_2 gave diphenolic dithiaporphyrins **31**–**35** (83–95%), which were then alkylated in the presence of K_2CO_3 and ethyl bromoacetate in acetone to produce ester porphyrins **36**–**40**. Final diacid dithiaporphyrins **4**, **5**, **8**, **10**, and **11** were prepared by hydrolysis of the esters with NaOH in a 1:1 solution of distilled water and tetrahydrofuran (THF).

In the preparation of di-4-methoxyphenyl- and di-4-hydroxyphenyldithiaporphyrin **7** and **9**, the upper scheme could not be applied due to possible problems in either the demethylation of **7** or the alkylation of **9**. Consequently, slightly modified routes were devised (Scheme 2). To avoid any difficulty in selective demethylation of a tetramethoxy porphyrin in the preparation of dimethoxy porphyrin **7**, ester porphyrin **29** was prepared directly by cyclization of 2,5-bis[1-(4-methoxyphenyl)-1-

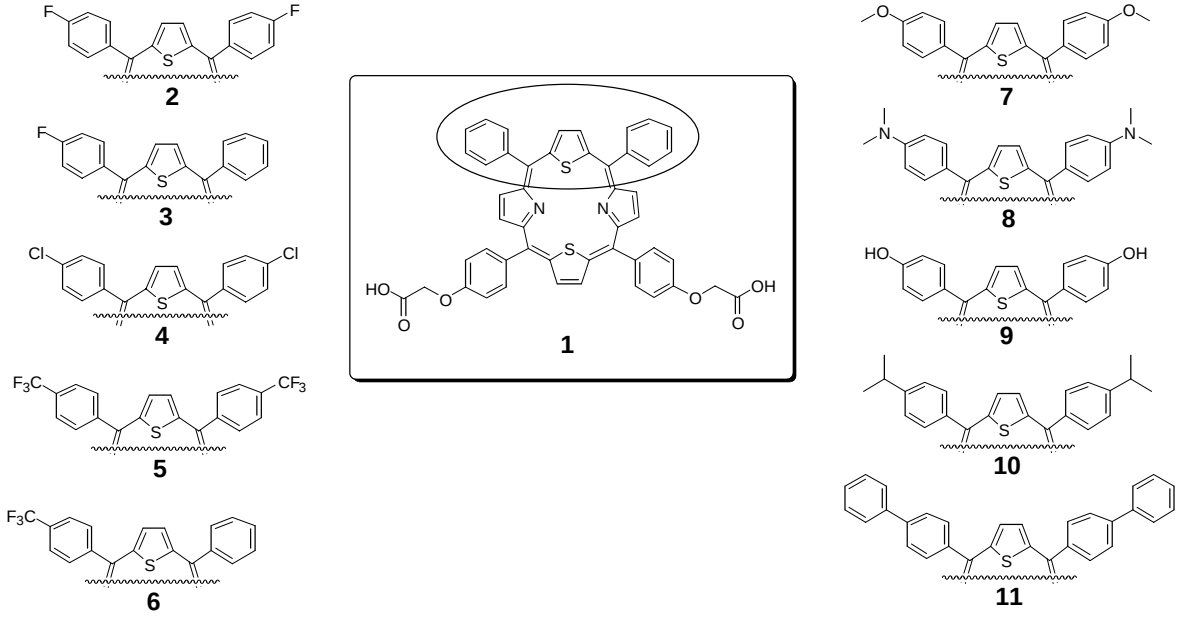
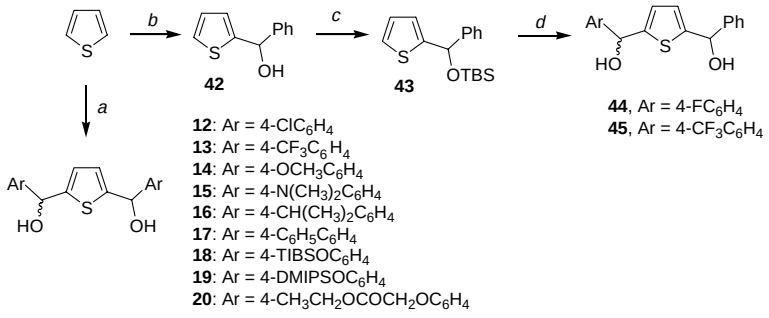
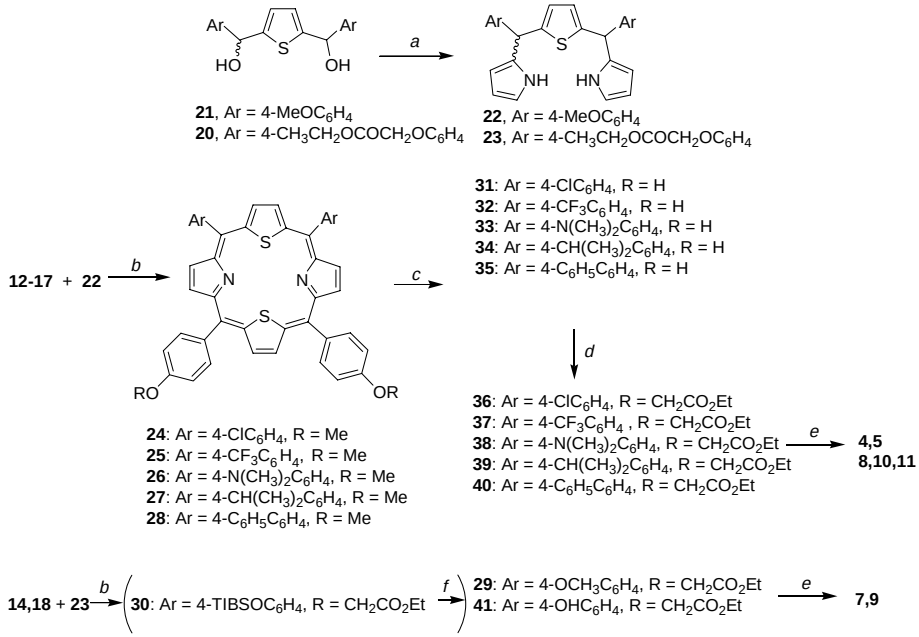


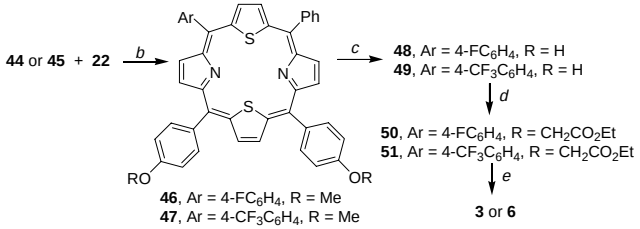
Figure 1. Structures of 21,23-dithiaporphyrins with various group substitutions at the 5,20-*meso*-positions.



Scheme 1. Reagents: (a) i. 2.5 equiv *n*-BuLi, ii. 2 equiv aryl aldehyde; (b) i. 1 equiv BuLi, ii. 1 equiv benzaldehyde; (c) TBSCl, DMAP, Et_3N; (d) i. 1 equiv *n*-BuLi, ii. 1 equiv aryl aldehyde, iii. aqueous HCl.



Scheme 2. Reagents: (a) pyrrole, $BF_3{\cdot}OEt_2$; (b) TCBQ, TsOH, CH_2Cl_2; (c) BBr_3, CH_2Cl_2; (d) $BrCH_2CO_2Et$, K_2CO_3, acetone; (e) NaOH, aqueous THF; (f) TBAF.



Scheme 3. Reagents: (a) pyrrole, $BF_3{\cdot}OEt_2$; (b) TCBQ, TsOH, CH_2Cl_2; (c) BBr_3, CH_2Cl_2; (d) $BrCH_2CO_2Et$, K_2CO_3, acetone; (e) NaOH, aqueous THF.

hydroxymethyl]thiophene **14** and diethyl 2,5-bis[1-(4-carboxylatomethoxyphenyl)-1-pyrrolomethyl]thiophene **23**. For the preparation of **9**, protection of the phenolic functionality was necessary. Protected diol, 2,5-bis[1-(4-triisobutylsilyoxy)phenyl-1-hydroxymethyl]thiophene **18**, was synthesized and condensed with **23** to give hydroxyl-protected ester **30** in 32% isolated yield. Deprotection of **30** with tetrabutylammonium fluoride (TBAF) in THF provided ester **41**.

2.1.2. Synthesis of unsymmetrical dicarboxylic acid derivatives 3 and 6. Reported methods to prepare unsymmetrical core-modified porphyrins were used in the preparation of dithiaporphyrins **3** and **6** with 4-fluorophenyl and 4-trifluoromethylphenyl substituents, respectively (Scheme 3). Unsymmetric diols **44** and **45** were prepared from 2-lithiothiophene via the *tert*-butylsilyl (TBS)-protected monohydroxythiophene **43**. Cyclization of **44** and **45** with **22** gave dimethoxydithiaporphyrins **46** and **47** in 5% and 7% isolated yields, respectively. Diacid porphyrins **3** and **6** were successfully synthesized through demethylation, alkylation, and hydrolysis, under the same conditions as those used for the symmetrical analogues.

2.2. Photophysical properties

2.2.1. Absorption maxima. The absorption maximum and molar extinction coefficient of band I of porphyrins are important parameters in evaluating potential photosensitizers for PDT. Longer wavelength light (650–800 nm) reaches deeper into tissue to activate photosensitizers.[15] Photosensitizers with higher extinction coefficients harvest the irradiating light more efficiently. So, photosensitizers having longer-wavelength absorption maxima (~800 nm) and higher extinction coefficient are highly desirable. Although most 4-aryl substituents at the *meso*-positions have minimal impact on the absorption maximum of band I, introduction of fluoro **2** or dimethylamino **8** groups results in a significant redshift from the diphenyl derivative **1** ($\Delta\lambda_{max}$ = +19 and +16 nm, respectively, Table 1). Also noteworthy is the extinction coefficient of band I for compound

Table 1. UV–vis–near-IR band maxima and molar absorptivities for dithiaporphyrins **1**–**11** in methanol[a]

Compound	Soret	Band IV	Band III	Band II	Band I
1	435 (314)	513 (27.7)	549 (10.7)	632 (3.2)	698 (7.0)
2[b]	442 (127)	533 (14.0)	573 (10.8)	645 (2.5)	717 (4.8)
3	435 (407)	514 (26.9)	548 (9.9)	634 (1.8)	698 (5.3)
4	436 (296)	515 (21.4)	550 (8.8)	634 (1.7)	699 (4.6)
5	435 (297)	514 (24.3)	548 (9.2)	633 (1.8)	697 (4.6)
6	435 (327)	514 (25.4)	549 (11.3)	634 (2.1)	698 (5.6)
7[c]	440 (176)	517 (14.6)	554 (10.3)	638 (1.2)	704 (4.1)
8[c]	449 (100)	522 (17.7)	573 (19.4)	—	714 (8.9)
9[c]	440 (263)	518 (21.5)	555 (12.3)	639 (1.6)	704 (5.9)
10	436 (306)	515 (21.6)	551 (9.6)	635 (1.6)	700 (5.5)
11[c]	439 (97.6)	518 (13.7)	553 (7.5)	637 (1.1)	702 (3.8)

[a] λ_{max} nm ($\varepsilon \times 10^3$ M^{-1} cm^{-1}).
[b] Di-sodium salts and data from Ref. 12.
[c] In THF.

8 (8.9×10^3 M^{-1} cm^{-1}), which is the highest among the dithiaporphyrin derivatives.

2.2.2. Quantum yields for the generation of singlet oxygen. Singlet oxygen ($^1O_2$) is thought to be the toxic species that damages tumor cells following irradiation of the photosensitizer.[16] Higher quantum yields for the generation of singlet oxygen [$\phi(^1O_2)$] endow photosensitizers with greater potential for biological activity, that is, phototoxicity. Values of $\phi(^1O_2)$ for **1**–**11** were determined by direct detection of singlet-oxygen luminescence at 1270 nm, which was compared with the standard, rose Bengal [$\phi(^1O_2) = 0.80$]. Excitation was effected with a frequency-doubled neodinium–YAG laser emitting at 532 nm. All the core-modified porphyrins **1**–**11** showed high values of $\phi(^1O_2)$ (>0.73), with the exception of two compounds, 4-dimethylaminophenyl derivative **8** [$\phi(^1O_2) = 0.32$] and 4-hydroxyphenyl derivative **9** [$\phi(^1O_2) = 0.03$] (Table 2).

2.2.3. Quantum yields for fluorescence. Molecular fluorescence is a useful tool to study the localization and pharmacokinetics of dyes both in vitro and in vivo. Quantum yields of fluorescence (ϕ_F) were determined for the compounds **1**–**11** compared to rhodamine 6G ($\phi_F = 1.0$). Interesting enough is the increase of ϕ_F of compound **8** (0.029), which is theoretically consistent with its low value of $\phi(^1O_2)$, 0.32 (Table 2). In contrast, compound **9** displayed low quantum yields for both the generation of singlet oxygen [$\phi(^1O_2) = 0.03$] and for fluorescence ($\phi_F = 0.002$). All the other compounds have poor fluorescence with values of $\phi_F < 0.012$.

2.2.4. *n*-Octanol/water partition coefficients. The lipophilicity of a molecule is an important determinant of biomembrane permeability. The partition between *n*-octanol and pH 7.4 buffer was measured by a slightly modified 'shake-flask' method.[17] The change in substituents on the *meso*-aryl groups gave a range of values of $\log D_{7.4}$ from −0.16 for 4-isopropylphenyl derivative **10** to 0.78 for 4-hydroxyphenyl derivative **9** (Table 2). Interestingly, the effects of the hydroxyl and isopropyl groups were contrary to our expectations. The isopropyl group increases $\log D_{7.4}$ ($\Delta\log D_{7.4} = +0.74$) and hydroxyl group decreases $\log D_{7.4}$($\Delta\log D_{7.4} = -0.20$) from compound **1** ($\log D_{7.4} = 0.04$, Table 2), even though the hydrophobic constants (π) of isopropyl and hydroxyl groups are 1.53 and −0.67, respectively.[18] This observation strongly suggests that $\log D_{7.4}$ might be influenced by other factors, such as dimerization or aggregation in solution.

Table 2. Quantum yields for the generation of singlet oxygen [$\phi(^1O_2)$], quantum yields for fluorescence (ϕ_F), and *n*-octanol/water partition coefficients in pH 7.4 phosphate buffer ($\log D_{7.4}$) for **1**–**11**[a]

Compound	$\phi(^1O_2)$	ϕ_F	$\log D_{7.4}$
1	0.80	0.007	0.04 ± 0.02
2	0.71[b]	0.003[b]	ND[c]
3	0.83	0.010	−0.06 ± 0.01
4	0.76	0.011	0.19 ± 0.06
5	0.75	0.010	0.27 ± 0.05
6	0.87	0.009	−0.08 ± 0.01
7	0.81	0.012	−0.15 ± 0.08
8	0.32	0.029	0.56 ± 0.15
9	0.03	0.002	0.78 ± 0.08
10	0.74	0.010	−0.16 ± 0.06
11	0.73	0.012	0.12 ± 0.14

[a] Detailed methods for measurements above are presented in Section 4.
[b] Ref.12.
[c] ND (not determined) indicates samples for which measurements were not performed.

2.3. Biology

2.3.1. Intracellular accumulation of core-modified porphyrins into cultured R3230AC cells. The cellular uptake of core-modified porphyrins after 24 h incubation was determined by fluorescence techniques (Fig. 2). Following exposure to photosensitizers, cells were digested and the porphyrins were solubilized with 25% Scintigest (100% DMSO for compound **9**). Owing to low values of ϕ_F for porphyrins (Table 2), higher concentrations of photosensitizer were employed, 5×10^{-6} and 1×10^{-5} M, in the uptake experiment, relative to the phototoxicity experiments, although there was no significant dark toxicity with any of the compounds at 1×10^{-5} M.

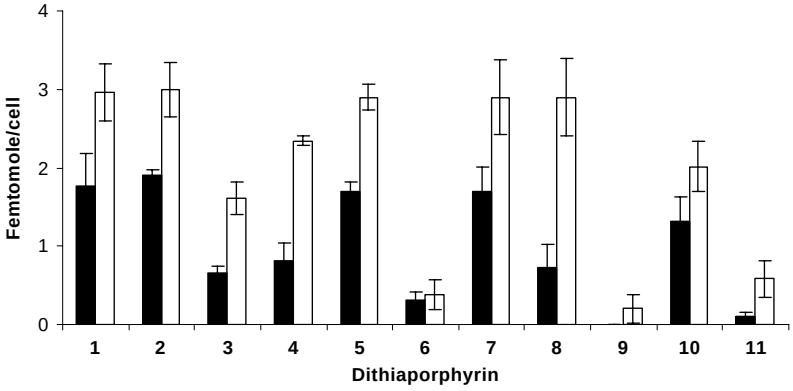


Figure 2. Cellular uptake of 21,23-dithiaporphyrins in cultured R3230AC rat mammary adenocarcinoma cells. Each bar represents the mean intracellular uptake of each compound incubated with R3230AC cells for 24 h at 5×10^{-6} M (black bars) or 1×10^{-5} M (white bars). Data are expressed as femtomole porphyrin/cell and error bars are the SEM.

Cellular uptake of the dithiaporphyrins at 5×10^{-6} M of the photosensitizer covered a range from 0.1 fmol/cell for **11** to 1.9 fmol/cell for **2**. Cellular uptake was similar for the symmetrically substituted dithiaporphyrins **1**, **2**, **5**, **7**, and **10** (1.8, 1.9, 1.7, 1.7, and 1.8 fmol/cell, respectively) and was somewhat lower for 4-chlorophenyl derivative **4** (0.8 fmol/cell) and 4-dimethylaminophenyl derivative **8** (0.7 fmol/cell). Cellular uptake of the unsymmetrically substituted derivatives **3** (0.7 fmol/cell) and **6** (0.3 fmol/cell) was significantly less than the corresponding symmetrical derivatives **1**, **2**, and **5** for these substituents ($P < 0.05$ for all pairwise comparisons). The lowest cellular uptake was observed with compound **11** (0.1 fmol/cell) with bulky biphenyl substituents. The value of ϕ_F for **9** is much smaller than any of the other derivatives and no fluorescence could be detected following cell digestion of cells treated with 5×10^{-6} M photosensitizer. At 1×10^{-5} M photosensitizer, uptake of compound **9** (0.2 fmol/cell) was comparable to the uptake of compounds **6** (0.4 fmol/cell) and **11** (0.6 fmol/cell), but the uptake of these compounds was still less than for any of the others at either 5×10^{-6} M or 1×10^{-5} M.

The uptake does not appear to be strictly a function of liphophilicity. log $D_{7.4}$ values for compounds **1**, **5**, **7**, and **10** with the highest cellular uptake and compounds **6** and **11** with two of the lowest values of cellular uptake are all near 0. Additionally, compound **9** with the highest value of log $D_{7.4}$ at 0.78 showed the lowest uptake, which might be explained by either loss of amphiphilicity of the molecule or formation of aggregates in the media.

2.3.2. Dark toxicity and phototoxicity of core-modified porphyrins toward cultured R3230AC cells. Dark toxicity and phototoxicity of the core-modified porphyrins toward R3230AC rat mammary adenocarcinoma cells were determined using the MTT colorimetric assay. Cells were incubated for 24 h with 5×10^{-8} to 1×10^{-6} M core-modified porphyrin. Treated cells were then irradiated with 1.4 mW cm^{-2} broadband light (350–750 nm) for 1 h giving a total fluence of 5 J cm^{-2}. Cell survival was then determined 24 h following irradiation of treated cells and 24 h later for dark controls. For the dark controls, cell survival was >85% for all dithiaporphyrins at concentrations up to 1×10^{-5} M.

Phototoxicity with the porphyrins at 1×10^{-7} and 5×10^{-7} M is given in Figure 3. Dithiaporphyrins **2**–**6** with the electron-withdrawing substituents –F and –CF_3, dithiaporphyrin **8** with dimethylamino substituents, and dithiaporphyrin **1** with phenyl substituents showed comparable phototoxicity with <20% survival at 5×10^{-7} M. However, compound **3** with *meso*-phenyl and 4-fluorophenyl substituents gave only 33% cell survival in R3230AC cells treated with 1×10^{-7} M **3**. Dithiaporphyrin **4** with chloro substituents and dithiaporphyrin **7** with methoxy substituents were not as phototoxic with treated cells displaying 44% and 54% cell survival, respectively, at 5×10^{-7} M. Dithiaporphyrin **9** with hydroxyl substituents and dithiaporphyrins **10** and **11** with bulky substituents showed essentially no phototoxicity at 5×10^{-7} M. Even at 1×10^{-6} M, compounds **10** and **11** showed 63% and 75% survival, respectively, with 5 J cm^{-2} of 350–750 nm light in treated cells. This is consistent with our earlier observations on dithiaporphyrins with two bulky substituents.[14]

Examination of the quantum yields for the generation of singlet oxygen, cellular uptake, and phototoxicity of the various dithiaporphyrins revealed some inconsistencies. Compounds **1**, **2**, **6**, and **8** were the most phototoxic compounds in the series **1**–**11**, yet $\phi(^1O_2)$ was 0.80 for **1**, 0.71 for **2**, and 0.87 for **6** in solution but only 0.32 for **8**. Furthermore, cellular uptake was 1.8 fmol/cell for **1**, 1.9 fmol/cell for **2**, and only 0.3 and 0.7 fmol/cell for **6** and **8**, respectively, when the R3230AC cells were exposed to 5×10^{-6} M photosensitizer. In contrast, the photosensitizer **10** with $\phi(^1O_2)$ of 0.73 and cellular uptake of 1.3 fmol/cell in cells treated with 5×10^{-7} **10** was one of the poorest photosensitizers in the series. Clearly, efficacy of photosensitizers in the series **1**–**11** cannot be predicted by either values of $\phi(^1O_2)$ or by cellular uptake or by a combination of the two.

Values of log $D_{7.4}$ also did not correlate with efficacy. Compounds **1**, **2**, **6**, and **10** had values of log $D_{7.4}$ near 0, while compound **8** was more lipophilic with log $D_{7.4}$ of 0.56. Compound **10** showed no phototoxicity in

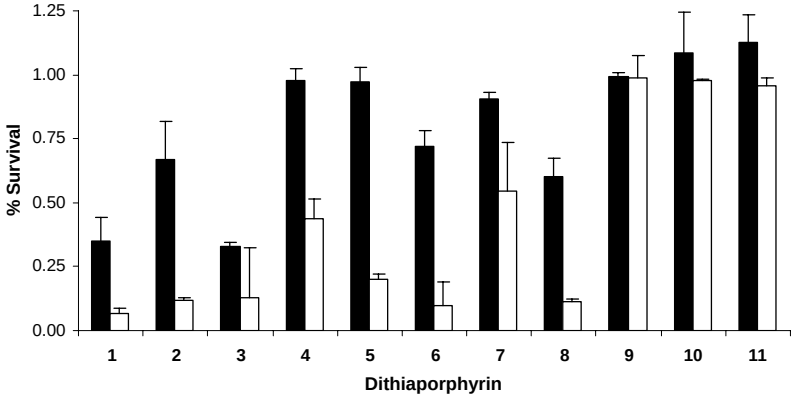


Figure 3. Cell viability of cultured R3230AC cells after photosensitization with 5 J cm^{-2} of broadband light (350–750 nm) in the presence of 21,23-dithiaporphyrins, 1×10^{-7} M (black bars) or 5×10^{-7} M (white bars). Each data point represents the mean of at least three separate experiments performed in duplicate and error bars are the SEM. Data are expressed as the surviving fraction of viable cells relative to untreated controls.

marked contrast to compounds **1**, **2**, and **6** with similar values of log $D_{7.4}$, uptake, and $\phi(^1O_2)$. Furthermore, the more lipophilic compound **8** was similar in potency to the amphiphilic molecules **1**, **2**, and **6**. In the absence of a single parameter to predict phototoxic behavior, one needs to consider the possibilities of differences in uptake and phototoxicity among monomeric and aggregate species, as well as the possibility of specific cellular sites of localization.

3. Summary and conclusions

As an extension of our previous study of structure–activity relationships that focused on the effects of steric bulk and symmetry in dithiaporphyrins, ten new core-modified porphyrins were prepared whose substituents varied in electronic properties. These derivatives were successfully prepared through the synthetic methods developed in our previous work.[13] However, the preparation of dimethoxy and dihydroxy compounds, **7** and **9**, respectively, required new synthetic approaches, as shown in Scheme 2.

The differences in electronic properties among the substituents had minimal impact on physical and photophysical features, such as absorption maxima (λ_{max}), quantum yields for the generation of singlet oxygen [$\phi(^1O_2)$] and fluorescence (ϕ_F), and *n*-octanol/water partition coefficients (log $D_{7.4}$). Compounds **2** and **8** with two 4-fluorophenyl or two 4-dimethylaminophenyl substituents in the *meso*-positions displayed a small bathochromic shift in λ_{max}, relative to the other derivatives, compound **8** had a value of $\phi(^1O_2)$ that was less than half of any other derivative in the series, and compounds **8** and **9** were both more lipophilic than other derivatives in the series based on the values of log $D_{7.4}$.

In the series **1**–**11**, five of the dithiaporphyrins (compounds **2**, **3**, **5**, **6**, and **8**) were efficient photosensitizers, giving less than 20% cell survival in R3230AC rat mammary adenocarcinoma cells following treatment with 5×10^{-7} M photosensitizer and 5 J cm^{-2} of 350–750 nm light. Compound **3** with *meso*-phenyl and 4-fluorophenyl substituents was the most potent photosensitizer among these five toward R3230AC cells, with only 33% cell survival following treatment with 1×10^{-7} M photosensitizer and 5 J cm^{-2} of 350–750 nm light. Dark controls indicated that there was no significant cellular toxicity in the absence of light.

Empirically, the substituent studies of this manuscript and our previous work have identified two dithiaporphyrins with two 4-(carboxylatomethoxy)phenyl substituents at the 10- and 15-positions, a phenyl substituent at the 5-position, and either a 4-fluorophenyl substituent (compound **3** of this study) or a 2-thienyl substituent (**IY69** of our previous study)[14] at the 20-position as superior photosensitizers with submicromolar EC_{50}'s and 5 J cm^{-2} of 350–750 nm light. As was observed in our earlier work with dithiaporphyrins with two 2,4,6-trimethylphenyl substituents or two 4-*tert*-butylphenyl substituents,[14] compounds **10** and **11** with two bulky 4-isopropylphenyl or 4-biphenyl substituents, respectively, showed essentially no phototoxicity. The presence of two bulky *meso*-substituents leads to an ineffective photosensitizer. In studies of over thirty dithiaporphyrin derivatives, no clear correlation of either physical or photophysical properties has allowed prediction of efficacy. While two derivatives appear to be superior in studies in vitro, we have as yet to determine a molecular target, although mitochondria are implicated as a general site of action.[14] The efficacy of **IY69** and compound **3** may be due to a specific molecular target or may be due to some physical phenomenon peculiar to these derivatives, relative to the others, such as aggregation/deaggregation in the cell. Future studies will focus on compounds **IY69** and **3** to identify reasons for their added efficacy.

4. Experimental

4.1. General methods

Solvents and reagents were used as received from Sigma–Aldrich Chemical (St. Louis, MO) unless otherwise noted. Cell culture medium was purchased from GIBCO (Grand Island, NY). Fetal bovine serum (FBS) was obtained from Atlanta Biologicals (Atlanta, GA). Concentration in vacuo was performed on a Buchi rotary evaporator. NMR spectra were recorded at 23 °C on a Varian Gemini-300, Inova 400, or Inova 500 instrument with residual solvent signal as the internal standard: $CDCl_3$ (δ 7.26 for proton, δ 77.16 for carbon). Infrared spectra were recorded on a Perkin-Elmer FT-IR instrument. UV–vis–near-IR spectra were recorded on a Perkin-Elmer Lambda 12 spectrophotometer. Elemental analyses were conducted by Atlantic Microlabs, Inc. Q-TOF 2 electrospray and ESI mass spectrometry were conducted at the Campus Chemical Instrumentation Center of The Ohio State University (Columbus, OH) and the Instrument Center of the Department of Chemistry at the University at Buffalo. Compounds **1**, **12**–**15**, **21**–**23**, **45**, and **46** were prepared, as previously described[12–14] and compound **2**, prepared in our earlier works,[12] was used as the disodium salt. In biological studies, core-modified porphyrins **1**–**11** were dissolved in DMSO to make a stock solution at 2×10^{-3} M. The stock solutions were then used after appropriate dilutions with sterilized doubly distilled water.

4.2. Synthesis

4.2.1. General method for the preparation of 2,5-bis(aryl-1-hydroxymethyl)thiophenes (16–18). Compounds **17** and **18** were prepared as described for the preparation of **16**.

4.2.2. 2,5-Bis[1-(4-isopropyl)phenyl-1-hydroxymethyl]thiophene (16). Thiophene (4.2 g, 50 mmol) was added to a solution of *n*-butyllithium (69 mL of a 1.6 M solution in hexanes, 110 mmol) and TMEDA (17 mL, 115 mmol) in 200 mL hexanes under an Ar atmosphere. The reaction mixture was heated at reflux for 1 h, cooled to ambient temperature, and transferred via a cannula to a pres-

sure-equalizing addition funnel. This dilithiothiophene suspension was then added dropwise to a solution of 4-isopropylbenzaldehyde (14 g, 95 mmol) in 200 mL of anhydrous THF cooled to 0 °C, which had been degassed with Ar for 15 min. After the addition was complete, the mixture was warmed to ambient temperature, 300 mL of NH_4Cl (aqueous 1 M solution) was added, and the organic phase was separated. The aqueous phase was extracted with ether (3× 300 mL). The combined organic extracts were washed with water (3× 300 mL) and brine (300 mL), dried over $MgSO_4$, and concentrated. The crude product was purified by a silica column with the mixture of hexanes and ethyl acetate to give 14 g (73%) of **16** as a light yellow oil. IR (film): 3415, 3036, 2940, 2870, 1699 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.17 (12H, d, $J = 7.0$ Hz), 3.16–3.20 (2H, m), 5.85 (2H, s), 6.62 (2H, s), 7.14 (4H, d, $J = 8.0$ Hz), 7.27 (4H, d, $J = 7.5$ Hz); ^{13}C NMR (126 MHz, $CDCl_3$): δ 24.10, 33.96, 72.62, 124.42, 124.45, 126.42, 126.47, 126.73, 140.47, 148.26, 148.85; High Resolution Q-TOF MS, *m/z* 403.1703 (calcd for $C_{24}H_{28}O_2S$+H, 403.1708).

4.2.3. 2,5-Bis(1-biphenyl-1-hydroxymethyl)thiophene (17). Yield: 70%; IR (film): 3392, 3030, 1732, 1698 cm^{-1}; ^1H NMR (500 MHz, CD_3OD): δ 5.44 (2H, s), 6.70 (2H, s), 7.28–7.35 (2H, m), 7.38–7.52 (8H, m), 7.54–7.62 (8H, m); ^{13}C NMR (126 MHz, 1:1 $CDCl_3/CD_3OD$): δ 81.41, 81.45, 125.14, 127.09, 127.11, 127.15, 127.33, 127.39, 127.44, 127.47, 127.51, 128.88, 140.02, 140.06, 140.84, 141.08, 146.29, 146.33; High Resolution ESI MS: *m/z* 448.1481 (calcd for $C_{30}H_{24}O_2S$, 448.1492).

4.2.4. 2,5-Bis[1-(4-triisobutylsilyoxy)phenyl-1-hydroxymethyl]thiophene (18). Yield: 58%; ^1H NMR (300 MHz, $CDCl_3$): δ 1.31 (18H, d, $J = 6.9$ Hz), 1.42–1.50 (6H, br s), 6.13 (2H, s), 6.88 (2H, s), 7.07 (4H, d, $J = 8.4$ Hz), 7.48 (4H, d, $J = 7.5$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ .83, 18.06, 72.46, 120.03, 124.44, 127.73, 135.60, 148.50, 156.10. High Resolution ESI MS: *m/z* 663.3344 (calcd for $C_{36}H_{56}O_4SSi_2$+Na, 663.3330).

4.2.5. 2-(1-Hydroxy-1-phenylmethyl)-5-[1-(4-fluorophenyl)-1-hydroxymethyl]-thiophene (44). 2-[1-(*tert*-Butyldimethylsilyloxy)-1-phenylmethyl]thiophene[14] (**43**, 6.0 g, 20 mmol) was added to a solution of *n*-butyllithium (14 mL of 1.6 M in hexanes, 22 mmol) and TMEDA (3.6 mL, 24 mmol) in 150 mL of hexanes under an Ar atmosphere. The reaction mixture was stirred at ambient temperature for 30 min and transferred via cannula to a pressure-equalizing addition funnel. The suspension of 2-lithio **43** was then added dropwise to a solution of 4-fluorobenzaldehyde (2.1 mL, 20 mmol) in 150 mL of anhydrous THF at 0 °C, which was degassed with Ar for 15 min. After the addition was complete, the mixture was warmed to ambient temperature, 300 mL of a 1 M solution of NH_4Cl was added, and the organic phase was separated. The aqueous phase was extracted with ether (3× 200 mL). The combined organic extracts were washed with water (3× 200 mL) and brine (200 mL), dried over $MgSO_4$, and concentrated to give a yellow oil. The oil was dissolved in a 1 M solution of Bu_4NF in THF (95 mL, 95 mmol) and stirred at ambient temperature for 1 h at which point 100 mL of saturated aqueous NH_4Cl was added. The resulting mixture was extracted with ether (4× 100 mL). The combined organic extracts were washed with water (3× 200 mL) and brine (200 mL), dried over $MgSO_4$, and concentrated to give the crude diol. The crude diol was purified by column chromatography on SiO_2 eluted with a mixture of hexanes and ethyl acetate to give 3.5 g (56%) of **44** as a light yellow oil. IR (film): 3406, 3063, 2874, 1700, 1604 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 6.22 (2H, s), 6.97 (2H, s), 6.78 (1H, d, $J = 3.0$ Hz), 6.85 (1H, t, $J = 4.8$ Hz), 6.98 (2H, t, $J = 8.4$ Hz), 7.22 (1H, d, $J = 4.8$ Hz), 7.44 (2H, dd, $J_1 = 8.3$, $J_2 = 5.7$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 71.92, 72.62, 115.47 (d, $J = 22$), 124.60, 126.41, 128.16 (d, $J = 8$), 128.19, 128.69, 138.80, 142.94, 148.02, 148.38, 162.51 (d, $J = 244$), 164.14; High Resolution Q-TOF MS: *m/z* 337.0693 (calcd for $C_{18}H_{15}FN_2O_2S$+Na, 337.0674).

4.2.6. 2-(1-Hydroxy-1-phenylmethyl)-5-[1-(4-trifluoromethylphenyl)-1-hydroxymethyl]-thiophene (45). Compound **45** was prepared with the same method as that used for the preparation of **44**. Yield: 57%; IR (film): 3428, 3063, 2874, 1700, 1620 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 5.82 (1 H, s), 5.89 (1H, s), 6.21 (1H, s), 6.42 (1H, s), 6.68 (1H, d, $J = 10.4$ Hz), 6.71 (1H, d, $J = 11.6$ Hz), 7.18–7.25 (1H, m), 7.30 (2H, br s), 7.35 (2H, br s), 7.60 (2H, br s), 7.66 (2H, br s); ^{13}C NMR (75 MHz, DMSO-d_6): δ 70.50, 71.13, 123.54 (123.90), 125.48 (125.52), 126.31 (126.39), 127.02 (127.08), 127.59 (127.64), 128.56, 145.02 (145.08), 148.35 (148.52), 149.67, 149.91 (150.12); High Resolution Q-TOF MS: *m/z* 387.0635 (calcd for $C_{19}H_{15}F_3N_2O_2S$+Na, 387.0643).

4.2.7. Diethyl 2,5-bis[1-(4-carboxylatomethoxyphenyl)-1-pyrrolomethyl]thiophene (23). Diol **20** (3.2 g, 5.8 mmol) was dissolved in excess pyrrole (16 mL) and the resulting solution was degassed with Ar. Boron trifluoride etherate was added (0.10 mL, 1.1 mmol) and the resulting mixture was stirred for 1 h at ambient temperature. The reaction was stopped by the addition of CH_2Cl_2 (100 mL), followed by 40% NaOH (50 mL). The organic layer was separated, washed with water (3× 150 mL) and brine (150 mL), dried over $MgSO_4$, and concentrated. The excess pyrrole was removed at reduced pressure at ambient temperature. The residual oil was purified via chromatography on SiO_2 eluted with the mixture of hexanes and ethyl acetate to give 2.7 g (63%) of **23** as a yellow oil. ^1H NMR (500 MHz, $CDCl_3$): δ 1.10 (18H, d, $J = 7.5$ Hz), 1.40–1.48 (6H, s), 5.51 (2H, s), 5.90 (2H, s), 6.14 (2H, br s), 6.58 (2H, s), 6.68 (2H, s), 6.82 (4H, d, $J = 8.5$ Hz), 7.07 (4H, d, $J = 8.5$ Hz), 7.89 (2H, br s); ^{13}C NMR (126 MHz, $CDCl_3$): δ 12.76, 18.05, 45.33, 107.45, 108.35, 117.20, 120.01, 125.17, 129.44, 133.62, 135.26, 146.46, 155.14; High Resolution ESI MS: *m/z* 761.3958 (calcd for $C_{44}H_{62}N_2O_2SSi_2$+Na, 761.3963).

4.2.8. General method for the preparation of 5,20-diaryl-10,15-bis(4-methoxyphenyl)-21,23-dithiaporphyrins (24–30, 46, 47). Compounds, **24–30**, **46**, and **47**, were prepared with similar methods described for the preparation of **24**.

4.2.9. 5,20-Bis(4-chlorophenyl)-10,15-bis(4-methoxyphenyl)-21,23-dithiaporphyrin (24). Diol **12** (3.0 g, 0.8 mmol), 2,5-bis[1-(4-chlorophenyl)-1-pyrrolomethyl]thiophene (**22**, 3.8 g, 0.8 mmol), and 2,3,5,6-tetrachloro-1,4-benzoquinone (TCBQ, 6.1 g, 25 mmol) were dissolved in 600 mL CH_2Cl_2. Boron trifluoride etherate (0.57 mL, 0.45 mmol) was added and the reaction mixture was stirred for 0.5 h in the dark. The reaction mixture was concentrated and the residue was redissolved in minimal CH_2Cl_2. The crude product was purified via chromatography on basic alumina eluted with CH_2Cl_2. Dithiaporphyrin **24** was isolated as the first red band. The crude product was washed with acetone to give 0.32 g (5%) of **24** as a purple solid. Mp: >300 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.11 (6H, s), 7.36 (4H, d, J = 8.4 Hz), 7.80 (4H, d, J = 8.0 Hz), 8.168 (4H, d, J = 8.4 Hz), 8.169 (4H, d, J = 8.0 Hz), 8.64 (2H, d, J = 4.4 Hz), 8.72 (2H, d, J = 4.4 Hz), 9.63 (2H, s), 9.73 (2H, s); ^{13}C NMR (75 MHz, 1:1 $CDCl_3$/CD_3OD): δ 55.79, 113.29, 127.93, 132.36, 133.70, 134.22, 134.63, 134.80, 135.13, 135.21, 135.32, 135.63, 135.86, 139.86, 147.59, 148.60, 156.38, 156.96, 160.04; High Resolution Q-TOF MS: *m*/*z* 777.1204 (calcd for $C_{46}H_{30}Cl_2N_2O_2S_2$+H, 777.1204).

4.2.10. 5,20-Bis(4-trifluoromethylphenyl)-10,15-bis(4-methoxyphenyl)-21,23-dithiaporphyrin (25). Yield: 3%; mp: >300 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.10 (6H, s), 7.37 (4H, d, J = 7.6 Hz), 8.09 (4H, d, J = 7.2 Hz), 8.18 (4H, d, J = 8.0 Hz), 8.36 (4H, d, J = 7.2 Hz), 8.60 (2H, d, J = 4.4 Hz), 8.74 (2H, d, J = 4.0 Hz), 9.59 (2H, s), 9.75 (2H, s); High Resolution Q-TOF MS: *m*/*z* 845.1735 (calcd for $C_{48}H_{30}F_6N_2O_2S_2$+H, 845.1731).

4.2.11. 5,20-Bis(4-dimethylaminophenyl)-10,15-bis(4-methoxyphenyl)-21,23-dithiaporphyrin (26). Yield: 6.4%; mp: >300 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.25 (12H, s), 4.10 (6H, s), 7.17 (4H, d, J = 8.8 Hz), 7.35 (4H, d, J = 8.8 Hz), 8.15 (4H, d, J = 5.2 Hz), 8.18 (2H, d, J = 5.2 Hz), 8.66 (2H, d, J = 4.4 Hz), 8.75 (2H, d, J = 4.8 Hz), 9.64 (2H, s), 9.76 (2H, s); High Resolution Q-TOF MS: *m*/*z* 795.2834 (calcd for $C_{40}H_{42}N_4O_2S_2$+H, 795.2827).

4.2.12. 5,20-Bis(4-isobutylphenyl)-10,15-bis(4-methoxyphenyl)-21,23-dithiaporphyrin (27). Yield: 30%; mp: >300 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.56 (12H, d, J = 6.8 Hz), 3.26–3.30 (2H, m), 4.10 (6H, s), 7.35 (4H, d, J = 8.4 Hz), 7.67 (4H, d, J = 7.6 Hz), 8.18 (8H, d, J = 8.0 Hz), 8.45 (2H, d, J = 4.4 Hz), 8.73 (2H, d, J = 4.4 Hz), 9.71 (2H, s), 9.72 (2H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.40, 34.28, 55.72, 113.15, 125.67, 133.19, 133.95, 134.26, 134.53, 134.67, 135.55, 138.86, 148.02, 148.73, 156.62, 156.71, 159.84. High Resolution Q-TOF MS: *m*/*z* 793.2938 (calcd for $C_{52}H_{44}N_2O_2S_2$+H, 793.2922).

4.2.13. 5,20-Di(biphenyl)-10,15-bis(4-methoxyphenyl)-21,23-dithiaporphyrin (28). Yield: 18%; mp: 175–177 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.12 (6H, s), 7.37 (4H, d, J = 7.5 Hz), 7.48–7.52 (2H, m), 7.61 (4H, t, J = 7.5 Hz), 7.93 (4H, d, J = 7.5 Hz), 8.06 (4H, d, J = 7.5 Hz), 8.20 (4H, d, J = 7.5 Hz), 8.34 (4H, d, J = 7.5 Hz), 8.73 (2H, d, J = 4.5 Hz), 8.76 (2H, d, J = 4.5 Hz), 9.73 (2H, s), 9.77 (2 H, s); High Resolution ESI MS: *m*/*z* 861.2592 (calcd for $C_{58}H_{40}N_2O_2S_2$+H, 861.2604).

4.2.14. Diethyl 5,20-bis(4-methoxyphenyl)-10,15-bis(4-carboxylatomethoxyphenyl)-21,23-dithiaporphyrin (29). Yield: 18%; mp: 117–119 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.42 (6H, t, J = 7.0 Hz), 4.10 (6H, s), 4.42 (4H, q, J = 7.0 Hz), 4.92 (4H, s), 7.36 (8H, d, J = 7.0 Hz), 8.17 (8H, d, J = 7.5 Hz), 8.67 (2H, d, J = 5.0 Hz), 8.72 (2H, d, J = 4.5 Hz), 9.68 (2H, s), 9.70 (2H, s); High Resolution ESI MS: *m*/*z* 913.2645 (calcd for $C_{54}H_{44}N_2O_8S_2$+H, 913.2612).

4.2.15. Diethyl 5,20-bis(4-triisobutylsilyoxyphenyl)-10,15-bis(4-carboxylatomethoxyphenyl)-21,23-dithiaporphyrin (30). Yield: 32%; mp: 195–198 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.29 (36H, d, J = 7.5 Hz), 1.42 (6H, t, J = 7.0 Hz), 1.45–1.51 (6H, s), 4.42 (4H, q, J = 7.0 Hz), 4.93 (4H, s), 7.32–7.39 (8H, s), 8.09 (4H, d, J = 6.5 Hz), 8.18 (4H, d, J = 7.0 Hz), 8.66–8.70 (4H, s), 9.68 (2H, s), 9.71 (2H, s); High Resolution ESI MS: *m*/*z* 1197.4987 (calcd for $C_{70}H_{80}N_2O_8S_2Si_2$+H, 1197.4967).

4.2.16. 5-Phenyl-20-(4-fluorophenyl)-10,15-bis(4-methoxyphenyl)-21,23-dithiaporphyrin (46). Yield: 5%; mp: >300 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.10 (6H, s), 7.36 (4H, d, J = 8.1 Hz), 7.45 (2H, t, J = 8.1 Hz), 7.81 (3H, br s), 8.18 (4H, d, J = 8.1 Hz), 8.16–8.30 (4H, m), 8.60–8.76 (4H, m), 9.63 (1H, d, J = 4.8 Hz), 9.69 (1H, d, J = 5.1 Hz), 9.73 (2H, br s); High Resolution Q-TOF MS: *m*/*z* 727.1874 (calcd for $C_{46}H_{31}FN_2O_2S_2$+H, 727.1889).

4.2.17. 5-Phenyl-20-(4-trifluoromethylphenyl)-10,15-bis(4-methoxyphenyl)-21,23-dithiaporphyrin (47). Yield: 7%; mp: 125–127 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 11 (6H, s), 7.37 (4H, d, J = 8.4 Hz), 7.79–7.85 (3H, m), 8.08 (2H, d, J = 8.0 Hz), 8.18 (4H, d, J = 8.0 Hz), 8.22–8.27 (2H, m), 8.37 (2H, d, J = 8.0 Hz), 8.60 (1H, d, J = 4.4 Hz), 8.68 (1H, d, J = 4.4 Hz), 8.72 (1H, d, J = 4.4 Hz), 8.74 (1H, d, J = 4.4 Hz), 9.58 (1H, d, J = 5.2 Hz), 9.68 (1H, d, J = 5.2 Hz), 9.74 (2H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.78, 111.07, 113.27, 124.57, 127.63, 128.25, 130.82, 131.53, 133.71, 133.99, 134.33, 134.62, 134.79, 134.95, 135.17, 135.61, 135.75, 135.85, 141.32, 145.20, 147.47, 147.70, 148.48, 148.67, 150.65, 155.96, 156.80, 160.01, 160.92; High Resolution Q-TOF MS: *m*/*z* 777.1868 (calcd for $C_{47}H_{31}F_3N_2O_2S_2$+H, 777.1857).

4.2.18. General method for the preparation of 5,20-diaryl-10,15-bis(4-hydroxyphenyl)-21,23-dithiaporphyrins (31–35, 48, 49). Compounds, **31**–**35**, **48**, and **49**, were prepared, as described for the preparation of **31**.

4.2.19. 5,20-Bis(4-chlorophenyl)-10,15-bis(4-hydroxyphenyl)-21,23-dithiaporphyrin (31). Dithiaporphyrin **24** (0.27 g, 0.35 mmol) was dissolved in 50 mL CH_2Cl_2 and BBr_3 (0.32 mL, 3.5 mmol) was added at 0 °C. The resulting solution was stirred for 5 h at ambient temperature. The reaction mixture was added to 150 mL EtOAc and 150 mL of saturated $NaHCO_3$. The organic

layer was separated and washed three times with 150 mL of brine, dried over $MgSO_4$, and concentrated. The crude solid was washed with 25% EtOAc/hexanes several times to give 0.23 g (88%) of **31** as a dark blue solid. Mp: >300 °C; ^{1}H NMR (400 MHz, 1:1 $CDCl_3$/CD_3OD): δ 7.18 (4H, d, J = 8.4 Hz), 7.69 (4H, d, J = 8.0 Hz), 7.98 (4H, d, J = 8.4 Hz), 8.05 (4H, d, J = 8.0 Hz), 8.52 (2H, d, J = 4.4 Hz), 8.64 (2H, d, J = 4.4 Hz), 9.53 (2H, s), 9.67 (2H, s); ^{13}C NMR (75 MHz, 1:1 $CDCl_3$/CD_3OD): δ 114.53, 127.67, 132.00, 132.34, 133.79, 134.55, 134.98, 135.08, 135.60, 135.79, 139.55, 147.16, 148.40, 156.13, 156.81, 157.32; High Resolution Q-TOF MS: m/z 749.0891 (calcd for $C_{44}H_{26}Cl_2N_2O_2S_2$+H, 749.0888).

4.2.20. 5,20-Bis(4-trifluoromethylphenyl)-10,15-bis(4-hydroxyphenyl)-21,23-dithiaporphyrin (32). Yield: 88%; mp: >300 °C; ^{1}H NMR (400 MHz, 1:1 $CDCl_3$/CD_3OD): δ 7.23–7.33 (4H, m), 8.00–8.13 (8H, m), 8.31 (4H, d, J = 7.6 Hz), 8.54 (2H, d, J = 4.4 Hz), 8.72 (2H, d, J = 4.4 Hz), 9.56 (2H, d, J = 3.2 Hz), 9.75 (2H, d, J = 2.4 Hz); High Resolution Q-TOF MS: m/z 817.1425 (calcd for $C_{46}H_{26}F_6N_2O_6S_2$+H, 817.1418).

4.2.21. 5,20-Bis(4-dimethylaminophenyl)-10,15-bis(4-hydroxyphenyl)-21,23-dithiaporphyrin (33). Yield: 83%; mp: >300 °C; ^{1}H NMR (400 MHz, 1:1 $CDCl_3$/CD_3OD): δ 3.21 (12H, s), 7.16 (4H, d, J = 7.6 Hz), 7.25 (4H, d, J = 8.0 Hz), 8.02 (4H, d, J = 5.2 Hz), 8.06 (4H, d, J = 5.2 Hz), 8.59 (2H, s), 8.62 (2H, s), 9.65 (2H, s), 9.69 (2H, s); HI ESI MS: 767.2521 (calcd for $C_{48}H_{38}N_4O_2S_2$+H, 767.2514).

4.2.22. 5,20-Bis(4-isobutylphenyl)-10,15-bis(4-hydroxyphenyl)-21,23-dithiaporphyrin (34). Yield: 95%; mp: 234–236 °C; ^{1}H NMR (500 MHz, acetone-d_6): δ 1.54 (12H, d, J = 7.0 Hz), 3.21–3.34 (2H, m), 7.40 (4H, d, J = 8.0 Hz), 7.75 (4H, d, J = 7.5 Hz), 8.15 (4H, d, J = 8.5 Hz), 8.17 (4H, d, J = 8.0 Hz), 8.66 (2H, d, J = 4.0 Hz), 8.74 (2H, d, J = 4.5 Hz), 9.73 (2H, s), 9.83 (2H, s); ^{13}C NMR (75 MHz, 1:1:1 $CDCl_3$/CD_3OD/DMSO-d_6): δ 24.33, 34.00, 115.00, 125.79, 131.70, 133.87, 134.34, 134.46, 134.61, 135.67, 138.31, 147.36, 147.86, 148.69, 156.10, 156.32, 158.10; High Resolution Q-TOF MS: m/z 765.2614 (calcd for $C_{50}H_{40}N_2O_2S_2$+H, 765.2609).

4.2.23. 5,20-Di(biphenyl)-10,15-bis(4-hydroxyphenyl)-21,23-dithiaporphyrin (35). Yield: 86%; mp: >300 °C; ^{1}H NMR (400 MHz, CD_3OD): δ 7.28 (4H, br s), 7.45 (2H, br s), 7.55 (4H, br s), 7.86 (4H, br s), 7.93–8.08 (8H, m), 8.18 (4H, br s), 8.62 (4H, br s), 9.68 (4H, br s); High Resolution ESI MS: m/z 833.2274 (calcd for $C_{56}H_{36}N_2O_2S_2$+H, 833.2291).

4.2.24. 5-Phenyl-20-(4-fluorophenyl)-10,15-bis(4-hydroxyphenyl)-21,23-dithiaporphyrin (48). Yield: 93%; mp: >300 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.29 (4H, d, J = 8.0 Hz), 7.49–7.57 (3H, m), 7.81 (2H, br s), 8.08 (4H, d, J = 8.5 Hz), 8.18–8.24 (4H, m), 8.63 (1H, d, J = 5.0 Hz), 8.65 (1H, d, J = 4.5 Hz), 7.59 (2H, t, J = 10.5 Hz), 9.65 (1H, d, J = 5.0 Hz), 9.69 (1H, d, J = 5.0 Hz), 9.78 (2H, s); High Resolution Q-TOF MS: m/z 699.1519 (calcd for $C_{44}H_{27}FN_2O_2S_2$+H, 699.1498).

4.2.25. 5-Phenyl-20-(4-trifluoromethylphenyl)-10,15-bis(4-hydroxyphenyl)-21,23-dithiaporphyrin (49). Yield: 93%; mp: >300 °C; ^{1}H NMR (400 MHz, 1:1:1 $CDCl_3$/CD_3OD/DMSO-d_6) δ 7.03 (4H, d, J = 8.4 Hz), 7.51–7.58 (3H, m), 7.78 (2H, d, J = 8.4 Hz), 7.81 (4H, d, J = 8.0 Hz), 8.16–8.22 (2H, m), 8.08 (2H, d, J = 8.0 Hz), 8.30 (1H, d, J = 4.8 Hz), 8.36 (1H, d, J = 4.4 Hz), 8.44 (1H, d, J = 4.4 Hz), 8.46 (1H, d, J = 4.8 Hz), 9.30 (1H, d, J = 5.2 Hz), 9.39 (1H, d, J = 5.2 Hz), 9.50 (2H, s); High Resolution Q-TOF MS: m/z 749.1551 (calcd for $C_{45}H_{27}F_3N_2O_2S_2$+H, 749.1544).

4.2.26. General method for the preparation of diethyl 5,20-diaryl-10,15-bis(4-carboxylatomethoxyphenyl)-21,23-dithiaporphyrins (36–40, 50, 51). Compounds, **36**–**40**, **50**, and **51**, were prepared as described for the preparation of **36**.

4.2.27. Diethyl 5,20-bis(4-chlorophenyl)-10,15-bis(4-carboxylatomethoxyphenyl)-21,23-dithiaporphyrin (36). Dithiaporphyrin **31** (0.20 g, 0.27 mmol), K_2CO_3 (1.8 g, 13 mmol), and ethyl bromoacetate (2.96 mL, 27 mmol) in 50 mL acetone were heated at reflux for 10 h. The reaction mixture was cooled to ambient temperature and the K_2CO_3 was removed by filtration. The filter cake was washed with acetone until the filtrate became colorless. The combined filtrates were concentrated. The crude product was washed with MeOH to give 0.20 g (81%) of **36** as a purple solid. Mp: 212–214 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.45 (6H, t, J = 7.6 Hz), 4.44 (4H, q, J = 6.8 Hz), 4.92 (4H, s), 7.36 (4H, d, J = 8.4 Hz), 7.80 (4H, d, J = 8.0 Hz), 8.17 (4H, d, J = 8.0 Hz), 8.17 (4H, d, J = 8.0 Hz), 8.66 (2H, d, J = 4.4 Hz), 8.72 (2H, d, J = 4.8 Hz), 9.65 (2H, s), 9.73 (2H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.43, 61.73, 65.86, 113.97, 127.88, 132.45, 134.17, 134.29, 134.66, 134.78, 134.88, 135.02, 134.27, 135.54, 135.79, 139.73, 147.62, 148.44, 156.37, 156.84, 158.28; High Resolution Q-TOF MS: m/z 921.1629 (calcd for $C_{52}H_{38}Cl_2N_2O_6S_2$+H, 921.1626).

4.2.28. Diethyl 5,20-bis(4-trifluoromethylphenyl)-10,15-bis(4-carboxylatomethoxyphenyl)-21,23-dithiaporphyrin (37). Yield: 86%; mp: 133–135 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.38 (6H, t, J = 7.0 Hz), 4.38 (4H, q, J = 7.0 Hz), 4.88 (4H, s), 7.40 (4 H, d, J = 9.0 Hz), 8.12 (4H, d, J = 7.5 Hz), 8.20 (4H, d, J = 8.0 Hz), 8.38 (4H, d, J = 8.0 Hz), 8.63 (2H, d, J = 4.5 Hz), 8.75 (2H, d, J = 4.0 Hz), 9.62 (2H, s), 9.76 (2H, s); High Resolution Q-TOF MS: m/z 989.2190 (calcd for $C_{54}H_{38}F_6N_2O_6S_2$+H, 989.2922).

4.2.29. Diethyl 5,20-bis(4-dimethylaminophenyl)-10,15-bis(4-carboxylatomethoxyphenyl)-21,23-dithiaporphyrin (38). Yield: 68%; mp: >300 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.42 (6H, t, J = 7.0 Hz), 3.25 (12H, s), 4.42 (4H, q, J = 7.5 Hz), 4.92 (4H, s), 7.18 (4H, d, J = 7.0 Hz), 7.35 (4H, d, J = 8.5 Hz), 8.16 (8H, t, J = 8.5 Hz), 8.63 (2H, d, J = 4.5 Hz), 8.74 (2H, d, J = 4.5 Hz), 9.62 (2H, s), 9.76 (2H, s); High Resolution ESI MS: m/z 939.3260 (calcd for $C_{56}H_{50}N_4O_6S_2$+H, 939.3250).

4.2.30. Diethyl 5,20-bis(4-isopropylphenyl)-10,15-bis(4-carboxylatomethoxyphenyl)-21,23-dithiaporphyrin (39). Yield: 82%; mp: 180–182 °C; ^{1}H NMR (400 MHz,

$CDCl_3$): δ 1.43 (6H, t, J = 7.2 Hz), 1.56 (12H, d, J = 6.8 Hz), 3.23–3.34 (2H, m), 4.43 (4H, q, J = 6.8 Hz), 4.93 (4H, s), 7.36 (4H, d, J = 8.4 Hz), 7.67 (4H, d, J = 8.0 Hz), 8.17 (4H, d, J = 8.0 Hz), 8.19 (4H, d, J = 8.4 Hz), 8.68 (2H, d, J = 4.4 Hz), 8.72 (2H, d, J = 4.4 Hz), 9.68 (2H, s), 9.72 (2H, s); ^{13}C NMR (75 MHz, 1:1 $CDCl_3$/DMSO-d_6): δ 14.44, 24.40, 34.29, 61.73, 65.93, 111.04, 113.91, 125.68, 133.44, 134.42, 134.54, 134.78, 135.00, 135.34, 135.52, 135.65, 138.82, 148.03, 148.12, 148.78, 156.67, 158.19, 169.16; High Resolution Q-TOF MS: m/z 937.3388 (calcd for $C_{58}H_{52}N_2O_6S_2$+H, 937.3345).

4.2.31. Diethyl 5,20-di(biphenyl)-10,15-bis(4-carboxylatomethoxyphenyl)-21,23-dithiaporphyrin (40). Yield: 87%; mp: 122–124 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.42 (6H, t, J = 7.0 Hz), 4.42 (4H, q, J = 7.0 Hz), 4.93 (4H, s), 7.38 (4H, d, J = 7.5 Hz), 7.49 (2H, t, J = 7.5 Hz), 7.61 (4H, t, J = 7.5 Hz), 7.93 (4H, d, J = 7.0 Hz), 8.06 (4H, d, J = 7.5 Hz), 8.20 (4H, d, J = 8.0 Hz), 8.33 (4H, d, J = 7.5 Hz), 8.71 (2H, d, J = 4.5 Hz), 8.76 (2H, d, J = 4.5 Hz), 9.71 (2H, s), 9.78 (2H, s); High Resolution ESI MS: m/z 1005.3010 (calcd for $C_{64}H_{48}N_2O_6S_2$+H, 1005.3027).

4.2.32. Diethyl 5-phenyl-20-(4-fluorophenyl)-10,15-bis(4-carboxylatomethoxyphenyl)-21,23-dithiaporphyrin (50). Yield: 81%; mp: 145–147 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.43 (6H, t, J = 7.2 Hz), 4.43 (4H, q, J = 6.8 Hz), 4.93 (4H, s), 7.37 (4H, d, J = 8.4 Hz), 7.52 (2H, t, J = 8.4 Hz), 7.79–7.86 (3H, m), 8.18 (4H, d, J = 8.4 Hz), 8.18–8.28 (4H, m), 8.65 (1H, d, J = 4.4 Hz), 8.67–8.72 (3H, m), 9.63 (1H, d, J = 5.2 Hz), 9.68 (1H, d, J = 5.2 Hz), 9.70 (2H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.37, 61.68, 64.46, 65.82, 110.97, 113.87, 114.59 (d, J = 22), 127.52, 128.15, 133.83, 134.24, 134.73, 135.11, 135.47, 141.25, 147.81, 148.18, 156.70, 158.17, 162.97, (d, J = 320), 169.06; High Resolution Q-TOF MS: 871.2320 (calcd for $C_{52}H_{39}FN_2O_6S_2$+H, 871.2312).

4.2.33. Diethyl 5-phenyl-20-(4-trifluoromethylphenyl)-10,15-bis(4-carboxylatomethoxyphenyl)-21,23-dithiaporphyrin (51). Yield: 87%; mp: 125–127 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.44 (6H, t, J = 6.8 Hz), 4.44 (4H, q, J = 6.8 Hz), 4.93 (4H, s), 7.38 (4H, d, J = 4.0 Hz), 7.79–7.89 (3H, m), 8.09 (2H, d, J = 8.0 Hz), 8.18 (4H, d, J = 8.0 Hz), 8.23–8.29 (2H, m), 8.37 (2H, d, J = 8.4 Hz), 8.62 (1H, d, J = 4.4 Hz), 8.68–8.76 (3H, m), 9.59 (1H, d, J = 5.2 Hz), 9.70 (1H, d, J = 4.8 Hz), 9.73 (2H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.43, 61.74, 65.88, 113.96, 124.55, 127.62, 128.27, 131.65, 134.02, 134.09, 134.31, 134.44, 134.73, 134.86, 135.08, 135.55, 135.71, 135.80, 135.91, 141.23, 145.10, 147.51, 147.76, 148.33, 148.52, 155.97, 156.82, 158.29, 169.10; High Resolution Q-TOF MS: m/z 921.2308 (calcd for $C_{53}H_{39}F_3N_2O_6S_2$+H, 921.2280).

4.2.34. Diethyl 5,20-bis(4-hydroxyphenyl)-10,15-bis(4-carboxylatomethoxyphenyl)-21,23-dithiaporphyrin (41). Yield: 84%; mp: 172–174 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.31 (6H, t, J = 6.5 Hz), 4.30 (4H, q, J = 7.0 Hz), 5.09 (4H, s), 7.28 (4H, d, J = 7.5 Hz), 7.44 (4H, d, J = 7.5 Hz), 8.06 (4H, d, J = 8.0 Hz), 8.17 (4H, d, J = 7.5 Hz), 8.60 (2H, s), 8.66 (2H, s), 9.70 (2H, s), 9.76 (2H, s), 10.08 (2H, s); High Resolution ESI MS: m/z 885.2299 (calcd for $C_{52}H_{40}N_2O_8S_2$+H, 885.2316).

4.2.35. General method for the preparation of diethyl 5,20-diaryl-10,15-bis(4-carboxylatomethoxyphenyl)-21,23-dithiaporphyrins (3–11). Compounds **3**–**11** were prepared, as described for the preparation of **4**.

4.2.36. 5,20-Bis(4-chlorophenyl)-10,15-bis(4-carboxylatomethoxyphenyl)-21,23-dithiaporphyrin (4). Core-modified porphyrin **36** (0.13 g, 0.14 mmol) was dissolved in 20 mL THF and 10 mL of 1 M aqueous NaOH was added. The resulting solution was stirred at ambient temperature for 15 h. The solution was acidified by the addition of 4.3 mL acetic acid. The reaction mixture was diluted with 100 mL H_2O and the products were extracted with EtOAc (3× 100 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated. The crude product was washed with several portions of hexanes/MeOH to give 0.11 g (90%) of **4** as a purple solid. Mp: 210–212 °C: ^{1}H NMR (400 MHz, 1:1 $CDCl_3$/CD_3OD): δ 4.93 (4H, s), 7.40 (4H, d, J = 8.4 Hz), 7.80 (4H, d, J = 7.6 Hz), 8.12–8.21 (8H, m), 8.65 (2H, d, J = 4.0 Hz), 8.71 (2H, d, J = 4.4 Hz), 9.66 (2H, s), 9.75 (2H, s); ^{13}C NMR (75 MHz, DMSO-d_6): 65.65, 114.17, 128.09, 132.74, 134.46, 134.54, 134.62, 135.04, 135.20, 135.48, 135.60, 135.78, 136.14, 139.80, 147.75, 148.59, 156.60, 157.10, 158.57, 171.57; High Resolution Q-TOF MS: m/z 865.1021 (calcd for $C_{48}H_{30}Cl_2N_2O_6S_2$+H, 865.1000); Anal. Calcd for $C_{48}H_{30}Cl_2N_2O_6S_2$: C, 66.59; H, 3.49; N, 3.24. Found: C, 66.99; H, 3.82; N, 2.94.

4.2.37. 5,20-Bis(4-trifluoromethylphenyl)-10,15-bis(4-carboxylatomethoxyphenyl)-21,23-dithiaporphyrin (5). Yield: 92%; mp: 220–222 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.90 (4H, s), 7.38 (4H, d, J = 8.4 Hz), 8.05 (8H, t, J = 6.3 Hz), 8.36 (4H, d, J = 7.6 Hz), 8.58 (2H, d, J = 4.4 Hz), 8.69 (2H, d, J = 4.4 Hz), 9.62 (2H, s), 9.76 (2 H, s); High Resolution Q-TOF MS: m/z 933.1529 (calcd for $C_{50}H_{30}F_6N_2O_6S_2$+H, 933.1528); Anal. Calcd for $C_{50}H_{30}F_6N_2O_6S_2$: C, 64.37; H, 3.24; N, 3.00. Found: C, 64.20; H, 3.02; N, 2.96.

4.2.38. 5,20-Bis(4-methoxyphenyl)-10,15-bis(4-carboxylatomethoxyphenyl)-21,23-dithiaporphyrin (7). Yield: 80%; mp: >300 °C; ^{1}H NMR (400 MHz, 1:1 $CDCl_3$/CD_3OD): δ 4.06 (6H, s), 4.89 (4H, s), 7.33 (4H, d, J = 8.4 Hz), 7.37 (4H, d, J = 8.4 Hz), 8.09 (4H, d, J = 6.8 Hz), 8.11 (4H, d, J = 6.4 Hz), 8.62 (4H, s), 9.67 (4H, s); High Resolution ESI MS: m/z 857.1994 (calcd for $C_{50}H_{36}N_2O_8S_2$+H, 857.1986); Anal. Calcd for $C_{50}H_{36}N_2O_8S_2$: C, 70.08; H, 4.23; N, 3.27. Found: C, 70.23; H, 4.00; N, 3.24.

4.2.39. 5,20-Bis(4-dimethylaminophenyl)-10,15-bis(4-carboxylatomethoxyphenyl)-21,23-dithiaporphyrin (8). Yield: 86%; mp: >300 °C; ^{1}H NMR (400 MHz, 1:1 $CDCl_3$/CD_3OD): δ 3.28 (12H, s), 4.91 (4H, s), 7.21 (4H, d, J = 8.4 Hz), 7.41 (4H, d, J = 6.8 Hz), 8.10 (8H, t, J = 7.6 Hz), 8.52 (2H, d, J = 4.0 Hz), 8.62 (2H, d, J = 4.0 Hz), 9.57 (2H, s), 9.65 (2H, s); ^{13}C NMR (75 MHz, 1:1 $CDCl_3$/CD_3OD): δ 29.02, 64.87, 110.95,

113.31, 128.40, 132.21, 133.33, 133.77, 134.17, 134.78, 135.05, 135.32, 146.75, 147.65, 155.56, 155.86, 170.26; High Resolution ESI MS: *m*/*z* 883.2625 (calcd for $C_{52}H_{42}N_4O_6S_2$+H, 883.2624); Anal. Calcd for $C_{52}H_{42}N_4O_6S_2$: C, 70.73; H, 4.79; N, 6.34. Found: C, 70.62; H, 4.70; N, 6.28.

4.2.40. 5,20-Bis(4-isopropylphenyl)-10,15-bis(4-carboxylatomethoxyphenyl)-21,23-dithiaporphyrin (10). Yield: 93%; mp: 220–222 °C; ^{1}H NMR (500 MHz, 1:1 $CDCl_3$/DMSO-d_6): δ 1.49 (12H, d, J = 7.0 Hz), 2.47–2.53 (2H, m), 4.87 (4H, s), 7.36 (4H, d, J = 8.5 Hz), 7.65 (4H, d, J = 7.5 Hz), 8.10 (4H, d, J = 8.0 Hz), 8.11 (4H, d, J = 8.5 Hz), 8.12–8.21 (8H, m), 8.62 (2H, d, J = 4.5 Hz), 8.64 (2H, d, J = 4.5 Hz), 9.68 (2H, s), 9.68 (2H, s); ^{13}C NMR (75 MHz, 1:1 $CDCl_3$/DMSO-d_6): δ 24.55, 34.20, 65.59, 114.27, 126.05, 133.90, 134.06, 134.44, 134.56, 134.78, 135.00, 135.63, 135.85, 135.98, 138.42, 147.76, 147.84, 148.94, 156.40, 156.46, 158.58, 170.79; High Resolution Q-TOF MS: *m*/*z* 881.2663 (calcd for $C_{54}H_{44}N_2O_6S_2$+H, 881.2719); Anal. Calcd for $C_{54}H_{44}N_2O_6S_2$: C, 73.61; H, 5.03; N, 3.18. Found: C, 73.34; H, 5.15; N, 3.08.

4.2.41. 5,20-Di(biphenyl)-10,15-bis(4-carboxylatomethoxyphenyl)-21,23-dithiaporphyrin (11). Yield: 85%; mp: >300 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 4.97 (4H, s), 7.42 (4H, d, J = 8.0 Hz), 7.49 (2H, t, J = 7.0 Hz), 7.59 (4H, t, J = 7.0 Hz), 7.94 (4H, d, J = 7.0 Hz), 8.09 (4H, d, J = 7.5 Hz), 8.17 (4H, d, J = 8.0 Hz), 8.26 (4H, d, J = 7.5 Hz), 8.65 (4H, s), 9.76 (4H, d, J = 4.5 Hz), 13.22 (2H, s); High Resolution Q-TOF MS: *m*/*z* 949.2401 (calcd for $C_{60}H_{40}N_2O_6S_2$+H, 949.2397); Anal. Calcd for $C_{60}H_{40}N_2O_6S_2$: C, 75.93; H, 4.25; N, 2.95. Found: C, 76.28; H, 4.24; N, 2.86.

4.2.42. 5,20-Bis(4-hydroxyphenyl)-10,15-bis(4-carboxylatomethoxyphenyl)-21,23-dithiaporphyrin (9). Yield: 80%; mp: >300 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 4.98 (4H, s), 7.28 (4H, d, J = 8.0 Hz), 7.42 (4H, d, J = 8.0 Hz), 8.06 (4H, d, J = 8.0 Hz), 8.17 (4H, d, J = 7.5 Hz), 8.60 (2H, d, J = 4.0 Hz), 8.66 (2H, d, J = 4.5 Hz), 9.71 (2H, s), 9.75 (2H, s), 10.07 (2H, s), 13.20 (2H, s); High Resolution Q-TOF MS: *m*/*z* 829.1673 (calcd for $C_{48}H_{32}N_2O_8S_2$+H, 829.1678); Anal. Calcd for $C_{48}H_{32}N_2O_8S_2$: C, 69.55; H, 3.89; N, 3.38. Found: C, 69.23; H, 3.83; N, 3.33.

4.2.43. 5-Phenyl-20-(4-fluorophenyl)-10,15-bis(4-carboxylatomethoxyphenyl)-21,23-dithiaporphyrin (3). Yield: 88%; mp: 218–220 °C; ^{1}H NMR (400 MHz, 1:1 $CDCl_3$/CD_3OD): δ 4.85 (4H, s), 7.33 (4H, d, J = 6.4 Hz), 7.43–7.45 (2H, m), 7.73–7.79 (3H, m), 8.11 (4H, d, J = 6.0 Hz), 8.13–8.20 (4H, m), 8.60–8.67 (3H, m), 9.57–9.61 (1H, m), 9.62–9.66 (1H, m), 9.66–9.70 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ 65.27, 113.73, 114.42 (d, J = 22), 127.38, 128.06, 132.47, 133.78, 133.83, 134.04, 134.35, 134.48, 134.57, 135.33, 135.42, 135.50, 136.99, 140.95, 147.58, 147.99, 156.31, 156.44, 156.57, 158.08, 163.02 (d, J = 246), 171.11; High Resolution Q-TOF MS: *m*/*z* 815.1666 (calcd for $C_{48}H_{31}F_1N_2O_6S_2$+H, 815.1686); Anal. Calcd for $C_{48}H_{31}F_1N_2O_6S_2$: C, 70.75; H, 3.83; N, 3.44. Found: C, 71.13; H, 3.92; N, 3.46.

4.2.44. 5-Phenyl-20-(4-trifluoromethylphenyl)-10,15-bis(4-carboxylatomethoxyphenyl)-21,23-dithiaporphyrin (6). Yield: 90%; mp: 208–210 °C; ^{1}H NMR (400 MHz, 1:1 $CDCl_3$/CD_3OD): δ 4.87 (4H, s), 7.34 (4H, d, J = 8.4 Hz), 7.74–7.80 (3H, m), 8.02 (2H, d, J = 8.0 Hz), 8.12 (4H, d, J = 8.4 Hz), 8.15–8.21 (2H, m), 8.30 (2H, d, J = 7.6 Hz), 8.55 (1H, d, J = 4.4 Hz), 8.60–8.69 (3H, m), 9.54 (1H, d, J = 5.2 Hz), 9.65 (1H, d, J = 4.8 Hz), 9.68 (2H, s); High Resolution Q-TOF MS: *m*/*z* 887.1414 (calcd for $C_{49}H_{31}F_3N_2O_6S_2$+H, 887.1473); Anal. Calcd for $C_{49}H_{31}F_3N_2O_6S_2$: C, 68.04; H, 3.61; N, 3.24. Found: C, 67.79; H, 3.37; N, 3.26.

4.3. Photophysical properties

4.3.1. Determination of quantum yields for the generation of singlet oxygen. The quantum yields for singlet oxygen generation [$\phi(^1O_2)$] of 21,23-dithiaproprphyrins, **2**–**11**, were measured by direct methods in MeOH in a manner identical to the determination of $\phi(^1O_2)$ for **1**.[13,19] A SPEX 270M spectrometer (Jobin Yvon) equipped with InGaAs photodetector (Electrooptical Systems Inc., U.S.A.) was used for recording singlet oxygen emission spectra. A diode-pumped solid-state laser (Millenia X, Spectra-Physics) at 532 nm was the excitation source. The sample solution, in a quartz cuvette, was placed directly in front of the entrance slit of the spectrometer, and the emission signal was collected at 90° relative to the exciting laser beam. An additional long-pass filter (850LP) was used to attenuate the excitation laser and the fluorescence from the photosensitizer.

4.3.2. Determination of quantum yields for fluorescence. The quantum yields for fluorescence (ϕ_F) of the core-modified porphyrins were measured in MeOH, as described previously,[20] and were compared to the standard Rhodamine 6G (ϕ_F = 1.0). Steady-state fluorescence spectra of the porphyrins were measured with excitation at 532 nm using Fluorolog-3 spectrofluorometer (Jobin Yvon).

4.3.3. Determination of *n*-octanol/water partition coefficients at pH 7.4. The *n*-octanol/water partition coefficients were determined at pH 7.4 using the absorbance of the core-modified porphyrins. A 'shake-flask' direct measurement[17] with 3–5 min mixing, followed by a 4 h settling period, was used. Equilibration and measurements were made at 23 °C using a Perkin-Elmer Lambda 12 spectrophotometer. Values are reported as log $D_{7.4}$.

4.4. Biology

4.4.1. Cells and culture conditions. Cells cultured from the rodent mammary adenocarcinoma (R3230AC) were used for these studies. The R3230AC tumors were maintained by transplantation in the abdominal region of 100–120 g Fischer female rats, using the sterile trochar technique described earlier by Hilf et al.[21] R3230AC cells were cultured from tumor homogenates using the method described earlier.[22] All cell lines were maintained in passage culture on 35 mm diameter polystyrene dishes (Becton Dickinson, Franklin Lakes, NJ) in

3.0 mL of minimum essential medium (α-MEM) supplemented with 10% FBS, 50 units/mL penicillin G, 50 μg/mL streptomycin, and 1.0 μg/mL Fungizone (complete medium). Only cells from passages 1 to 10 were used for experiments and cells from passages 1 to 4, stored at −86 °C, were used to initiate cultures. Cultures were maintained at 37 °C in a 5% CO_2 humidified atmosphere (Forma Scientific, Marietta, OH). Passage was accomplished by removing the culture medium, adding a 1.0 mL solution containing 0.25% trypsin, and incubating at 37 °C for 2–5 min to remove the cells from the surface, followed by seeding new culture dishes with an appropriate number of cells in 3.0 mL α-MEM. Cell counts were performed using a particle counter (model ZM, Coulter Electronics, Hialeah, FL).

4.4.2. Incubation of cell cultures with dithiaporphyrins. For experiments designed to determine the amount of intracellular porphyrin after incubation with core-modified porphyrins, R3230AC cells were seeded on 96-well plates as above. Compounds **1**–**11** were added at appropriate concentrations in complete medium 24 h after cell seeding. Cells were incubated at 37 °C in the dark for various periods, the medium was removed, monolayers were washed once with 0.9% NaCl, and 200 μL of a 25% solution of Scintigest (100% DMSO was used for compound **9**) was added to solubilize the cells. The intracellular porphyrin content was determined using a fluorescence multi-well plate reader (Molecular Devices, Sunnyvale, CA) set at appropriate excitation and emission wavelengths. Intracellular dye concentration was determined by comparing fluorescence values obtained from solubilized cells with dye standards dissolved in 25% Scintigest (100% DMSO was used for compound **9**). Data are expressed as femtomole porphyrin/cell.

For experiments designed to determine cell viability in the presence of individual core-modified porphyrins **1**–**11** in the dark or after light exposure, R3230AC cells were seeded on 96-well plates at 1–1.5 × 10^4 cells/well in complete medium. Cultures were then incubated for 24 h after which appropriate concentrations of **1–10** were added directly to the wells in complete medium.

4.4.3. Irradiation of cultured cells. Following incubation of R3230AC cells with porphyrins, the medium was removed, cells were washed once with 0.2 mL of 0.9% NaCl and 0.2 mL of medium minus FBS, and phenol red (clear medium) was added. Plates, with lids removed, were positioned on an orbital shaker (LabLine, Melrose Park, IL) and exposed for various times to broadband visible light (350–750 nm) delivered at 1.4 mW cm^{-2} from a filtered 750 W halogen source defocused to encompass the whole 96-well plate. The culture plates were gently orbited on the shaker to ensure uniform illumination of all wells on the plate. The clear medium was then removed, 0.2 mL of fresh complete medium was added, and cultures were incubated at 37 °C for 24 h in the dark. Cell monolayers were also maintained in the dark undergoing the same medium changes and addition of dyes as those that were irradiated. Cell counts, as above, were performed on irradiated cells, cells maintained in the dark or cells exposed to neither porphyrins nor light (control cells). Cell viability, obtained for experimental samples, is expressed as the percent of control cell counts.

4.4.4. Statistical analyses. All statistical analyses were performed using Student's *t*-test for pairwise comparisons. A P value of <0.05 was considered significant.

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