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An Approach to Pyrazoline-Fused Chlorins by Dipolar [3 + 2]-Cycloaddition of Iminonitriles to *meso*-Tetrakis(pentafluorophenyl)porphyrin: Synthesis of New PDT Photosensitizers

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meso-Tetrakis(pentafluorophenyl)porphyrin reacts at higher temperature with unstable iminonitriles (R–C≡N^+–N^-–Ar), affording pyrazoline-fused chlorins, according to dipolar [3 + 2]-cycloaddition pathway. The respective iminonitriles were in situ generated from the corresponding functionalized α-halogenohydrazine derivatives by 1,3-elimination of HX in the presence of base (NEt_3, DABCO). This method allows synthesis of very attractive moieties which may be of potential use as sensitizers in photodynamic therapy (PDT).

[3 + 2]-Cycloaddition is a useful tool in the modification of porphyrin skeleton and it has been well documented in the recent literature in research articles, as well as in reviews.[1–27] Reactions of 1,3-dipoles such as azomethine ylides,[3–14] diazoalkanes,[15–17] nitrones,[18–20] nitrile *N*-oxides,[21–26] or carbonyl ylides[27] with porphyrin derivatives gave the expected [3 + 2]-cycloadducts. These products are very attractive chlorins and bacteriochlorins which are sought as photosensitizers in photodynamic cancer therapy (PDT).[28–30]

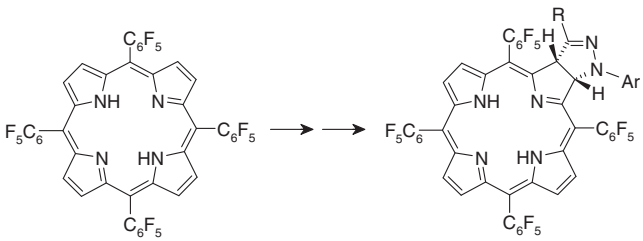
PDT is currently evaluated in multiple clinical trials with promising results.[31–34] It is a simple and relatively new technique based on the administration of tumor-localizing photosensitizers. They are subsequently activated by visible light to destroy cancer cells, however their mode of action is still not clear.

The clinical use of PDT requires the presence of a photosensitizing agent, oxygen, and light of a specific wavelength, which matches the absorption characteristic of the photosensitizer. This is a first step in the process leading to the formation of toxic, short-lived species of oxygen (singlet $^1O_2$), which is thought to mediate cellular death.[35]

Iminonitriles could be also used as substrates in [3 + 2]-cycloaddition to porphyrins, thus affording very attractive pyrazoline-fused chlorins. In the recent past, Cavaleiro and co-workers have published a paper[36] concerning synthesis of the above compounds, however the yields of the respective products were very low. At the same time we were in the midst of our investigations focused on the preparation of such chlorins (Scheme 1). The results of these studies are presented in this paper.

Results and Discussion

Synthesis of Chlorins. Many chlorins and bacteriochlorins that may be of potential use as sensitizers in PDT were synthesized by [3 + 2]-cycloaddition. As it was mentioned above little use has been made of iminonitriles, which could also serve as 1,3-dipoles in this methodology. They are usually generated in situ from α-halogenohydrazine derivatives **4** by 1,3-elimination of HX.[37] The desired precursors **4** were obtained according to Scheme 2.



Scheme 1.

Iminonitriles **5** are very unstable and they readily enter into dimerization.[37–39] Thus, they were generated in situ in the presence of dipolarophile (porphyrin, in this case). As a porphyrin partner for these reactions the highly active *meso*-tetrakis(pentafluorophenyl)porphyrin (**6**) was selected, because the bulk of porphyrins (bearing vinyl-like double bonds) are dipolarophiles of moderate reactivity.

In the first experiment porphyrin **6** was preheated in boiling toluene with 2-(chloro(phenyl)methylene)-1-phenylhydrazine (**4a**) in the presence of NEt_3 (Scheme 3). To supplement the loss of the formed in situ iminonitrile new portions of precursor **4a** and NEt_3 were added every 9 h (the mixture was heated for about 45 h). The desired chlorin **7a** was formed in 29% yield (yield for converted **6**: 41%; 30% of the starting porphyrin was recovered). Additionally, we isolated some amounts of by-product **8a** (12%). Its molecular mass $M_r = 1168$ determined by MS (FD) is identical to M_r of chlorin **7a**. The structure of this compound was proposed on the basis of ^{1}H NMR spectrum. At $\delta = 8.96$ we found the diagnostic singlet originating from β-proton of monosubstituted pyrrole ring. Another singlet ($\delta = 7.55$) is probably a signal of NH-proton. This compound

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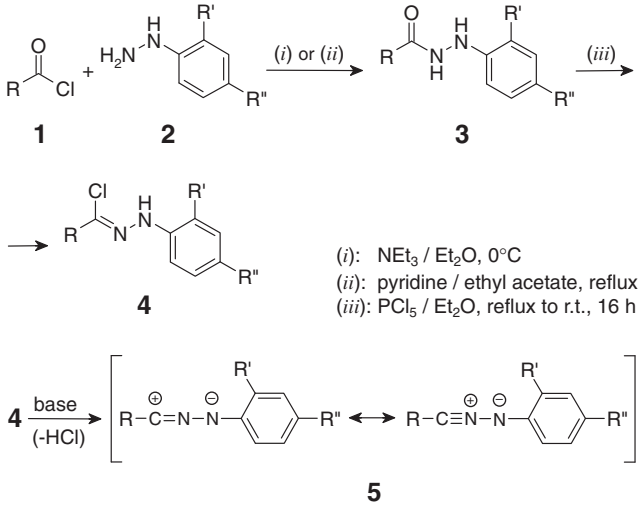


a: R = C_6H_5, R',R" = H; **b**: R = *p*-$CH_3C_6H_4$, R',R" = H;
c: R = *p*-$CH_3OC_6H_4$, R',R" = H; **d**: R = *p*-$CH_3C_6H_4$, R' = C_2H_5, R" = H;
e: R = *p*-$CH_3OC_6H_4$, R' = C_2H_5, R" = H; **f**: R = C_6H_5, R' = H, R" = NO_2;
g: R = CH_3, R' = NO_2, R" = NO_2; **h**: R = C_6H_5, R' = NO_2, R" = NO_2

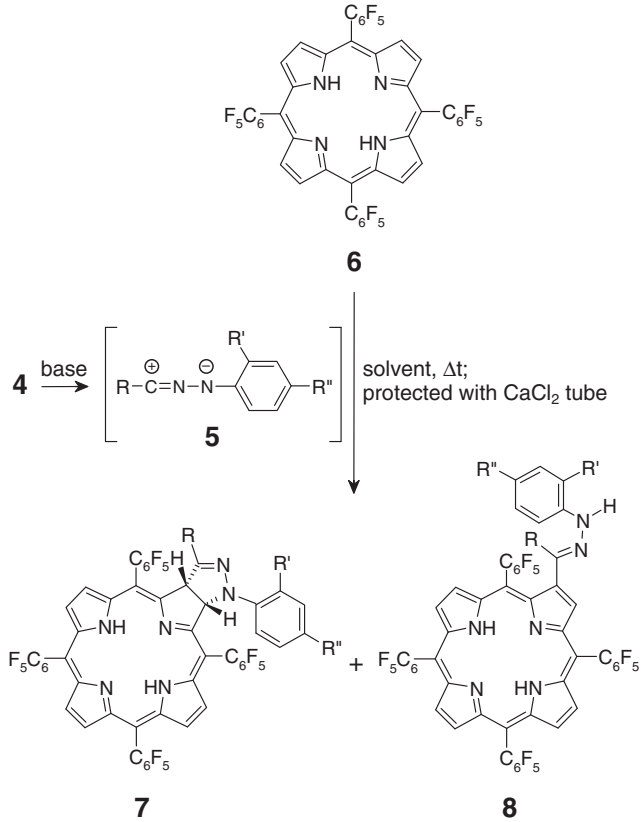
Scheme 2.

may be an effect of ring-opening reaction of chlorin **7a** or could be a product of electrophilic substitution at the β-position in porphyrin **6** with iminonitrile. One of the mesomeric structures of the latter possesses positive charge localized at the carbon atom (Schemes 1 and 2). Its participation should be considerable thus allowing electrophilic attack.

By this method we synthesized several pyrazoline-fused chlorins **7a**–**7e**. Most of the reactions were carried out in boiling toluene for 20 h. Manipulation in conditions (reaction time, solvent) gave, in some cases, better results. For example, the reaction carried out in boiling cyclooctane (NEt_3, precursor **4a**) allowed us to effectively shorten the reaction time, and the yield was even higher (29%, Entry 3). When NEt_3 was exchanged for DABCO, the yield of **7a** was similar (ca. 25%, Entry 4) as compared to the NEt_3/toluene system. But in the case of chlorin **7b** the yield was higher, 32% (60% for converted substrate). However, the more important herein was shortening of the reaction time (from 20/45 to 6 h).

In the case of *ortho*-substituted *N*-aryl rings (R′ = Et), the yield dramatically decreased, probably due to steric hindrance caused by this group. In consequence, the product of electrophilic substitution prevailed, and it was formed in good yield (**8d**, 43%; **8e**, 32%).

On the other hand, the reaction is very sensitive to electronic effects. Nitro-substitution in *N*-aryl ring (*ortho*- or *para*-position), suppresses effectively this process. The NO_2 group as a very strong electron-withdrawing substituent, considerably decreasing the negative charge at nitrogen atom (see resonance structure in Figure 1), makes the system unreactive. Thus, none of the product was formed. It is worth mentioning that the positive charge on carbon atom could be decreased by the resonance effect of OCH_3 group occupying the *para*-position in R-aryl substituents. However, we practically did not observe this effect (compare Entries 2 and 7).



a: R = C_6H_5, R',R" = H
b: R = *p*-$CH_3C_6H_4$, R',R" = H
c: R = *p*-$CH_3OC_6H_4$, R',R" = H
d: R = *p*-$CH_3C_6H_4$, R' = C_2H_5, R" = H
e: R = *p*-$CH_3OC_6H_4$, R' = C_2H_5, R" = H
f: R = C_6H_5, R' = H, R" = NO_2
g: R = CH_3, R' = NO_2, R" = NO_2
h: R = C_6H_5, R' = NO_2, R" = NO_2

Scheme 3.

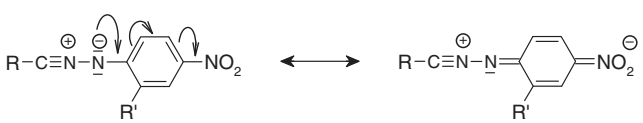
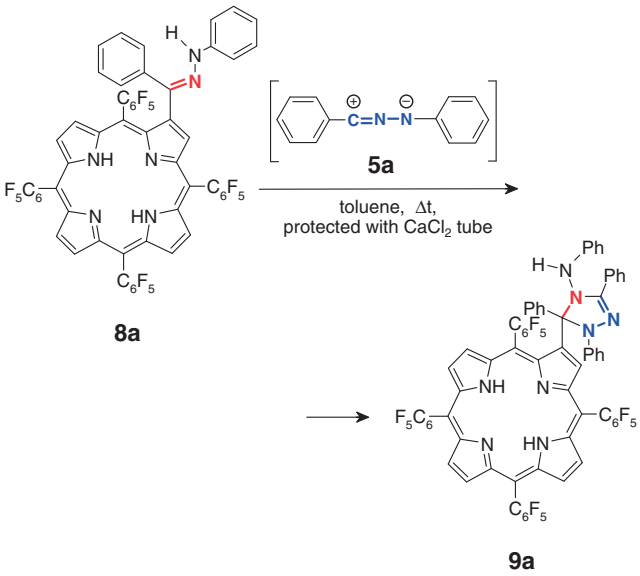


Figure 1.

In some reactions, e.g., **6** with **4a**, traces of product that was formed due to double (cyclo)addition of iminonitrile **5a** to porphyrin were observed (by MS spectrometry; $m/z = 1363$, $[M + H]^+$). It must be a product in which the additional moiety is incorporated outside the porphyrin ring. We deduced this from the ^{1}H NMR chemical shift of NH protons in the core ring ($\delta = -3.57$). These data are characteristic for unchanged 22π-electron porphyrin system. Thus, we proposed for this product structure of dihydro-1,2,4-triazole derivative **9a** as an result of [3 + 2]-cycloaddition reaction to imine bond of compound **8a** (Scheme 4).

Spectroscopic Confirmation of the Structures. All the structures of chlorins **7a**–**7e** were easily elucidated on the basis of ^{1}H NMR, UV–vis, and MS spectra. For example in compound **7a** signals of H^β protons of pyrrole rings neighboring



Scheme 4.

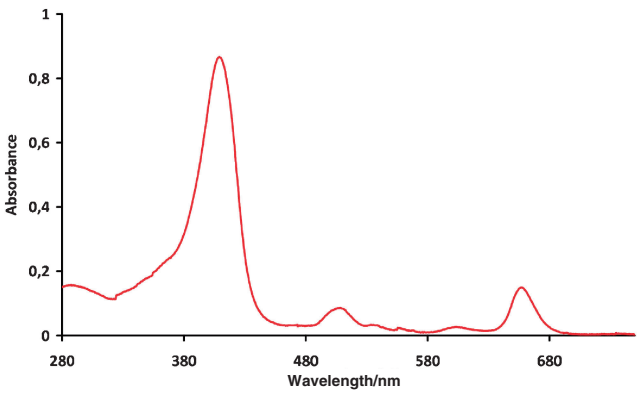


Figure 2. UV–vis spectrum of chlorin **7a**.

the *chlorin ring* were found as four doublets [$\delta = 8.68$, 8.31 ($J = 5.0$ Hz); and $\delta = 8.64$, 8.24 ($J = 5.0$ Hz)]. The two remaining β-protons from the five-membered ring opposite to chlorin junction appeared as an AB system ($\delta = 8.49$ and 8.48, $J = 5.0$ Hz). Finally, the diagnostic chlorin protons were observed as two doublets ($\delta = 7.51$ and 6.60, $J = 8.5$ Hz). Two-dimensional COSY spectrum also confirms the structure. The above NMR pattern is typical for all the synthesized pyrazoline-fused chlorins.

In the UV–vis spectrum the last Q-band reveals characteristic absorption enhancement as it is expected for chlorins (for **7a**: $\lambda_{max} = 657$ nm, $\log \varepsilon = 4.41$; Figure 2). Such properties are sought for PDT therapy.

Also, to confirm structures **8a**–**8e**, additional ^{1}H NMR spectra were recorded (for selected product **8b**, Figure 3). Addition of D_2O to NMR sample of **8b** during NMR measurement allowed us to observe fast hydrogen–deuterium exchange (for signal $\delta = 7.55$). This is expected for NH proton in the above compound **8b**, while rather not for vinylic =CH proton in another possible isomer **10b**, which could be a product of ring-opening reaction. Thus, the latter structure was definitively rejected. In this NMR experiment the NH protons

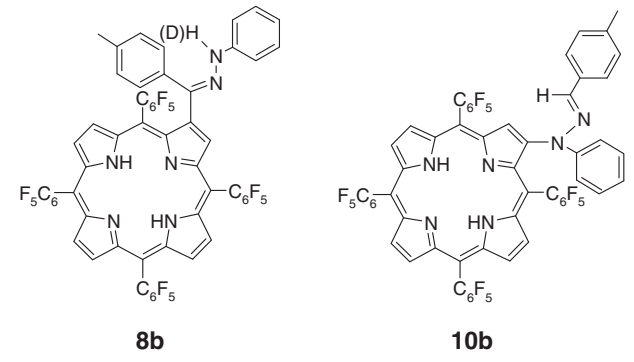


Figure 3.

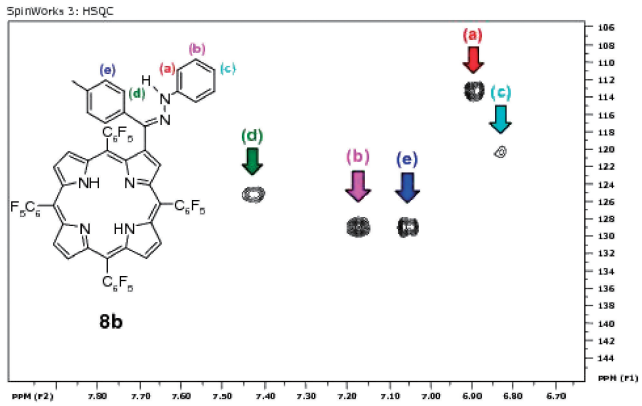


Figure 4. HSQC spectrum of compound **8b**.

inside the core ring ($\delta = -2.76$) also underwent the hydrogen–deuterium exchange.

Additionally, we recorded for this product a two-dimensional HSQC spectrum from which one-bond correlations ^{1}H–^{13}C are observed. For compound **10b** we could expect five *aromatic correlations* (Ph and Tol rings; in the region $\delta =$ 6.0–8.0) and one additional at $\delta = 7.55$ (in this case, postulated =CH). While in the spectrum recorded we found only five correlations ($\delta = 7.43/125.2$ (Tol); 7.18/128.9 (Ph); 7.06/128.9 (Tol); 6.89/113.2 (Ph); 6.83/120.3 (Ph). The proton at $\delta = 7.55$ does not correlate with any carbon atom. Thus, it must be NH proton, as we anticipated earlier, and the structure of compound is **8b**. The spectrum is shown in Figure 4.

Conclusion

We presented herein an approach to fused pyrazoline-type chlorins by dipolar [3 + 2]-cycloaddition of unstable iminonitriles to *meso*-tetrakis(pentafluorophenyl)porphyrin. Synthesis this type of compounds is of significant importance because the products obtained are potentially attractive and versatile intermediates for the further derivatization of *meso*-arylchlorins designed as second generation photosensitizers[28] in PDT. They exhibit properties similar to isoxazoline-fused chlorins,[21–26] however their last Q-bands (in UV–vis spectrum) reveal much stronger absorption of the light ($\lambda_{max} \approx 660$ nm; Figure 2) as compared to the latters. Additionally, the fused pyrazoline ring conceivably may be easily cleaved[40] to polar functionalities.

Such chlorins are sought and could be practically applied as photosensitizers in antitumor PDT because in their structures all the desired properties are deposited: they absorb low-energy

UV–vis light, and subsequently may be easily converted to soluble in physiological milieu moieties.

Experimental

General. NMR spectra were recorded with a Varian MR-400 spectrometer operating at 400 MHz for ^{1}H and 100 MHz for ^{13}C. Coupling constants J are expressed in hertz (Hz). Mass spectra were measured with a MARINER (ESI-TOF) PerSeptive Biosystems spectrometer (ESI method) and GCT Premier (FD-TOF) Waters spectrometer (FD method); m/z intensity values for peaks are given as % of relative intensity. UV–vis spectra were measured with a Beckman DU-68 spectrometer. TLC analysis was performed on aluminium foil plates precoated with silica gel (60F 254, Merck); the products have lower R_f values as compared to the starting porphyrin **6** (TLC: $CHCl_3$). The products synthesized were isolated by column chromatography (silica gel, 230–400 mesh; Merck AG). Analytically pure samples were obtained via repeated chromatography on preparative TLC plates.

Molecular formulas of the compounds were confirmed by elemental analysis, HR-MS (ESI and FD) and by comparing the isotope molecular patterns (theoretical and experimental). Melting points are uncorrected.

All the phenylhydrazine derivatives and carboxylic acid chlorides used were commercial products.

Synthesis of *N*′-Phenylbenzhydrazide Derivatives. Hydrazides **3a**–**3c** and **3f**–**3h** were synthesized according to procedures described in the previous papers.[41,42] Their ^{1}H NMR spectra and melting points were in agreement with those reported earlier in the literature: *N*′-phenylbenzhydrazide (**3a**);[42] *N*′-phenyl-4-methylbenzhydrazide (**3b**);[43,44] *N*′-phenyl-4-methoxybenzhydrazide (**3c**);[43,44] *N*′-(4-nitrophenyl)benzhydrazide (**3f**);[41,45] *N*′-(2,4-dinitrophenyl)acetohydrazide (**3g**);[46,47] *N*′-(2,4-dinitrophenyl)benzhydrazide (**3h**).[48,49] In a case of compound **3b** the additional data are given here for more detailed and accurate characterization of the product.

***N*′-Phenyl-4-methylbenzhydrazide (3b):** Known compound; mp 168–169 °C (MeOH), lit.[44] 167–168 °C. ^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.7 (C=O), 148.1, 142.7, 129.4, 129.3, 129.1, 127.1, 121.3, 113.8, 21.5 (CH_3).

***N*′-(2-Ethylphenyl)-4-methylbenzhydrazide (3d) and *N*′-(2-Ethylphenyl)-4-methoxybenzhydrazide (3e).** To a stirred suspension of 2-ethylphenylhydrazine hydrochloride (**2d** × HCl; 3.80 g, 22.0 mmol) in diethyl ether (50 mL), NEt_3 (7.7 mL, 55.2 mmol) was added dropwise. The reaction mixture was stirred at 0 °C over 2 h, then the solution of carboxylic acid chloride (**1b** or **1c**, 20.0 mmol) in diethyl ether (10 mL) was added dropwise. After 30 min of stirring the precipitate was filtered on a Büchner funnel, washed with cold water, and recrystallized from methanol to give the desired product: *N*′-(2-ethylphenyl)-4-methylbenzhydrazide (**3d**), 3.51 g (69%) or *N*′-(2-ethylphenyl)-4-methoxybenzhydrazide (**3e**), 3.68 g (68%).

***N*′-(2-Ethylphenyl)-4-methylbenzhydrazide (3d):** Mp 169–170 °C (MeOH). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.32 (s, 1H, NH), 7.71 (d, $J = 7.8$ Hz, 2H, H-Tol), 7.20 (d, $J = 7.8$ Hz, 2H, H-Tol), 7.15–7.05 (m, 2H, H-Ar(Et)), 6.94 (apparent d, $J = 8.0$ Hz, 1H, H-Ar(Et)), 6.89 (apparent t, $J = 7.4$ Hz, 1H, H-Ar(Et)), 6.44–6.35 (m, 1H, NH), 2.64 (q, $J = 7.5$ Hz, 2H, CH_2CH_3), 2.40 (s, 3H, CH_3-Tol), 1.29 (t, $J = 7.5$ Hz, 3H, CH_2CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.6 (C=O), 145.3, 142.6, 129.4, 129.3, 129.2, 128.3, 127.1, 126.7, 121.2, 112.4, 23.5, 21.4, 13.2. Elemental Anal. Found: C, 73.09; H, 7.23; N, 10.56%. Calcd for $C_{16}H_{18}N_2O_1 \cdot 1/2H_2O$: C, 72.98; H, 7.27; N, 10.64%.

***N*′-(2-Ethylphenyl)-4-methoxybenzhydrazide (3e):** Mp 155–156 °C (MeOH). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.11 (s, 1H, NH), 7.79 (d, $J = 8.4$ Hz, 2H, H-ArOMe), 7.16–7.06 (m, 2H, H-Ar(Et)), 6.95 (d, $J = 7.9$ Hz, 1H, H-Ar(Et)), 6.93–6.85 (m, 3H, 2H of H-ArOMe and 1H of H-Ar(Et)), 6.39 (s, 1H, NH), 3.85 (s, 3H, OCH_3), 2.65 (q, $J = 7.3$ Hz, 2H, CH_2CH_3), 1.30 (t, $J = 7.3$ Hz, 3H, CH_2CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.2 (C=O), 162.7, 145.4, 129.2, 129.0, 128.3, 126.7, 124.5, 121.2, 113.9, 112.5, 55.4, 23.6, 13.2. Elemental Anal. Found: C, 69.94; H, 6.73; N, 10.03%. Calcd for $C_{16}H_{18}N_2O_2 \cdot 1/4H_2O$: C, 69.92; H, 6.78; N, 10.19%.

Synthesis of *N*-Phenylbenzohydrazonyl Chloride Derivatives. Derivatives **4a**–**4h** were obtained according to modified procedure described in the previous literature:[41] To a stirred solution (or suspension) of hydrazide **3a**–**3h** (20.0 mmol) in a dry diethyl ether (15 mL), PCl_5 (5.0 g, 24.0 mmol) was added dropwise over a period of ca. 15 min. The reaction mixture was heated in reflux for 1 h, then it was cooled to room temperature and continued for the next 15 h. A solution of phenol (5.0 g, 53.0 mmol) in diethyl ether (5 mL) was added and after 15 min methanol (15 mL) was carefully added dropwise.

Isolation of Benzohydrazonyl Chlorides 4a–4e. The reaction mixture was poured into 100 mL of water and the product was extracted with chloroform (3 × 25 mL). The combined organic layers were washed with water (ca. 50 mL) and dried over anhydrous $MgSO_4$. After evaporating the solvent the products were isolated by column chromatography (eluent: $CHCl_3$/*n*-hexane, 1:1 for **4a**; $CHCl_3$ for **4b**–**4e**).

Isolation of Benzohydrazonyl Chlorides 4f–4h. The precipitate was filtered on a Büchner funnel, washed several times with cold water and recrystallized from methanol/acetone mixture.

The analytically pure products were obtained: **4a**,[42,50] 2.72 g (59%); **4b**,[51,52] 2.26 g (46%); **4c**,[52] 1.57 g (30%); **4d**, 1.59 g (29%); **4e**, 2.33 g (40%); **4f**,[53] 2.17 g (39%); **4g**,[54] 2.08 g (40%); **4h**,[48,54] 5.60 g (87%).

In cases of new compounds and known compounds but characterized partially in the earlier literature the additional data are given below for more detailed and accurate characterization of these intermediates.

***N*-Phenyl-4-methylbenzohydrazonyl Chloride (4b):** Known compound; mp 134–135 °C ($CHCl_3$), lit.[51] 136–137 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.00 (s, 1H, NH), 7.83 (apparent d, $J = 8.2$ Hz, 2H, H-Tol), 7.32 (apparent t, $J = 7.9$ Hz, 2H, H-Ph), 7.24–7.16 (m, 4H, 2H of H-Tol and 2H of H-Ph), 6.95 (apparent t, $J = 7.3$ Hz, 1H, H-Ph), 2.40 (s, 3H, CH_3-Tol).

***N*-Phenyl-4-methoxybenzohydrazonyl Chloride (4c):** Known compound; mp 130–131 °C (Et_2O), lit.[52] 126–128 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.96 (s, 1H, NH), 7.88 (apparent d, $J = 8.8$ Hz, 2H, H-ArOMe), 7.33 (apparent t, $J = 7.8$ Hz, 2H, H-Ph), 7.19 (apparent d, $J = 8.0$ Hz, 2H, H-Ph), 7.00–6.91 (m, 3H, 2H of H-ArOMe and 1H of H-Ph), 3.86 (s, 3H, OCH_3).

Table 1. [3 + 2]-Cycloaddition Reaction of Porphyrin **6** with Iminonitriles

	Iminonitrile precursor	Conditions	Products and Yields/%[a)]
1	**4a**	NEt_3, toluene, reflux, 45 h	**7a**, 29 (41); **8a**, ca. 12 (17)
2	**4a**	NEt_3, toluene, reflux, 20 h	**7a**, 23 (31); **8a**, 12 (16)
3	**4a**	NEt_3, cyclooctane, 150 °C, 8 h	**7a**, 29 (40); **8a**, 8 (11)
4	**4a**	DABCO, cyclooctane, 150 °C, 6 h	**7a**, ca. 25 (60); **8a**, 10 (24)
5	**4b**	NEt_3, toluene, reflux, 20 h	**7b**, 23 (27); **8b**, 15 (18)
6	**4b**	DABCO, cyclooctane, 150 °C, 6 h	**7b**, 32 (60); **8b**, 5 (9)
7	**4c**	NEt_3, toluene, reflux, 20 h	**7c**, 19; **8c**, 12
8	**4d**	NEt_3, toluene, reflux, 20 h	**7d**, 7; **8d**, 43
9	**4d**	NEt_3, cyclooctane, 150 °C, 8 h	**7d**, 7 (16); **8d**, 10 (23)
10	**4e**	NEt_3, toluene, reflux, 20 h	**7e**, 3 (5); **8e**, 32 (52)
11	**4f**	NEt_3, toluene, reflux, 20 h	—
12	**4g**	NEt_3, toluene, reflux, 20 h	—
13	**4h**	NEt_3, toluene, reflux, 20 h	—

a) In brackets: yields for the recovered substrate.

***N*-(2-Ethylphenyl)-4-methylbenzohydrazonyl Chloride (4d):** Mp 46–47 °C ($CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.08 (s, 1H, NH), 7.87 (apparent d, $J = 8.2$ Hz, 2H, H-Tol), 7.60 (d, $J = 8.1$ Hz, 1H, H-Ar(Et)), 7.31–7.22 (m, 3H, 2H of H-Tol and 1H of H-Ar(Et)), 7.19 (d, $J = 7.4$ Hz, 1H, H-Ar(Et)), 6.96 (apparent td, $J = 7.4$, 0.8 Hz, 1H, H-Ar(Et)), 2.70 (q, $J = 7.5$ Hz, 2H, CH_2CH_3), 2.43 (s, 3H, CH_3-Tol), 1.37 (t, $J = 7.5$ Hz, 3H, CH_2CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 140.7, 139.4, 131.8, 129.1, 128.4, 127.2, 126.9, 126.4, 125.6, 120.8, 113.5, 23.7, 21.2, 13.2. Elemental Anal. Found: C, 70.49; H, 6.35; N, 10.32; Cl, 12.96%. Calcd for $C_{16}H_{17}Cl_1N_2$: C, 70.45; H, 6.28; N, 10.27; Cl, 13.00%.

***N*-(2-Ethylphenyl)-4-methoxybenzohydrazonyl Chloride (4e):** Mp 44–45 °C ($CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.99 (s, 1H, NH), 7.91–7.85 (part of AA′XX′, 2H, H-ArOMe), 7.54 (d, $J = 8.0$ Hz, 1H, H-Ar(Et)), 7.23 (apparent t, $J = 7.7$ Hz, 1H, H-Ar(Et)), 7.15 (d, $J = 7.4$ Hz, 1H, H-Ar(Et)), 6.96–6.88 (m, 3H, 2H of H-ArOMe and 1H of H-Ar(Et)), 3.86 (s, 3H, OCH_3), 2.66 (q, $J = 7.6$ Hz, 2H, CH_2CH_3), 1.34 (t, $J = 7.6$ Hz, 3H, CH_2CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 160.6, 140.8, 128.4, 127.9, 127.2, 126.9, 125.5, 120.7, 113.8, 113.4, 55.4, 23.7, 13.2. Elemental Anal. Found: C, 66.58; H, 5.88; N, 9.72; Cl, 12.32%. Calcd for $C_{16}H_{17}Cl_1N_2O_1$: C, 66.55; H, 5.93; N, 9.70; Cl, 12.28%.

***N*-(4-Nitrophenyl)benzohydrazonyl Chloride (4f):** Known compound;[53] ^{1}H NMR (DMSO-d_6, 400 MHz): δ 10.72 (s, 1H, NH), 8.18 (apparent d, $J = 9.2$ Hz, 2H, H-Ar(NO_2)), 8.00–7.92 (m, 2H, H-Ar(NO_2)), 7.55–7.46 (m, 5H, H-Ph).

Cycloaddition Reactions of Iminonitriles to *meso*-Tetrakis(pentafluorophenyl)porphyrin (Table 1). Procedure A: To a solution of *meso*-tetrakis(pentafluorophenyl)porphyrin (**6**; 98 mg, 0.101 mmol), *N*-phenylbenzohydrazonyl chloride (**4a**; 116 mg, 0.503 mmol) in a dry toluene (2 mL) a solution of NEt_3 (0.4 mL, solution 1.8 mol L^{-1}) in toluene (2 mL) was added. Then, the reaction mixture was heated to reflux in a flask equipped with a reflux condenser protected at the top with a $CaCl_2$ tube. The new portions of precursor **4a** (116 mg, 0.503 mmol; in 2 mL of toluene) were added, followed by addition of NEt_3 (0.4 mL, 1.8 mol L^{-1}; in 2 mL of toluene) every 9 h. After 45 h the reaction mixture was cooled to room temperature and transferred quantitatively to a separatory funnel filled with 100 mL of water. The product was extracted with chloroform (4 × 25 mL). The combined organic layers were washed with brine (100 mL) and dried over anhydrous $MgSO_4$. After evaporating the solvent the products were isolated by column chromatography (eluent: $CHCl_3$/*n*-hexane, 1:1). Yields: chlorin **7a** 34.0 mg, 29% (41% for converted **6**); porphyrin **8a** contaminated with **9a** 13.9 mg, ca. 12%. Additionally, 29.6 mg of substrate **6** was recovered (30%).

Procedure B: A solution of *meso*-tetrakis(pentafluorophenyl)porphyrin (**6**; 97.5 mg, 0.100 mmol), iminonitrile precursor **4a**–**4h** (0.40 mmol), and NEt_3 (61 mg, 0.60 mmol) in a dry toluene (3 mL) was heated at reflux in a flask equipped with a reflux condenser protected at the top with a $CaCl_2$ tube over a period of ca. 20 h. The new portions of precursor **4** (0.40 mmol) and NEt_3 (61 mg, 0.60 mmol) were added via microsyringe (septum) every 5 h (3 times). The reaction mixture was cooled to room temperature and transferred quantitatively to a separatory funnel filled with 100 mL of water. The product was extracted with chloroform (4 × 25 mL). The combined organic layers were washed with brine (100 mL) and dried over anhydrous $MgSO_4$. After evaporating the solvent the products were isolated by column chromatography (eluent: $CHCl_3$/*n*-hexane, from 1:1 to 2:1). Yields: chlorin **7a** 27 mg, 23% (31% for converted **6**) and porphyrin **8a** 14 mg, 12% (16%); chlorin **7b** 27 mg, 23% (27%) and porphyrin **8b** 18 mg, 15% (18%); chlorin **7c** 23 mg, 19%, and porphyrin **8c** 14 mg, 12%; chlorin **7d** 9 mg, 7%, and porphyrin **8d** 52 mg, 43%; chlorin **7e** 4 mg, 3% (5%) and porphyrin **8e** 39 mg, 32% (52%).

Procedure C: A solution of *meso*-tetrakis(pentafluorophenyl)porphyrin (**6**; 97.5 mg, 0.100 mmol), iminonitrile precursor **4a** and **4b** (0.40 mmol), and DABCO (45 mg, 0.40 mmol) in cyclooctane (3 mL) was heated at reflux (under argon) over a period of ca. 3 h. Then, new portions of iminonitrile precursor (0.40 mmol) and DABCO (45 mg, 0.40 mmol) were added, and the reaction was continued for the next 3 h. The products were isolated as in *Procedure B*. Yields: chlorin **7a** 29 mg, 25% (60% for converted **6**) and porphyrin **8a** 12 mg, 10% (24%); chlorin **7b** 38 mg, 32% (60%) and porphyrin **8b** 6 mg, 5% (9%).

Procedure D: A solution of *meso*-tetrakis(pentafluorophenyl)porphyrin (**6**; 97.5 mg, 0.100 mmol), iminonitrile pre-

cursor **4a** and **4d** (0.40 mmol), and NEt_3 (120 mg, 1.19 mmol) in cyclooctane (3 mL) was heated at reflux (under argon) over a period of ca. 4 h. Then, new portions of iminonitrile precursor (0.40 mmol) and NEt_3 (120 mg, 1.19 mmol) were added, and the reaction was continued for the next 4 h. The products were isolated as in *Procedure B*. Yields: chlorin **7a** 34 mg, 29% (40% for converted **6**) and porphyrin **8a** 9 mg, 8% (11%); chlorin **7d** 9 mg, 7% (16%) and porphyrin **8d** 12 mg, 10% (23%).

Chlorin 7a; Mp >300 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.68 (d, $J = 5.0$ Hz, 1H, H^{β}), 8.64 (d, $J = 5.0$ Hz, 1H, H^{β}), 8.49 and 8.48 (AB, $J \approx 5.0$ Hz, 2H, 2 × H^{β}), 8.31 (d, $J \approx 5.0$ Hz, 1H, H^{β}), 8.24 (d, $J \approx 5.0$ Hz, 1H, H^{β}), 7.51 (d, $J = 8.5$ Hz, 1H, CH-chlorin), 7.32–7.22 (m, 3H, H-Ph), 7.15–7.07 (m, 5H, H-Ph), 6.88 (apparent d, $J = 7.3$ Hz, 2H, H-Ph), 6.60 (d, 1H, $J = 8.5$ Hz, 1H, CH-chlorin), −1.54 (s, 2H, 2 × NH). NMR-COSY ($CDCl_3$, 400 MHz): δ (diagnostic ^{1}H–^{1}H correlations) = 8.68/8.31 ($2H^{\beta}$), 8.64/8.24 ($2H^{\beta}$), 7.51/6.60 (2H-chlorin), ca. 7.10/6.88 (H-Ph). NMR-HSQC ($CDCl_3$, 400/100 MHz): δ (diagnostic ^{1}H–^{13}C correlations) = 7.51/76.6 (CH-chlorin), 6.60/62.6 (CH-chlorin). UV–vis ($CHCl_3$): λ_{max} ($\log \varepsilon$) 409 (5.17, Soret), 508 (4.17), 534 (3.75), 604 (3.65), 657 nm (4.41). MS (ESI): m/z 1172 (9), 1171 (30), 1170 (74), 1169 (100%) [isotope $(M + H)^+$]. HR-MS (ESI): $(M + H)^+$, found 1169.1533; $C_{57}H_{21}N_6F_{20}$ requires 1169.1508.

Chlorin 7b; Mp >300 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.66 (d, $J = 5.0$ Hz, 1H, H^{β}), 8.63 (d, $J = 4.9$ Hz, 1H, H^{β}), 8.48 and 8.47 (AB, $J \approx 5.0$ Hz, 2H, 2 × H^{β}), 8.30 (d, $J = 5.0$ Hz, 1H, H^{β}), 8.23 (d, $J = 4.9$ Hz, 1H, H^{β}), 7.46 (d, $J = 8.4$ Hz, 1H, CH-chlorin), 7.30–7.23 (m, 2H, H-Ph), 7.13–7.06 (m, 3H, H-Ph), 6.92 (apparent d, $J = 8.0$ Hz, 2H, H-Tol), 6.78 (apparent d, $J = 8.0$ Hz, 2H, H-Tol), 6.57 (d, $J = 8.4$ Hz, 1H, CH-chlorin), 2.28 (s, 3H, CH_3-Tol), −1.56 (s, 2H, 2 × NH). UV–vis ($CHCl_3$): λ_{max} ($\log \varepsilon$) 288 (4.40), 408.5 (5.19, Soret), 508 (4.14), 534.5 (3.68), 603.5 (3.56), 656.5 nm (4.43). MS (FD): m/z 1185 (5), 1184 (18), 1183 (61), 1182 (100%) [isotope M^+]. HR-MS (FD): M^+, found 1182.1628; $C_{58}H_{22}N_6F_{20}$ requires 1182.1587.

Chlorin 7c; Mp >300 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.67 (d, $J = 5.0$ Hz, 1H, H^{β}), 8.64 (d, $J = 5.0$ Hz, 1H, H^{β}), 8.48 and 8.47 (AB, $J = 4.7$ Hz, 2H, 2 × H^{β}), 8.30 (d, $J = 5.0$ Hz, 1H, H^{β}), 8.25 (d, $J = 4.9$ Hz, 1H, H^{β}), 7.50 (d, $J = 8.4$ Hz, 1H, CH-chlorin), 7.28 (apparent t, $J = 7.8$ Hz, 2H, H-Ph), 7.13 (d, $J = 7.9$ Hz, 2H, H-Ph), 7.08 (t, $J = 7.4$ Hz, 1H, H-Ph), 6.80 (apparent d, $J = 8.7$ Hz, 2H, H-ArOMe), 6.61 (apparent d, $J = 8.7$ Hz, 2H, H-ArOMe), 6.52 (d, 1H, $J = 8.4$ Hz, 1H, CH-chlorin), 3.72 (s, 3H, OCH_3), −1.52 (s, 2H, 2 × NH). UV–vis ($CHCl_3$): λ_{max} ($\log \varepsilon$) 287 (4.57), 408.5 (5.28, Soret), 508 (4.25), 534.5 (3.79), 603.5 (3.66), 657.5 nm (4.50). MS (FD): m/z 1201 (6), 1200 (20), 1199 (64), 1198 (100%) [isotope M^+]. HR-MS (FD): M^+, found 1198.1494; $C_{58}H_{22}N_6F_{20}O$ requires 1198.1536.

Chlorin 7d; Mp >300 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.70–8.65 (m, 2H, 2 × H^{β}), 8.53 and 8.51 (AB, $J = 4.6$ Hz, 2H, 2 × H^{β}), 8.31 (d, $J = 4.7$ Hz, 1H, H^{β}), 8.18 (d, $J = 4.8$ Hz, 1H, H^{β}), 7.40 (apparent d, $J = 8.0$ Hz, 2H, H-Tol), 7.23–7.15 (m, 3H, 2H of H-Tol and 1H of H-Ar(Et)), 7.14–7.05 (m, 3H, 2H of H-Ar(Et) and CH-chlorin), 7.03 (apparent d, $J = 7.5$ Hz, 1H, H-Ar(Et)), 6.71 (d, 1H, $J = 8.4$ Hz, CH-chlorin), 2.48 (s, 3H, CH_3-Tol), 1.49 (apparent sextet, $J \approx 14.6$, 7.5 Hz, 1H of CH_2CH_3), 1.32 (apparent sextet, $J \approx 14.6$, 7.5 Hz, 1H of CH_2CH_3), 0.30 (t, $J = 7.5$ Hz, 3H, CH_2CH_3), −1.80 (s, 1H, NH), −1.82 (s, 1H, NH). NMR-COSY ($CDCl_3$, 400 MHz): δ (diagnostic ^{1}H–^{1}H correlations) = ca. 8.68/8.31 ($2H^{\beta}$), ca. 8.68/8.18 ($2H^{\beta}$), 8.53/8.51 ($2H^{\beta}$), 7.40/ca. 7.20 (H-Tol), ca. 7.20/ca. 7.08 (H-Ar(Et)), ca. 7.20/7.03 (H-Ar(Et)), ca. 7.12/6.71 (2H-chlorin). UV–vis ($CHCl_3$): λ_{max} ($\log \varepsilon$) 286 (4.55), 408.5 (5.25, Soret), 507.5 (4.23), 535 (3.78), 603.5 (3.68), 657 nm (4.47). MS (FD), m/z: 1213 (6), 1212 (20), 1211 (64), 1210 (100%) [isotope M^+]. HR-MS (FD): M^+, found 1210.1868; $C_{60}H_{26}N_6F_{20}$ requires 1210.1900.

Chlorin 7e; Mp >300 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.67 (apparent d, $J = 4.9$ Hz, 2H, 2 × H^{β}), 8.52 and 8.50 (AB, $J = 4.7$ Hz, 2H, 2 × H^{β}), 8.30 (d, $J = 4.9$ Hz, 1H, H^{β}), 8.18 (d, $J = 4.9$ Hz, 1H, H^{β}), 7.43 (apparent d, $J = 8.6$ Hz, 2H, H-ArOMe), 7.22–7.16 (m, 1H, H-Ar(Et)), 7.14–7.06 (m, 3H, 2H of H-Ar(Et) and CH-chlorin), 7.02 (d, $J = 7.5$ Hz, 1H, H-Ar(Et)), 6.91 (d, $J = 8.6$ Hz, 2H, H-ArOMe), 6.68 (d, $J = 8.3$ Hz, 1H, CH-chlorin), 3.93 (s, 3H, OCH_3), 1.51–1.36 (m, 2H, CH_2CH_3), 0.31 (t, $J = 7.5$ Hz, 3H, CH_2CH_3), −1.79 (s, 1H, NH), −1.80 (s, 1H, NH). NMR-COSY ($CDCl_3$, 400 MHz): δ (diagnostic ^{1}H–^{1}H correlations) = 8.67/8.30 ($2H^{\beta}$), 8.67/8.18 ($2H^{\beta}$), 7.43/6.91 (H-ArOMe), ca. 7.19/ca. 7.09 (H-Ar(Et)), ca. 7.19/7.02 (H-Ar(Et)), ca. 7.12/ca. 7.09 (H-Ar(Et)), ca. 7.11/6.68 (2H-chlorin), ca. 1.47/0.31 (CH_2CH_3), ca. 1.39/0.31 (CH_2CH_3). UV–vis ($CHCl_3$): λ_{max} ($\log \varepsilon$) 407.5 (5.45, Soret), 506.5 (4.33), 534 (3.86), 600 (3.78), 653 nm (4.75). MS (FD): m/z 1229 (7), 1228 (22), 1227 (63), 1226 (100%) [isotope M^+]. HR-MS (FD): M^+, found 1226.1906; $C_{60}H_{26}N_6F_{20}O$ requires 1226.1849.

Porphyrin 8a; Mp >300 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.02 and 9.00 (AB, $J = 4.9$ Hz, 2H, 2 × H^{β}), 8.96 (s, 1H, H^{β}), 8.91–8.85 (m, 3H, 3 × H^{β}), 8.79 (d, $J = 4.9$ Hz, 1H, H^{β}), 7.55 (s, 1H, NH), 7.43 (apparent d, $J = 7.0$ Hz, 2H, H-Ph), 7.29–7.14 (m, 5H, H-Ph), 6.92 (apparent d, $J = 8.0$ Hz, 2H, H-Ph), 6.85 (apparent t, $J = 7.3$ Hz, 1H, H-Ph), −2.76 (s, 2H, 2 × NH). UV–vis ($CHCl_3$): λ_{max} ($\log \varepsilon$) 364.5 (4.67), 416 (5.47, Soret), 509 (4.26), 589 nm (3.77). MS (ESI): m/z 1173 (4), 1172 (11), 1171 (30), 1170 (71), 1169 (100%) [isotope $(M + H)^+$]. The molecular formula was confirmed by comparing the theoretical and experimental isotope patterns for the $(M + H)^+$ ion ($C_{57}H_{21}N_6F_{20}$); it was found to be identical within the experimental error limits.

Porphyrin 8b; Mp >300 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.02 and 9.00 (AB, $J = 4.9$ Hz, 2H, 2 × H^{β}), 8.96 (s, 1H, H^{β}), 8.91–8.85 (m, 3H, 3 × H^{β}), 8.79 (d, $J = 4.9$ Hz, 1H, H^{β}), 7.55 (s, 1H, NH), 7.49–7.39 (m, 2H, H-Tol), 7.18 (apparent t, $J = 7.9$ Hz, 2H, H-Ph), 7.06 (d, $J = 8.0$ Hz, 2H, H-Tol), 6.89 (apparent d, $J = 8.0$ Hz, 2H, H-Ph), 6.83 (apparent t, $J = 7.3$ Hz, 1H, H-Ph), 2.34 (s, 3H, CH_3-Tol), −2.76 (s, 2H, 2 × NH); signal of $\delta = 7.55$ quickly disappeared after addition of D_2O. NMR-COSY ($CDCl_3$, 400 MHz): δ (diagnostic ^{1}H–^{1}H correlations) = ca. 7.43/7.06 (H-Tol), 7.18/6.89 (H-Ph), 7.18/6.83 (H-Ph). NMR-HSQC ($CDCl_3$, 400/100 MHz): δ (diagnostic ^{1}H–^{13}C correlations) = ca. 9.01/ca. 130.4 (CH^{β}), 8.96/135.8 (CH^{β}), ca. 8.88/ca. 130.0 (CH^{β}), 8.79/130.4 (CH^{β}), 7.43/125.2 (CH-Tol), 7.18/128.9 (CH-Ph), 7.06/128.9 (CH-Tol), 6.89/113.2 (CH-Ph), 6.83/120.3 (CH-Ph), 2.34/21.0 (CH_3-Tol). UV–vis ($CHCl_3$): λ_{max} ($\log \varepsilon$) 358.5 (4.82), 416 (5.50, Soret), 509

(4.32), 589 (3.87), 646.5 nm (3.25). MS (FD): m/z 1185 (5), 1184 (20), 1183 (63), 1182 (100%) [isotope M^+]. HR-MS (FD): M^+, found 1182.1553; $C_{58}H_{22}N_6F_{20}$ requires 1182.1587.

Porphyrin 8c; Mp >300 °C. ^{1}H NMR ($CDCl_3$, 400 MHz), δ 9.03 and 9.01 (AB, $J = 4.7$ Hz, 2H, 2 × H^{β}), 8.96 (s, 1H, H^{β}), 8.91–8.85 (m, 3H, 3 × H^{β}), 8.80 (d, $J = 5.0$ Hz, 1H, H^{β}), 7.49 (s, 1H, NH), 7.49–7.44 (m, 2H, H-ArOMe), 7.20–7.14 (m, 2H, H-Ph), 6.88 (d, $J = 7.7$ Hz, 2H, H-ArOMe), 6.85–6.76 (m, 3H, H-Ph), 3.79 (s, 3H, OCH_3), −2.76 (s, 2H, 2 × NH). UV–vis ($CHCl_3$): λ_{max} ($\log \varepsilon$) 300.5 (4.47), 367 (4.72), 416 (5.51, Soret), 509 (4.32), 589 (3.84), 655 nm (3.34). MS (FD): m/z 1201 (4), 1200 (17), 1199 (58), 1198 (100%) [isotope M^+]. HR-MS (FD): M^+, found 1198.1489; $C_{58}H_{22}N_6F_{20}O$ requires 1198.1536.

Porphyrin 8d; Mp >300 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.04 and 9.03 (AB, 2H, $J = 5.1$ Hz, 2 × H^{β}), 9.01 (s, 1H, H^{β}), 8.95–8.86 (m, 3H, 3 × H^{β}), 8.81 (d, $J = 4.9$ Hz, 1H, H^{β}), 7.89 (s, 1H, NH), 7.78 (apparent d, $J = 8.1$ Hz, 1H, H-Ar(Et)), 7.41–7.33 (m, 2H, H-Tol), 7.32 (apparent td, $J = 7.7$, 1.2 Hz, 1H, H-Ar(Et)), 7.03 (apparent d, $J = 8.2$ Hz, 2H, H-Tol), 6.92–6.87 (m, 1H, H-Ar(Et)), 6.83 (apparent td, $J = 7.3$, 0.9 Hz, 1H, H-Ar(Et)), 2.34 (s, 3H, CH_3-Tol), 1.71 (q, $J = 7.5$ Hz, 2H, CH_2CH_3), 0.42 (t, $J = 7.5$ Hz, 3H, CH_2CH_3), −2.74 (s, 2H, 2 × NH). NMR-COSY ($CDCl_3$, 400 MHz): δ (diagnostic ^{1}H–^{1}H correlations) = 7.78/7.32 (H-Ar(Et)), ca. 7.38/7.03 (H-Tol), 7.32/6.83 (H-Ar(Et)), ca. 6.90/6.83 (H-Ar(Et)). UV–vis ($CHCl_3$): λ_{max} ($\log \varepsilon$) 367 (4.67), 415.5 (5.49, Soret), 508.5 (4.28), 588.5 (3.83), 642.5 nm (3.11). MS (FD): m/z 1213 (4), 1212 (20), 1211 (65), 1210 (100%) [isotope M^+]. HR-MS (FD): M^+, found 1210.1858; $C_{60}H_{26}N_6F_{20}$ requires 1210.1900.

Porphyrin 8e; Mp >300 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.04 and 9.03 (AB, $J = 5.2$ Hz, 2H, 2 × H^{β}), 9.01 (s, 1H, H^{β}), 8.92–8.86 (m, 3H, 3 × H^{β}), 8.82 (d, $J = 4.9$ Hz, 1H, H^{β}), 7.83 (s, 1H, NH), 7.75 (d, $J = 8.2$ Hz, 1H, H-Ar(Et)), 7.50–7.35 (m, 2H, H-ArOMe), 7.34–7.28 (m, 1H, H-Ar(Et)), 6.91–6.86 (m, 1H, H-Ar(Et)), 6.82 (apparent td, $J = 7.0$, 0.5 Hz, 1H, H-Ar(Et)), 6.76 (apparent d, $J = 8.7$ Hz, 2H, H-ArOMe), 3.78 (s, 3H, OCH_3), 1.70 (q, $J = 7.5$ Hz, 2H, CH_2CH_3), 0.42 (t, $J = 7.5$ Hz, 3H, CH_2CH_3), −2.75 (s, 2H, 2 × NH). NMR-COSY ($CDCl_3$, 400 MHz): δ (diagnostic ^{1}H–^{1}H correlations) = 7.75/ca. 7.30 (H-Ar(Et)), ca. 7.40/6.76 (H-ArOMe), ca. 7.30/6.82 (H-Ar(Et)), ca. 6.90/6.82 (H-Ar(Et)). UV–vis ($CHCl_3$): λ_{max} ($\log \varepsilon$) 367 (4.82), 416 (5.64, Soret), 509 (4.40), 588.5 (3.89), 644.5 nm (2.99). MS (FD): m/z 1229 (6), 1228 (22), 1227 (64), 1226 (100%) [isotope M^+]. HR-MS (FD): M^+, found 1226.1880; $C_{60}H_{26}N_6F_{20}O$ requires 1226.1849.

Porphyrin 9a; This compound was isolated in a mixture with porphyrin **8a** (*Procedure A*). Its structure was proposed on the basis of MS and ^{1}H NMR spectra. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (diagnostic chemical shift) = −3.57 (s, 2H, 2 × NH). MS (ESI): m/z 1365 (41), 1364 (82), 1363 (100%) [isotope $(M + H)^+$]. The molecular formula was confirmed by comparing the theoretical and experimental isotope patterns for the $(M + H)^+$ ion ($C_{70}H_{31}N_8F_{20}$); it was found to be identical within the experimental error limits.

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