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Aust. J. Chem. **2011**, *64*, 939–944

Porphyrin–Phosphoramidate Conjugates: Synthesis, Photostability and Singlet Oxygen Generation

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meso-Tetrakis(pentafluorophenyl)porphyrin reacts with aminoalkylphosphoramidates to afford porphyrins substituted with one or four phosphoramidate groups in the 4-position of the *meso*-aryl groups. The new porphyrin derivatives show high photostability and some are better singlet oxygen generators than *meso*-tetrakis(1-methylpyridinium-4-yl)porphyrin, a well known good singlet oxygen producer.

Manuscript received: 7 January 2011.
Manuscript accepted: 29 March 2011.

Introduction

Natural porphyrins are involved in several vital biological functions such as photosynthesis, transport and storage of molecular oxygen, and catalytic oxidative transformations. Because of their structural complexity, natural porphyrins are frequently substituted by simple synthetic models, such as the *meso*-tetraarylporphyrins, in studies performed to look for new compounds that can mimic the functions of the natural ones. *meso*-Tetraarylporphyrins are especially interesting and useful compounds because they can be prepared in one step from simple reagents (pyrrole and aromatic aldehydes), in moderate to good yields;[1] such compounds display physico-chemical and biological properties similar to those of the natural counterparts. The potentiality of the *meso*-tetraarylporphyrin derivatives in a great number of scientific fields, e.g., medicine, catalysis, and in the production of new electronic materials, is well established.[2] Medicinal formulations which include the use of porphyrin derivatives as photosensitizers are already being considered in several countries for the photodynamic therapy (PDT) of malignant tumors and also for the treatment of age-related macular degeneration.[3]

Organophosphorus compounds also have a prominent place in medicine, being used as anticancer drugs, antivirals, antifungals, and inhibitors of bone resorption among other applications.[4] Porphyrin phosphonates, in particular, display interesting binding properties, where the P=O group plays a significant role as a strong hydrogen bond acceptor.[5] Such a characteristic is essential for the non-covalent bonding of proteins or other specific ligands to their substrates. Other examples of porphyrins bearing phosphonate groups are also known.[6]

Phosphoramidates possess a great biological activity and have been used in several prodrug strategies. It was shown that they enhance the nucleoside potency in cell cultures, presumably by improving cellular penetration and hence by increasing intracellular concentrations of the active nucleotide.[7] Therefore, the synthesis of porphyrins containing phosphoramidate moieties may lead to new compounds with interesting biological properties or with adequate properties to be used as photosensitizers in PDT.[8]

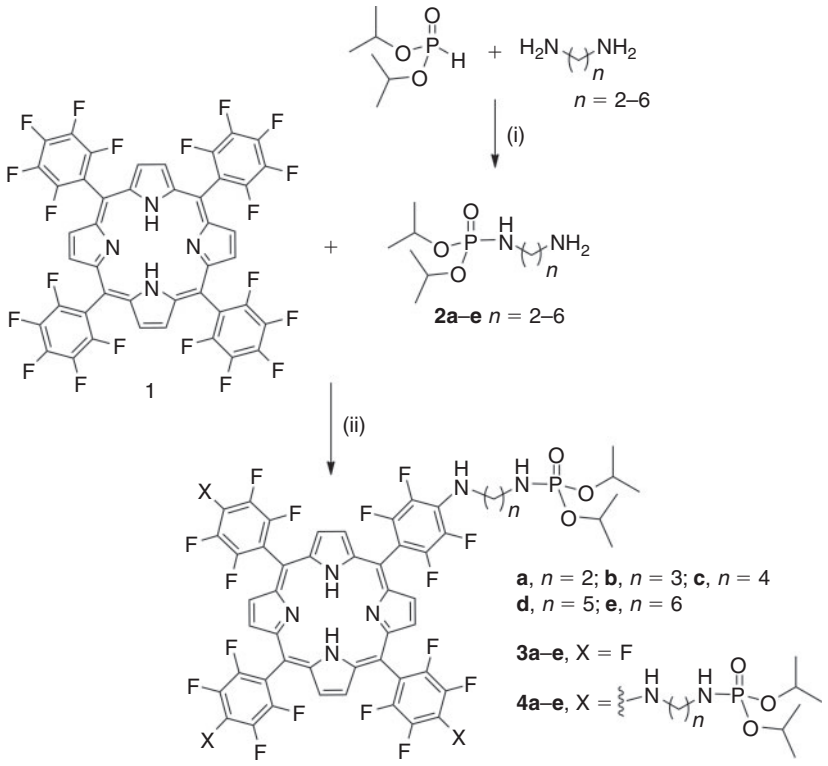
Recently, Albinsson and coworkers have studied the binding characteristics of DNA with a porphyrin-modified tymidine nucleoside presenting phenylethynylene spacers of different lengths. It was demonstrated that the hydrophobic porphyrin moiety is attached to a lipid membrane, while the polar tymidine part at the other end of the phenylethynylene chain interacts with DNA in the water phase, with the effectiveness of the interaction being a function of the chain length. Similarly, we describe here an easy synthetic approach to selectively prepare new porphyrin derivatives bearing one or four phosphoramidate groups with a spacer of variable length. The inclusion of the aminoalkyl spacer is expected to provide a greater mobility of the phosphoramidate group, which could facilitate the interaction with the lipid membranes and the cell DNA.[9]

Results and Discussion

Synthesis

The synthesis of the new porphyrin–phosphoramidate conjugates can be performed by nucleophilic aromatic substitution of the *p*-fluorine atoms in *meso*-tetrakis(pentafluorophenyl)porphyrin (**1**) by aminoalkylphosphoramidates **2a**–**e**. The starting porphyrin **1** is easily prepared from pentafluorobenzaldehyde and pyrrole under microwave irradiation[10] while the aminoalkylphosphoramidates **2a**–**e** are obtained by selective monophosphorylation of aliphatic diamines.[11]

10.1071/CH11013 0004-9425/11/070939



Scheme 1. Reagents and conditions: (i) CCl_4, EtOH, temperature 55–65°C, 10–25 min. (ii) toluene, reflux, 8–72 h.

The nucleophilic aromatic substitution of one to four *p*-fluorine atoms in porphyrin **1** by amines, phenoxides, alkoxides, or thiols has been used as a versatile route to new porphyrin derivatives.[12–14] In this work, we were able to synthesize selectively the monosubstituted porphyrins **3a**–**e** or the tetrasubstituted derivatives **4a**–**e** by selecting the appropriate porphyrin/phosphoramidate ratio (Scheme 1). For instance, the formation of the monosubstituted derivatives **3a**–**e** could be obtained in 63–83% yield by refluxing a toluene solution of the aminoalkyl phosphoramidates **2a**–**e** with an excess (2 equiv.) of porphyrin **1** for 8 to 12 h. Minor amounts of disubstituted products were also formed. The reaction of porphyrin **1** with 10 equivalents of aminoalkyl phosphoramidates **2a**–**e** in refluxing toluene for 56 to 72 h afforded the tetrasubstituted porphyrins **4a**–**e** in 50–77% yield along with a mixture of the di- and trisubstituted porphyrins. The new compounds were separated by column chromatography (silica gel) using ethyl acetate/methanol (97/3) as the eluent and were crystallized from chloroform/methanol (1/3).

The mono- (**3a**–**e**) and tetra- (**4a**–**e**) substituted porphyrin–phosphoramidates were fully characterized by ^1H, ^{19}F, and ^{31}P NMR spectroscopy and by high resolution mass spectrometry (HRMS). The ^1H NMR spectra of the monosubstituted compounds show a multiplet in the range of 8.87–9.04 ppm corresponding to the resonances of the β-pyrrolic protons whereas for the tetrasubstituted derivatives the resonances of the β-pyrrolic protons appear as a singlet around 8.95 ppm. The same spectra show broad singlets at approx. −2.85 ppm attributable to the inner NH protons. The resonances of the isopropyl protons appear as two doublets at 1.36–1.42 ppm and a doublet of heptets around 4.6 ppm with coupling constants in the range of 6.0–6.3 Hz ($J_{H–H}$) and 7.2–7.5 Hz ($J_{P–H}$). ^{31}P NMR signals were observed in the range of 7.8–8.2 ppm for all porphyrin–phosphoramidate conjugates. This is in agreement with the ^{31}P NMR data obtained for other aminophosphoramidates.[11] The HRMS (fast atom bombardment, positive ion detection (FAB^+)) of compounds **3a**–**e** show the $(M + H)^+$ ions while the spectra of compounds **4a**–**e** show the corresponding $(M + 2H)^{2+}$ ones.

Singlet Oxygen Generation

The ability of these porphyrin derivatives to generate singlet oxygen, the basis of the photoinactivation process, was qualitatively evaluated by monitoring the photodecomposition of 1,3-diphenylisobenzofuran (DPiBF). The results, summarized in Fig. 1 and Table 1, show that the DPiBF photodegradation was highly enhanced in the presence of any photosensitizer. This means that all porphyrin derivatives are able to produce singlet oxygen. In general, the tetrasubstituted porphyrin–phosphoramidate derivatives **4** are more efficient to generate singlet oxygen than the corresponding monosubstituted derivatives **3**. Derivatives **4**, excluding **4b**, with slopes in the range 0.038–0.058 (the slope is proportional to the rate of production of singlet oxygen), were shown to be, under the same experimental conditions, similar or more efficient $^1O_2$ producers than *meso*-tetrakis(1-methylpyridinium-4-yl)porphyrin (Tetra-Py^+-Me, slope 0.038), which is considered to be a good singlet oxygen producer.[15] It is evident from Fig. 1 that porphyrin **4c** is the best singlet oxygen generator of all new compounds. Although the monosubstituted phosphoramidate derivatives **3a**–**e** also generate singlet oxygen (slopes ranging from 0.013–0.025) they are less efficient than Tetra-Py^+-Me. It is well known that porphyrins easily undergo aggregation when in solution in particular in water or in polar solvents. This phenomenon causes fast quenching of the porphyrin triplet state and consequently restricts the formation of $^1O_2$.

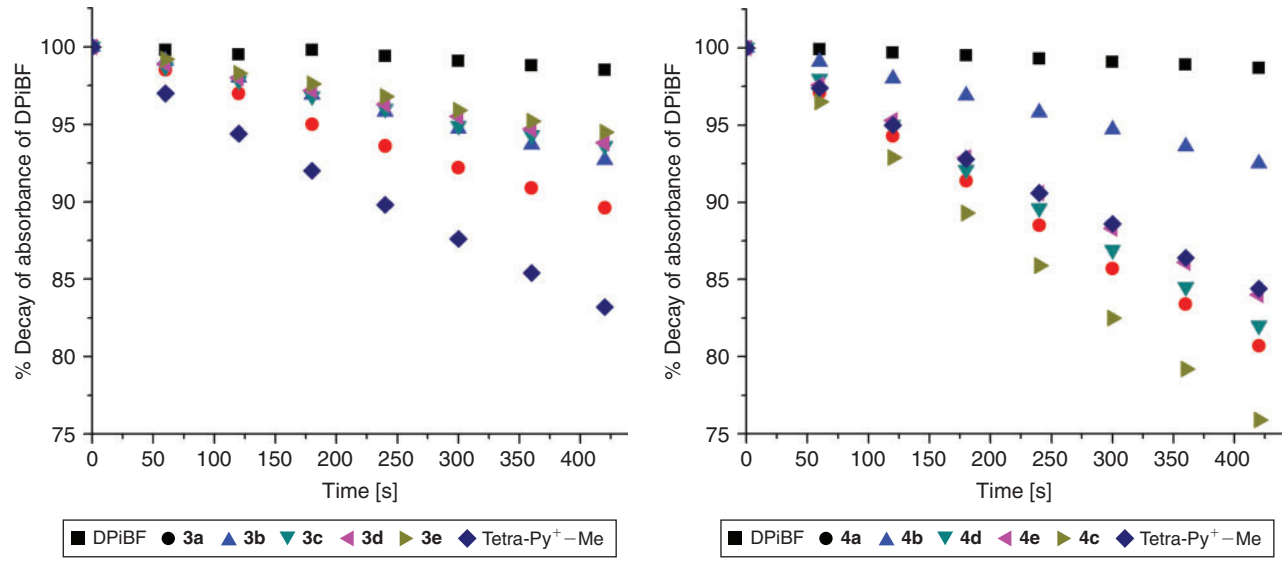


Fig. 1. Photodecomposition of 1,3-diphenylisobenzofuran (DPiBF) by singlet oxygen generated by porphyrin derivatives **3a**–**e** and **4a**–**e** after irradiation with white light filtered through a cut-off filter for wavelengths <550 nm (9 mW cm^{-2}). The tetracationic porphyrin *meso*-tetrakis(1-methylpyridinium-4-yl) porphyrin (Tetra-Py^+-Me) was used as a reference.

Table 1. Rate of $^1O_2$ production
(Tetra-Py^+-Me: *meso*-tetrakis(1-methylpyridinium-4-yl)porphyrin)

Porphyrin derivative	–Slope[A] [s^{-1}]
3a	0.025
3b	0.018
3c	0.015
3d	0.015
3e	0.013
4a	0.045
4b	0.018
4c	0.058
4d	0.043
4e	0.038
Tetra-Py^+-Me	0.038

[A]Values of slope of the plots of absorbance of 1,3-diphenylisobenzofuran in *N*,*N*-dimethylformamide/H_2O (9/1) versus illumination time.

Photostability of the Compounds

Porphyrins can undergo photobleaching when exposed to UV-vis light and oxygen.[16] The rate of photodegradation of a photosensitizer exposed to light is a very important parameter to assess for PDT application, because a fast photobleaching would cause the concentration of the drug to decrease, thus impairing the effectiveness of the treatment. To induce photobleaching, aerated solutions of compounds **3a**–**e** and **4a**–**e** in *N*,*N*-dimethylformamide (DMF)/water (9/1), under magnetic stirring, were irradiated with white light at a fluence rate of 40 mW cm^{-2}. For all studied compounds, the UV-vis spectra registered at different times of irradiation did not show any absorbance decay of the Soret and Q bands during the total irradiation period (30 min). The results point out that all studied porphyrin derivatives are highly stable under such conditions. As an example, the UV-vis spectra of compound **3a** before and after 30 min of irradiation are shown in Fig. 2.

Conclusions

The synthesis of 10 new porphyrin–phosphoramidates is described. The compounds were obtained in satisfactory yields by nucleophilic aromatic substitution of fluorine atoms in the *para*-position of the pentafluorophenyl groups of *meso*-tetrakis(pentafluorophenyl)porphyrin (**1**) with aminoalkylphosphoramidates (**2a**–**e**). The evaluation of the photodecomposition of 1,3-diphenylisobenzofuran in the presence of the new porphyrin derivatives **3a**–**e** and **4a**–**e** has shown that compound **4c** is the best singlet oxygen generator, being more efficient than Tetra-Py^+-Me. The photostability results point out that all new compounds are very photostable. Non-linearity was observed between the chain length of the aminoalkyl spacer of the phosphoramidate group and the photophysical properties of the photosensitizers. On the other hand, the introduction of the polar phosphoramidate ester moieties in both series **3** and **4** is related to a polarity increase for such porphyrins in relation with the unsubstituted *meso*-tetrakis(pentafluorophenyl)porphyrin. Further studies on the properties of these new porphyrin derivatives are currently under investigation in our laboratories.

Experimental

^1H, ^{19}F, and ^{31}P NMR spectra were recorded on a Bruker Avance 300 spectrometer at 300.13, 282.38, and 121.50 MHz, respectively. $CDCl_3$ was used as solvent (except when indicated). Chemical shifts are reported in ppm (δ) and coupling constants (J) are given in Hz. Mass spectra and HRMS were recorded on VG AutoSpec Q and M mass spectrometers. The UV-vis spectra were recorded on a Uvikon spectrophotometer. Melting points were measured on a Reichert Thermovar apparatus and are uncorrected. Flash chromatography was carried out with silica gel 35–70 mesh (Merck). Analytical TLC was carried out on precoated sheets with silica gel (0.2 mm thick, Merck). The aminoalkylphosphoramidates **2a**–**e** were synthesized in 50–53% yield from diisopropylphosphonate and aliphatic diamines, as described by Costa de Souza et al.[11] In order to guarantee monophosphorylation of the diamines, at least a 2.5-fold excess of

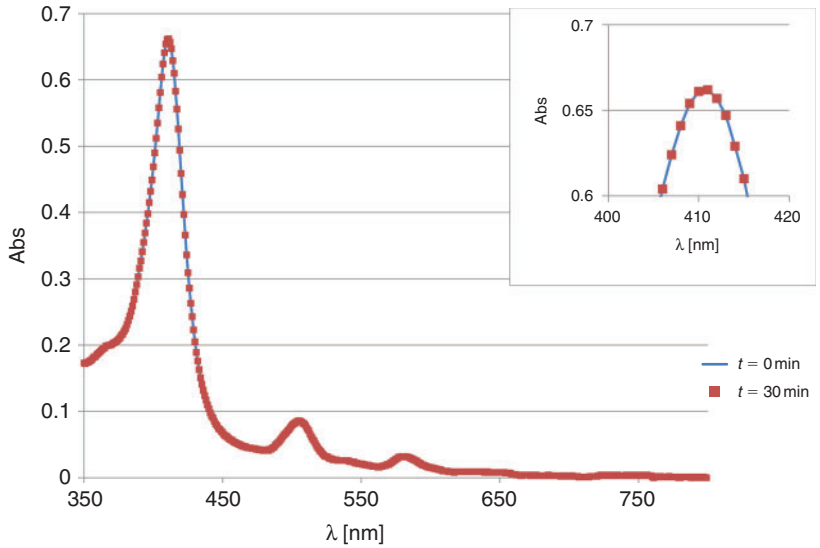


Fig. 2. Photostability of **3a** after irradiation with white light (400–800 nm) at a fluence rate of 40 mW cm^{-2}. Inset: expansion of Soret Band.

diamine in ethanol was employed to maintain the (alkaline) pH necessary to catalyze the reaction. Careful addition of diisopropylphosphonate in ethanol and carbon tetrachloride over the diamine solution should not exceed 10 min and the temperature must not be allowed to increase above 55–65°C, otherwise bis-phosphorylation will occur preferentially.

*Monosubstituted Porphyrin–Phosphoramidates **3a**–**e**: General Procedure*

Porphyrin **1** (0.04 mmol) and the aminoalkylphosphoramidate **2a**–**e** (0.02 mmol) were dissolved in toluene (5 mL). Triethylamine (1 mL) was added to this solution and the reaction mixture was heated at reflux until the disappearance of the starting aminoalkylphosphoramidate (8–12 h, monitored by TLC). After cooling to room temperature, the mixture was diluted with chloroform and washed with water (3 × 5 mL). The solvent was evaporated under reduced pressure and the crude solid was purified by preparative TLC using ethyl acetate as the eluent. Compounds **3a**–**e** were recrystallized from chloroform/methanol (1/3).

*5-(4-{[2-(Diisopropoxyphosphorylamino)ethyl]amino}-2,3,5,6-tetrafluorophenyl)-10,15,20-tris (pentafluorophenyl)porphyrin (**3a**)*

Compound **3a** was obtained in 71% yield (16.7 mg), mp >300°C. δ_H −2.91 (s, 2H, NH), 1.42, 1.43 (2d, *J* 6.2, 12H, CH_3), 2.92 (dd, *J* 6.8 and 16.8, 1H, NH–P), 3.40 (dt, *J* 6.8 and 11.6, 2H, CH_2NHP), 3.82 (br s, 2H, CH_2NH), 4.73 (dhep, *J* 6.2 and 7.4, 2H, CH), 5.01 (br s, 1H, N*H*CH_2), 8.87–9.04 (m, 8H, H-β). δ_F −185.08 to −184.80 (m, 6F, F-*meta*), −183.94 (d, *J* 19.3, 2F, F-*meta*), −175.00 to −174.94 (m, 3F, F-*para*), −164.10 (dd, *J* 5.1 and 19.3, 2F, F-*ortho*), −160.00 (dd, *J* 8.1 and 23.8, 6F, F-*ortho*). δ_P 8.02. λ_{max}/nm (log ε) 415 (5.38), 508 (4.28), 585 (3.78). *m/z* HRMS (FAB^+). Calc. for $C_{52}H_{31}F_{19}N_6O_3P$ $(M+H)^+$: 1179.1892. Found: 1179.1886.

*5-(4-{[3-(Diisopropoxyphosphorylamino)propyl]amino}-2,3,5,6-tetrafluorophenyl)-10,15,20-tris (pentafluorophenyl)porphyrin (**3b**)*

Compound **3b** was obtained in 83% yield (19.8 mg), mp >300°C. δ_H −2.91 (s, 2H, NH), 1.39, 1.40 (2d, *J* 6.1, 12H, CH_3), 2.01 (quint, *J* 6.3, 2H, $CH_2CH_2CH_2$), 2.34 (br s, 1H, NH–P), 2.68 (br s, 1H, N*H*CH_2), 3.24 (dt, *J* 6.3 and 10.3, 2H, CH_2NHP), 3.82 (t, *J* 6.3, 2H, CH_2NH), 4.69 (dhep, *J* 6.1 and 7.2, 2H, CH), 8.87–9.04 (m, 8H, H-β). δ_F −185.08 to −184.86 (m, 6F, F-*meta*), −184.27 (dd, *J* 4.3 and 19.3, 2F, F-*meta*), −175.01 to −174.87 (m, 3F, F-*para*), −164.21 (dd, *J* 4.8 and 19.3, 2F, F-*ortho*), −160.00 (dd, *J* 8.1 and 23.7, 6F, F-*ortho*). δ_P 8.23. λ_{max}/nm (log ε) 415 (5.40), 509 (4.33), 585 (3.84). *m/z* HRMS (FAB^+). Calc. for $C_{53}H_{33}F_{19}N_6O_3P$ $(M+H)^+$: 1193.2048. Found: 1193.2043.

*5-(4-{[4-(Diisopropoxyphosphorylamino)butyl]amino}-2,3,5,6-tetrafluorophenyl)-10,15,20-tris (pentafluorophenyl)porphyrin (**3c**)*

Compound **3c** was obtained in 63% yield (15.2 mg), mp >300°C. δ_H −2.91 (s, 2H, NH), 1.36, 1.39 (2d, *J* 6.2, 12H, CH_3), 1.73, 1.86 (2 m, 4H, CH_2CH_2NP and CH_2CH_2NH), 2.57 (br s, 1H, NH–P), 3.08 (m, 2H, CH_2NHP), 3.73 (m, 2H, CH_2NH), 4.34 (br s, 1H, N*H*CH_2), 4.66 (dhep, *J* 6.2 and 7.5, 2H, CH), 8.87–9.04 (m, 8H, H-β). δ_F −185.07 to −184.85 (m, 6F, F-*meta*), −184.37 (dd, *J* 4.9 and 19.8, 2F, F-*meta*), −175.00 to −174.94 (m, 3F, F-*para*), −164.08 (dd, *J* 5.2 and 19.8, 2F, F-*ortho*), −160.00 (dd, *J* 8.0 and 23.5, 6F, F-*ortho*). δ_P 7.84. λ_{max}/nm (log ε) 415 (5.40), 508 (4.31), 585 (3.85). *m/z* HRMS (FAB^+). Calc. for $C_{54}H_{35}F_{19}N_6O_3P$ $(M+H)^+$: 1207.2205. Found: 1207.2199.

*5-(4-{[5-(Diisopropoxyphosphorylamino)pentyl]amino}-2,3,5,6-tetrafluorophenyl)-10,15,20-tris (pentafluorophenyl)porphyrin (**3d**)*

Compound **3d** was obtained in 81% yield (19.8 mg), mp >300°C. δ_H −2.91 (s, 2H, NH), 1.36 (d, *J* 6.2, 12H, CH_3), 1.64, 1.86 (2m, 6H, $(CH_2)_3CH_2$NHP), 2.53 (br s, 1H, NH–P), 3.00 (m, 2H, CH_2NHP), 3.70 (t, *J* 6.8, 2H, CH_2NH), 4.64 (dhep, *J* 6.2 and 7.4, 2H, CH), 8.87–9.04 (m, 8H, H-β). δ_F −185.08 to −184.85 (m, 6F, F-*meta*), −184.42 (dd, *J* 4.8 and 19.9, 2F, F-*meta*), −175.00 to −174.96 (m, 3F, F-*para*), −164.19 (dd, *J* 5.1 and 19.9, 2F, F-*ortho*), −160.01 (dd, *J* 8.0 and 23.6, 6F, F-*ortho*). δ_P 7.92. λ_{max}/nm (log ε) 415 (5.40), 508 (4.32), 585 (3.86). *m/z* HRMS (FAB^+). Calc. for $C_{55}H_{37}F_{19}N_6O_3P$ $(M+H)^+$: 1221.2361. Found: 1221.2356.

*5-(4-{[6-(Diisopropoxyphosphorylamino)hexyl]amino}-2,3,5,6-tetrafluorophenyl)-10,15,20-tris (pentafluorophenyl)porphyrin (**3e**)*

Compound **3e** was obtained in 65% yield (16.1 mg), mp >300°C. δ_H −2.90 (s, 2H, NH), 1.34, (d, *J* 6.2, 12H, CH_3), 1.58 (m, 6H, $(CH_2)_3CH_2NH$), 1.85 (m, 2H, CH_2CH_2NHP), 2.49 (br s, 1H, NH–P), 2.97 (dd, *J* 7.2 and 15.0, 2H, CH_2NHP), 3.70 (t, *J* 6.9, 2H, CH_2NH), 4.62 (dhep, *J* 6.2 and 7.3, 2H, CH), 8.87–9.04 (m, 8H, H-β). δ_F −185.10 to −184.88 (m, 6F, F-*meta*), −184.44 (dd, *J* 4.5 and 19.5, 2F, F-*meta*), −175.03 to −174.98 (m, 3F, F-*para*), −164.22 (dd, *J* 5.1 and 19.5, 2F, F-*ortho*), −160.02 (dd, *J* 8.0 and 23.5, 6F, F-*ortho*). δ_P 7.91. λ_{max}/nm (log ε) 415 (5.42), 508 (4.34), 585 (3.86). *m/z* HRMS (FAB^+). Calc. for $C_{56}H_{39}F_{19}N_6O_3P$ $(M+H)^+$: 1235.2518. Found: 1235.2512.

*Tetrasubstituted Porphyrin–Phosphoramidates **4a–e**: General Procedure*

Porphyrin **1** (0.04 mmol) and the aminoalkylphosphoramidate **2a–e** (0.4 mmol; 2.5 equiv./aryl group) were dissolved in toluene (5 mL) and the reaction mixture was heated at reflux until the disappearance of the starting porphyrin (56–72 h, monitored by TLC). After cooling to room temperature, the mixture was diluted with chloroform and washed with water (3 × 5 mL). The solvent was evaporated under reduced pressure and the crude solid was purified by column chromatography (silica gel) using ethyl acetate/methanol (97/3) as the eluent. Compounds **4a**–**e** were recrystallized from chloroform/methanol (1/3).

*5,10,15,20-Tetrakis(4-{[2-(diisopropoxyphosphorylamino)ethyl]amino}-2,3,5,6-tetrafluorophenyl)porphyrin (**4a**)*

Compound **4a** was obtained in 50% yield (35.8 mg), mp >300°C. δ_H −2.85 (s, 2H, NH), 1.41, 1.42 (2d, *J* 6.1, 48H, CH_3), 3.01 (dd, *J* 6.7 and 16.4, 4H, NH–P), 3.38 (dt, *J* 6.7 and 11.4, 8H, CH_2NHP), 3.80 (m, 8H, CH_2NH), 4.72 (dhep, *J* 6.1 and 7.3, 8H, CH), 4.95 (br s, 4H, $NHCH_2$), 8.95 (s, 8H, H-β). δ_F −184.15 (d, *J* 19.6, 8F, F-*meta*), −163.9 (dd, *J* 5.2 and 19.6, 8F, F-*ortho*). δ_P 7.9. λ_{max}/nm (log ε) 422 (5.47), 512 (4.34), 588 (3.89). *m/z* HRMS (FAB^+). Calc. for $C_{76}H_{92}F_{16}N_{12}O_{12}P_4$ $(M+2H)^{2+}$: 896.2826. Found: 896.2821.

*5,10,15,20-Tetrakis(4-{[3-(diisopropoxyphosphorylamino)propyl]amino}-2,3,5,6-tetrafluorophenyl)porphyrin (**4b**)*

Compound **4b** was obtained in 77% yield (56.9 mg), mp >300°C. δ_H −2.86 (s, 2H, NH), 1.39, 1.41 (2d, *J* 6.1, 48H, CH_3), 2.01 (m, 8H, $CH_2CH_2CH_2$), 2.68 (dd, *J* 6.9 and 15.5, 4H, NH–P), 3.24 (dt, *J* 6.9 and 12.9, 8H, CH_2NHP), 3.81 (m, 8H, CH_2NH), 4.58 (br s, 4H, $NHCH_2$), 4.69 (dhep, *J* 6.1 and 7.3, 8H, CH), 8.95 (s, 8H, H-β). δ_F −184.41 (d, *J* 19.6, 8F, F-*meta*), −164.00 (dd, *J* 5.2 and 19.6, 8F, F-*ortho*). δ_P 8.2 λ_{max}/nm (log ε) 422 (5.31), 512 (4.17), 589 (3.76). *m/z* HRMS (FAB^+). Calc for $C_{80}H_{100}F_{16}N_{12}O_{12}P_4$ $(M+2H)^{2+}$: 924.3139. Found: 924.3134.

*5,10,15,20-Tetrakis(4-{[4-(diisopropoxyphosphorylamino)butyl]amino}-2,3,5,6-tetrafluorophenyl)porphyrin (**4c**)*

Compound **4c** was obtained in 75% yield (57.1 mg), mp >300°C. δ_H −2.86 (s, 2H, NH), 1.37 (d, *J* 6.2, 48H, CH_3), 1.76, 1.89 (2 m, 16H, CH_2CH_2NP and CH_2CH_2NH), 2.60 (br s, 4H, NH–P), 3.08 (m, 8H, CH_2NHP), 3.72 (t, *J* 6.7, 8H, CH_2NH), 4.27 (br s, 4H, $NHCH_2$), 4.67 (dhep, *J* 6.2 and 7.5, 8H, CH), 8.95 (s, 8H, H-β). δ_F −184.33 (d, *J* 19.5, 8F, F-*meta*), −163,97 (dd, *J* 5.3 and 19.5, 8F, F-*ortho*). δ_P 7.9. λ_{max}/nm (log ε) 422 (5.38), 512 (4.27), 588 (3.80). *m/z* HRMS (FAB^+). Calc. for $C_{84}H_{108}F_{16}N_{12}O_{12}P_4$ $(M+2H)^{2+}$: 952.3452. Found: 952.3447.

*5,10,15,20-Tetrakis(4-{[5-(diisopropoxyphosphorylamino)pentyl]amino}-2,3,5,6-tetrafluorophenyl)porphyrin, **4d***

Compound **4d** was obtained in52% yield (40.8 mg), mp >300°C. δ_H −2.86 (s, 2H, NH), 1.36 (d, *J* 6.0, 48H, CH_3), 1.63, 1.85 (2 m, 24H, $(CH_2)_3CH_2NHP$), 2.54 (br s, 4H, NH–P), 3.00 (m, 8H, CH_2NHP), 3.69 (t, *J* 6.1, 8H, CH_2NH), 4.25 (br s, 4H, $NHCH_2$), 4.63 (dhep, *J* 6.0 and 7.3, 8H, CH), 8.95 (s, 8H, H-β). δ_F −184.56 (d, *J* 19.4, 8F, F-*meta*), −164,03 (dd, *J* 5.3 and 19.4, 8F, F-*ortho*). δ_P 7.8. λ_{max}/nm (log ε) 422 (5.44), 512 (4.30), 588 (3.83). *m/z* HRMS (FAB^+) Calc. for $C_{88}H_{116}F_{16}N_{12}O_{12}P_4$ $(M+2H)^{2+}$: 980.3765. Found: 980.3760.

*5,10,15,20-Tetrakis(4-{[6-(diisopropoxyphosphorylamino)hexyl]amino}-2,3,5,6-tetrafluorophenyl)porphyrin (**4e**)*

Compound **4e** was obtained in 64% yield (51.6 mg), mp >300°C. δ_H −2.86 (s, 2H, NH), 1.32, 1.36 (2d, *J* 6.1, 48H, CH_3), 1.43 (m, 16H, $CH_2(CH_2)_2NHP$ and $CH_2(CH_2)_3NHP$), 1.84 (m, 16H, CH_2CH_2NHP and $CH_2CH_2NH_2$), 2.56 (br s, 4H, NH–P), 2.92 (m, 8H, CH_2NHP), 3.70 (m, 8H, CH_2NH), 4.26 (br s, 4H, $NHCH_2$), 4.62 (m, 8H, CH), 8.95 (s, 8H, H-ββ). δ_F −184.61 (d, *J* 19.9, 8F, F-*meta*), −164.08 (dd, *J* 5.2 and 19.9, 8F, F-*ortho*). δ_P 7.9. λ_{max}/nm (log ε) 423 (5.20), 513 (4.10), 590 (3.68).

Singlet Oxygen Generation and Photostability Studies

A stock solution of each porphyrin derivative at 0.1 mM in DMF/H_2O (9/1) and a stock solution of DPiBF at 10 mM in dimethyl sulfoxide (DMSO) were prepared. The reaction mixture of 10 μL of DPiBF and 10 μL of a porphyrin derivative in DMF/water (9/1) in glass cells (2 mL) was irradiated with white light filtered through a cut-off filter of wavelengths <550 nm, at a fluence rate of 9.0 mW cm^{-2}. During the irradiation period the solutions were stirred at room temperature. The breakdown of DPiBF was monitored by measuring the decreasing of the absorbance at 415 nm at irradiation intervals of 1 min.

The photostability of the photosensitizers was determined by irradiating 2 mL of 2 μM solutions of the porphyrins in DMF/H_2O (9/1) with white light (400–800 nm) at fluence rate of 40 mW cm^{-2}. During such irradiation the solutions were magnetically stirred and kept at room temperature. The concentration of the porphyrin derivative was quantified by visible absorption spectrophotometry at regular intervals.

Acknowledgements

The authors thank CNPq-Brazil and CAPES (Brazil)-GRICES/FCT (Portugal) joint protocol for funding. The authors also thank the Organic Chemistry Research Unit of the University of Aveiro. The authors acknowledge the Portuguese National NMR Network, supported from Fundação para a Ciência e a Tecnologia (FCT).

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