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Synthesis and characterization of biocompatible bimodal *meso*-sulfonamide-perfluorophenylporphyrins

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ABSTRACT

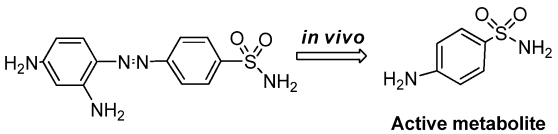
Herein we describe a synthetic strategy for preparing a set of *meso*-aryl sulfonamide-perfluorinated porphyrins by covalent binding in order to obtain new chemical entities that can potentially target bacteria and act both as bacteriostatic and photosensitizing agents. The conditions optimized allow to selectively obtain porphyrins containing the desired number of sulfonamide substituents. The new compounds showed a broad range of 1-octanol/water partition coefficients and singlet oxygen quantum yields from 0.59 to 0.74. Our results demonstrate that sulfonamide-perfluorinated porphyrins are a promising platform for biomedical applications, particularly in aPDT and medical imaging.

1. Introduction

The presence of fluorine atoms in organic compounds with potential application in pharmacology has been increasingly exploited in recent years [1–4]. Notably, nearly 20% of pharmaceutical compounds contain at least one fluorine atom nowadays [5], since it is well established that the replacement of a hydrogen by an electronegative fluorine atom, with C–F bond energy of 105.4 kcal/mol, can significantly influence pharmacological outcomes, metabolic stability, selectivity and physical properties. [6,7,1] Thus, the development and optimization of new organic molecules bearing fluorine atoms in their constitution is an area of increasing interest in medicinal chemistry. In addition, in our previous studies [8–10], we have demonstrated that the presence of fluorine atoms in a sulfonamide-tetrapyrrolic macrocycles originated photosensitizers with ideal PDT photophysical properties and/or remarkable photostability [11–21].

Sulfonamides are celebrated antibacterial agents since 1930, owing to the discovery of Prontosil (Scheme 1) and the recognition that sulfonamides can inhibit the enzyme dihydropteroate synthase [22,23]. Numerous active antibiotics containing this class of compounds have been discovered and marketed [23,24], but they have the major drawback of originating antibiotic-resistant bacteria [25,26]. According to the World Health Organization, National data obtained for *E. coli*, *S.* and *K. pneumoniae*, and *S. aureus* showed that the proportion resistant to commonly used antibacterial drugs exceeded 50% in many settings [27].

The development of new molecular entities capable of promoting the inactivation of bacteria without developing drug resistance depends on finding alternative mechanisms of action for antibiotics. Antimicrobial photodynamic therapy (aPDT) [28,29] is emerging as an alternative to classical antibiotics because aPDT is not associated with the development of microorganism resistance after treatment [30–32]. The most successful photosensitizing agents used in aPDT are porphyrin derivatives. The appropriate design and structural modulation of tetrapyrrolic macrocycles to enhance membrane permeation in all classes of microbial cells, along with appropriate photophysical properties, may drive aPDT to a clinically acceptable alternative to antibiotics.



Scheme 1. *In vivo* metabolism of Prontosil.

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The synthetic difficulties and scarce availability of natural porphyrinoids [29,33,34], led to the use of *meso*-substituted tetrapyrrolic macrocycles, easily obtained by sustainable synthetic methods [12,35–38], as the main choice for the development of new generations of PDT agents [8,9,39]. 5,10,15,20-Tetrakis(pentafluorophenyl)porphyrin (TPFPP) is an interesting template to functionalize *via* nucleophilic substitution reactions [40], making use of nucleophiles such as amines, thiols, alcohols and nitrogen heterocycles [41,42], to improve their avidity for bacteria. However, to the best of our knowledge, the use of sulfonamides as nucleophiles in this functionalization has not yet been described.

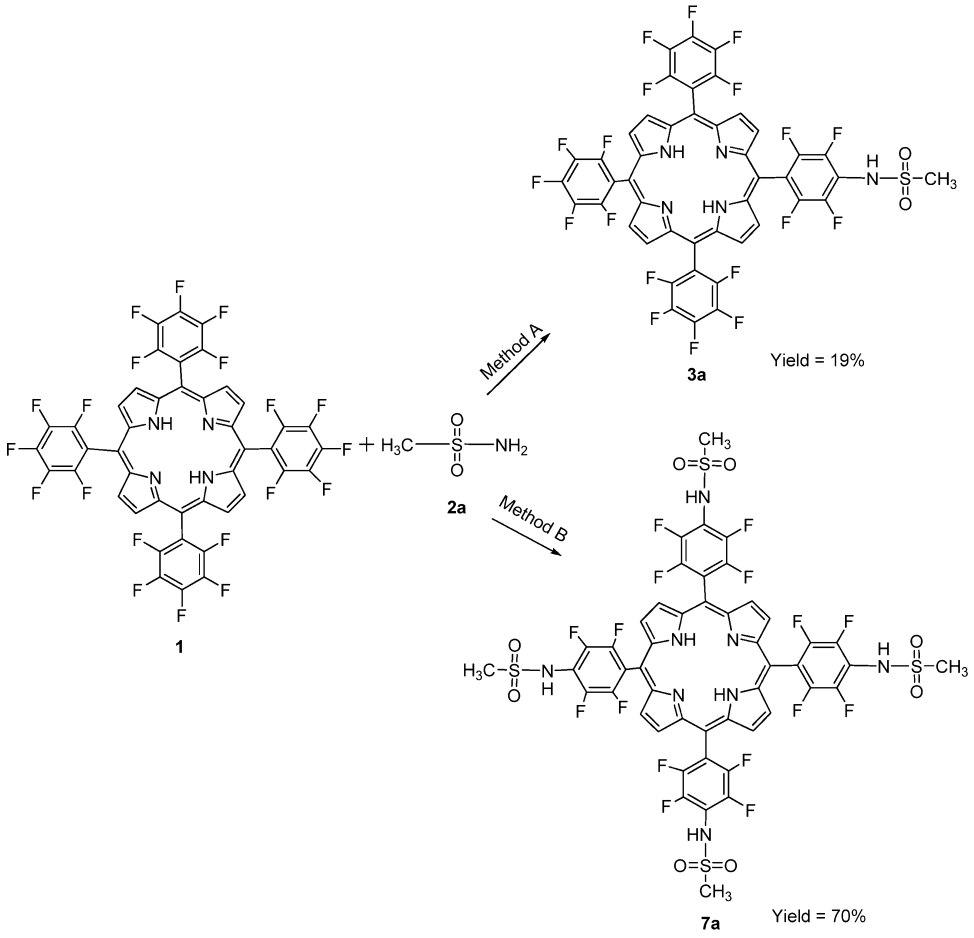
This work presents new methods for the synthesis of bimodal molecules that incorporate sulfonamides and 5,10,15,20-tetrakis(pentafluorophenyl)porphyrin in their structure, in order to attain new chemical entities that can potentially target bacteria and act both as bacteriostatic and photosensitizing agents. Additionally, this work presents the fundamental photophysical assessment of the new photosensitizers, namely in terms of their electronic absorptions, singlet oxygen quantum yields and 1-octanol/water partition coefficients. Our results show that sulfonamide TPFPPs are a promising platform for biomedical applications, particularly in aPDT and medical imaging.

2. Results and discussion

In order to prepare *meso*-aryl fluorinated porphyrins containing sulfonamide groups, we first synthesized 5,10,15,20-tetrakis(pentafluorophenyl)porphyrin **1** following our recent improvement of the nitrobenzene synthetic methodology [43]. NaY was used as recoverable Lewis acid catalyst for the condensation of pyrrole with pentafluorobenzaldehyde in an acetic acid/nitrobenzene mixture [35], yielding the desired porphyrin **1** in 9% yield. Next, the studies to selectively prepare the mono or tetra-substituted fluorinated-sulfonamide porphyrins were carried out using the commercially available methanesulfonamide as nucleophile (Scheme 2).

As expected, the concentration of the reactants was crucial to selectively obtain the mono *vs* tetrasubstituted compound. In a typical experiment, the fluorinated porphyrin **1** was dissolved in dioxane (5.1×10^{-3} M), mixed with six equivalents of methanesulfonamide (**2a**) and six equivalents of cesium carbonate (Scheme 2, Method A). Then, the reaction was kept at 100 °C for several hours. After work up the crude was purified by silica gel column chromatography (*n*-hexane:ethyl acetate 2:1), followed by preparative thin layer chromatography, affording the 5-[2′,3′,5′,6′-tetrafluoro-4′-methanesulfamoyl)phenyl]-10,15,20-tri-[(2′,3′,4′,5′,6′-penta-fluoro)phenyl]porphyrin **3a** in 19% yield (entry 1, Table 1).

In order to prepare the tetrasubstituted compound, the reaction conditions were changed by increasing the porphyrin concentration to 1.0×10^{-2} M and the ratio porphyrin:sulfonamide:base to 1:18:12 (Scheme 2, Method B). After 48 h at 100 °C, the initial porphyrin completely disappeared, concomitantly with the formation of a complex mixture of products observed by TLC. In addition, we carried out another reaction, under the same conditions, but increasing the concentration of porphyrin **1** to 1.5×10^{-2} M and, surprisingly, a dark solid precipitated out of the reaction, upon room temperature cooling. After filtration, the solid



Scheme 2. Synthesis of mono and tetra substituted fluorinated-sulfonamide porphyrins. Reaction conditions: Method A – porphyrin/sulfonamide ratio 1:6, $[C] = 5.1 \times 10^{-3}$ M; Method B – porphyrin/sulfonamide ratio 1:18, $[C] = 1.54 \times 10^{-2}$ M.

Table 1
Reaction products of 5,10,15,20-tetrakis(pentafluorophenyl)porphyrin **1** with sulfonamides **2a–c**.

Entry		R_2	R_3	R_4	R_5	Yield (%)
1	**3a**	F	F	F	$NHSO_2Me$	19[a]
2	**7a**	$NHSO_2Me$	$NHSO_2Me$	$NHSO_2Me$	$NHSO_2Me$	70[b]
3	**3b**	F	F	F	$NHSO_2PhMe$	4.5[a]
4	**4b,5b**	F	F	$NHSO_2PhMe$	$NHSO_2PhMe$	0.7[a]
5	**3c**	F	F	F	$NMeSO_2PhMe$	3.1[a]
6	**4c,5c**	F	F	$NMeSO_2PhMe$	$NMeSO_2PhMe$	1.5[a]
7	**6c**	F	$NMeSO_2PhMe$	$NMeSO_2PhMe$	$NMeSO_2PhMe$	0.6[a]

[a] Synthesized by Method A (porphyrin/sulfonamide ratio 1:6, $[C] = 5.1 \times 10^{-3}$ M).
[b] Synthesized by Method B (porphyrin/sulfonamide ratio 1:18, $[C] = 1.5 \times 10^{-2}$ M).

was washed with acetone, dissolved in water and purified *via* ultra-filtration membrane, using a 1 kDa Amicon membrane. After solvent evaporation and drying, we obtained 5,10,15,20-tetra-[(2′,3′,4′,5′,6′-methanesulfamoyl)phenyl]porphyrin **7a** in 70% yield (entry 2, Table 1).

Our methodology to selectively synthesize the mono or the tetrasubstituted compounds required careful adjustment of the concentrations of the reactants and of the porphyrin/sulfonamide ratio. The monosubstituted compound was obtained as the major product when the reaction was carried out with a porphyrin concentration of 5.1×10^{-3} M and an excess of six equivalents of sulfonamide was used (Scheme 2, Method A). The tetrasubstituted product required an excess of 18 sulfonamide equivalents and a porphyrin concentration of 1.54×10^{-2} M (Scheme 2, Method B).

Based on the conditions previously optimized for the preparation of monosubstituted sulfonamide porphyrin (5.1×10^{-3} M), we enlarged the reaction scope using *p*-toluenesulfonamide **2b** and *N*-methyl-*p*-toluenesulfonamide **2c** as nucleophiles. These sulfonamides were prepared in 48% and 94% isolated yields, respectively (Scheme 3 and Table 1, entries 3–7) by reacting *p*-toluenesulfonyl chloride with the corresponding amines.

The reaction of TPFPP with *p*-toluenesulfonamide **2b** (Scheme 3) at 100 °C for several hours afforded 5-[(2′,3′,5′,6′-tetrafluoro-4′-*p*-toluenesulfamoyl)phenyl]-10,15,20-tri-[(2′,3′,4′,5′,6′-pentafluoro)phenyl]porphyrin **3b** in 4.5% isolated yield and a mixture of 5,10-[(2′,3′,5′,6′-tetrafluoro-4′-*p*-toluenesulfamoyl)phenyl]-15,20-dis-[(2′,3′,4′,5′,6′-penta-fluoro)phenyl]porphyrin **4b** and 5,15-[(2′,3′,5′,6′-tetrafluoro-4′-p-toluenesulfamoyl)phenyl]-10,20-[(2′,3′,4′,5′,6′-pentafluoro)phenyl]porphyrin **5b** in 0.7% isolated yields, after preparative thin layer chromatography.

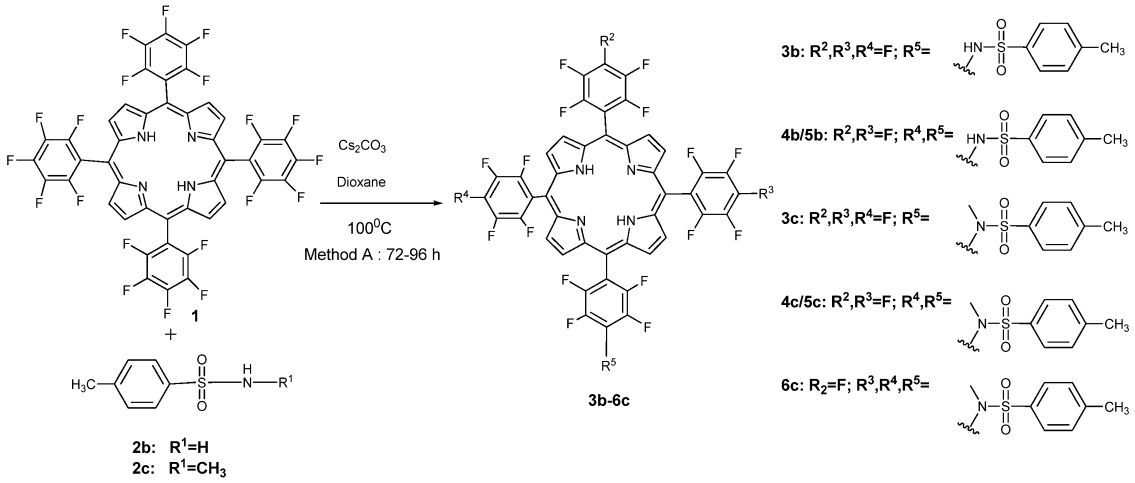
Nucleophilic substitution of 5,10,15,20-pentafluorophenyl porphyrin **1** with *N*-methyl-*p*-toluenesulfonamide **2c** (Scheme 3 yielded three products, namely 5-[(2′,3′,5′,6′-tetrafluoro-4′-*N*-methyl-*p*-toluenesulfamoyl)phenyl]-10,15,20-tri-[(2′,3′,4′,5′,6′-pentafluoro)phenyl]porphyrin **3c** (3.1% yield), a mixture of 5,10-[(2′,3′,5′,6′-tetrafluoro-4′-*N*-methyl-*p*-toluenesulfamoyl)phenyl]-15,20-dis-[(2′,3′,4′,5′,6′-pentafluoro)phenyl]porphyrin **4c** and 5,15-[(2′,3′,5′,6′-tetrafluoro-4′-*N*-methyl-*p*-toluenesulfamoyl)phenyl]-10,20-[(2′,3′,4′,5′,6′-pentafluoro)phenyl]porphyrin **5c**, (1.5% yield) together with 5,10,15-tri-[(2′,3′,5′,6′-tetrafluoro-4′-*N*-methyl-*p*-toluenesulfamoyl)phenyl]-20-[(2′,3′,4′,5′,6′-pentafluoro)phenyl]porphyrin **6c** (0.6% yield) (Table 1, entries 5–7).

As selected example the ^{19}F NMR spectra of the hydrophilic porphyrin **7a** is presented in Fig. 1.

As expected, ^{19}F NMR aromatic signals appeared as double doublets around $\delta \approx -144.71$ and -152.19 ppm, corresponding to the symmetric substitution pattern present in porphyrin **7a**. These narrow intense peaks shown by ^{19}F NMR allow them to be potential probes for ^{19}F MRI. These fluorinated amphiphilic compounds may find use as ^{19}F MRI probes for cancer detection because the fluorine atom has 100% NMR active isotope with intrinsic high sensitivity in biological systems [44], and it is well established that porphyrins preferentially accumulate in tumors [45].

We also evaluated the effect of the number of sulfonamide substituents on the 1-octanol/water partition coefficients using a minor modification of the shake-flask method [46–48]. The desired sulfonamide porphyrin was dissolved in 1-octanol saturated with phosphate buffer (PBS). This solution was then added to a PBS solution saturated with 1-octanol. The mixture of the two solvents was vigorously stirred, centrifuged and the solvents were separated. An appropriate volume of each phase was taken and a volume of pure 1-octanol should be added keeping equal dilutions of organic and water parts containing the compound. Optical absorption of the 1-octanol and of the PBS fractions were used to determine the logarithm of the partition coefficient, $\log P_{OW} = \log (A_{1\text{-oct}}/A_{PBS})$. Additionally, a correlation curve between experimental [10] and computational data of LogP was constructed for a family of sulfonamide-substituted porphyrins and their derivatives. The computational approach was made using the program Marvin Sketch 14.10.6.0. The results are presented in Table 2.

Upon analysis of the correlation curve, we could observe that the compounds presenting lower LogP (less lipophilic) were derivatives **3a** and **7a**. The determination of their experimental



Scheme 3. Synthesis of substituted fluorinated-sulfonamide porphyrins.

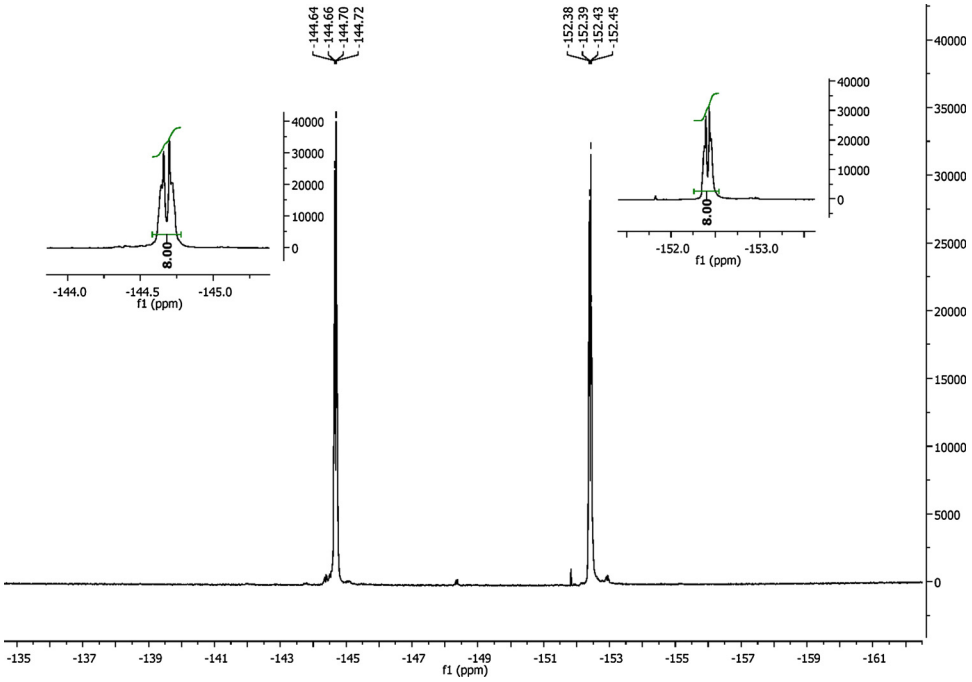


Fig. 1. ^{19}F NMR spectrum of the porphyrin **7a** in DMSO.

LogP gave values of LogP > 4 and LogP = 0.94, respectively, reason why we did not perform the experimental determination of the LogP values for the other compounds, since our LogP determination method is limited to values of LogP ≤ 4.

The log P_{OW} values of porphyrins **3a** and **7a** show that the number of methanesulfonamide fragments is crucial to modulate the amphiphilicity of the compounds. Whereas porphyrin **3a** (bearing just one sulfonamide substituent) displays a log $P_{OW} > 4$, meaning that the compound is very hydrophobic, porphyrin **7a** shows a value of log P_{OW} of 0.94 suggesting that this compound is the most biocompatible photosensitizer of the series.

The ground state absorption spectrum of sulfonamide porphyrins, recorded at room temperature in toluene (compounds **3**–**6**) and DMSO (**7a**) is presented in Fig. 2. The spectrum shows the characteristic bands from free base porphyrins with the D_{2h} symmetry, described by Gouterman's four orbitals model [49]. The intense Soret band is observed around 410 nm and four bands between 500 and 650 nm are assigned to the Q_x and Q_y (0,0) bands and their (1,0) vibronic progressions (Table 2). Using the measured absorbance for several concentrations, the molar absorption coefficients were determined using Beer's law. Their absorption band maxima and corresponding molar absorption coefficients are presented in Table 3. As expected, the compounds display their maxima peaks around similar wavelengths as well as similar molar absorption coefficient.

Table 2
Partition coefficients (log P_{OW}) in 1-octanol/water of sulfonamide porphyrin derivatives: theoretical, experimental, and values obtained from correlation curve ($^{+}$CC).

Sulfonamide derivatives	LogP theoretical	LogP $^{+}$CC	LogP experimental
3a	11.26	6.09	>4
3b	14.19	7.69	–
3c	14.4	7.80	–
4b/5b	14.92	8.09	–
4c/5c	15.34	8.32	–
6c	16.29	8.84	–
7a	4.68	2.49	0.94

The phototoxicity of porphyrin photosenstizers is mostly due to energy transfer from the porphyrin excited triplet state to molecular oxygen, with the formation of singlet oxygen [10]. This electronically excited state of molecular oxygen can oxidize a variety of biomolecules and trigger cell death mechanisms [50]. Hence, we measured the singlet oxygen quantum yields (ϕ_Δ) of the porphyrins synthesized in this work to assess their potential as PDT photosensitizers. The values of ϕ_Δ were obtained by comparing the intensities of singlet oxygen emission at 1270 nm in an air-equilibrated samples containing a given sensitizer against the intensity obtained from an optically matched sample containing a reference sensitizer, as a function of the pulsed laser excitation energy [11]. We used phenalenone as a reference and used its literature value for the singlet oxygen quantum yield in toluene, 0.98 [51]. All the compounds showed suitable singlet oxygen quantum yield for photosensitization applications, although the tertiary amines seemed to have lower ϕ_Δ values.

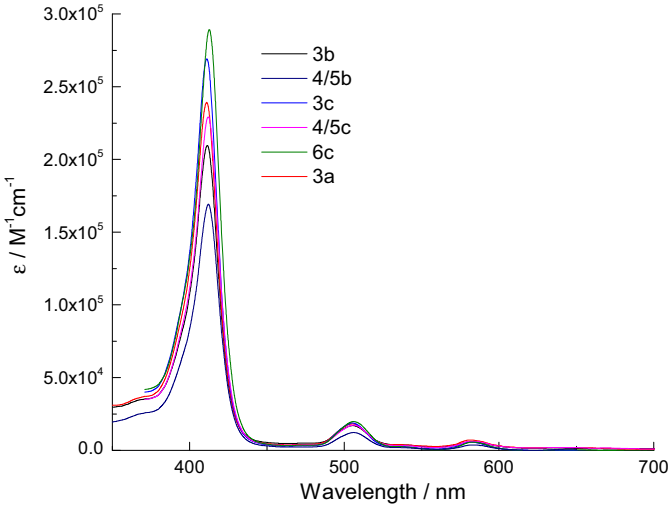


Fig. 2. Absorption spectra of the porphyrin derivatives here described, recorded in toluene.

Table 3
Absorption coefficients and singlet oxygen quantum yields for selected porphyrin derivatives.

Entry	Porphyrin	Absorption/nm (ε/M^{-1} cm^{-1})					
		B(0-0)	Qy(1,0)	Qy(0,0)	Qx(1,0)	Qx(0,0)	Φ_Δ
1	**3a**	411 (2.4×10^5)	505 (1.4×10^4)	Shoulder	582 (4.5×10^3)	636 (6.6×10^2)	0.74
2	**3b**	411 (2.1×10^5)	506 (1.7×10^4)	Shoulder	583 (5.4×10^3)	637 (8.2×10^2)	0.70
3	**3c**	411 (2.7×10^5)	505 (1.7×10^4)	Shoulder	582 (5.3×10^3)	636 (8.3×10^2)	0.66
4	**4b/5b**	412 (1.7×10^5)	506 (1.2×10^4)	Shoulder	583 (4.0×10^3)	644 (1.3×10^3)	0.71
5	**4c/5c**	412 (2.3×10^5)	506 (1.8×10^4)	Shoulder	583 (5.7×10^3)	642 (1.1×10^3)	0.63
6	**6c**	413 (2.9×10^5)	506 (1.7×10^4)	Shoulder	583 (5.6×10^3)	640 (9.6×10^2)	0.59
7	**7a**	413 (5.8×10^4)	509 (6.6×10^3)	Shoulder	585 (2.8×10^3)	638 (6.3×10^2)	0.70

3. Conclusions

Sulfonamides of perfluorophenylporphyrins can be prepared in large yields. It is specially noteworthy that adequate choices of the concentration of the starting perfluorophenylporphyrin and of the porphyrin/sulfonamide ratio can lead to very high isolated yields of mono or tetrasubstituted sulfonamide perfluorophenylporphyrins. The ability to control the degree of substitution is particularly useful to modulate the amphiphilicity of these photosensitizers. Surprisingly, the tetrasubstituted sulfonamide perfluorophenylporphyrin combines water solubility with a log P_{OW} = 0.94, which are desirable for intravenous administration in biocompatible solvents and for tumor localization.

The spectroscopic properties of these new sulfonamide perfluorophenylporphyrins are comparable to those of other porphyrin-based photosensitizers. The singlet oxygen quantum yields of the secondary sulfonamide perfluorophenylporphyrins are remarkably high. The high Φ_Δ of these compounds, the large number of fluorine atoms in their structure, the presence of a variable number of sulfonamide groups and the possibility of using biocompatible solvents to administer them, make this class of compounds an interesting starting point for new molecular templates for aPDT and medical imaging.

4. Experimental

4.1. Materials and characterization

All solvents were dried according to standard procedures. All reagents were obtained commercially from Sigma–Aldrich and Fluorochem and used without further purification. The spectra of proton nuclear magnetic resonance (^{1}H), carbon (^{13}C) and fluorine (^{19}F) were recorded on a spectrometer 400 Bruker Avance (400, 101 and 376.5 MHz, respectively), using tetramethylsilane (δ = 0.00 ppm) as internal standard for ^{1}H and ^{13}C and TFA (δ = −76.55 ppm) for ^{19}F NMR. The MALDI-TOF mass spectra were acquired using a *Bruker Daltonics flex Analysis* apparatus. UV–vis spectra were recorded on Hitachi U-2001 or Shimadzu 2100 spectrophotometers. The third harmonic of a Spectra-Physics Quanta-Ray GCR-130 Nd–YAG laser was used for the excitation of the photosensitizers in the determination of singlet oxygen quantum yields and phenalenone was used as a reference. Singlet oxygen phosphorescence was collected at 1270 nm through a Hamamatsu R5509-42 photomultiplier, cooled to 193 K in a liquid nitrogen chamber using a filter (Newport model 10LWF-1000-B) to block the porphyrins fluorescence.

4.2. General synthesis of sulfonamides

In a round bottom flask containing *p*-toluenesulfonyl chloride (2 g; 0.011 mol) and 200 ml of dichloromethane, the desired amine (1.2 mol) was added. The reaction mixture was stirred at room temperature until complete consumption of starting material was observed by TLC (thin layer chromatography) plates (4–5 h). The sulfonamides precipitates from the reaction medium and were isolated by filtration. The solid was dissolved in dichloromethane, washed with a saturated solution of sodium bicarbonate (4×) and then with water (4×) and dried over anhydrous Na_2SO_4. The solvent was evaporated, affording the title compounds.

4.2.1. p-Toluenesulfonamide

(**2b**): Yield 48% (0.88 g); ^{1}H NMR (400 MHz, CD_3OD): ppm, δ 2.42 (s, 3H), 7.35 (d, J = 7.8 Hz, 2H), 7.78 (d, J = 7.8 Hz, 2H); ^{13}C NMR (101 MHz, MeOD): ppm, δ 21.5, 127.2, 130.6, 144.2; MS ESI-TOF, *m/z*: calcd. for $C_7H_{10}NO_2S$ 172.0427 $[M + H]^+$; found 172.0422; the data is in agreement with the literature [52].

4.2.2. N-Methyl-p-toluenesulfonamide

(**2c**): Yield 94% (1.87 g). ^{1}H NMR(400 MHz, $CDCl_3$): ppm, δ 2.43 (s, 3H), 2.63 (d, J = 5.3 Hz, 3H), 4.59 (s, 1H), 7.31 (d, J = 8.1 Hz, 2H), 7.75 (d, J = 8.1 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): ppm, δ 21.5, 29.3, 127.28, 129.7, 135.7, 143.5; MS ESI-TOF, *m/z*: calcd. for $C_8H_{12}NO_2S$ 186.0583 $[M + H]^+$; found 186.0575; the data is in agreement with the literature [53].

4.3. Synthesis of 5,10,15,20-tetrakis(pentafluorophenyl)porphyrin (**1**)

The porphyrin 5,10,15,20-tetrakis(pentafluorophenyl)porphyrin (**1**) was synthesized accordingly to our recent methodology [35]. In a typical experiment, 18 g of catalyst (NaY) was introduced into a 1 l round flask, previously filled with a glacial acetic acid/nitrobenzene mixture (340 ml/190 ml) and pentafluorobenzaldehyde (0.04 mol). Addition of equimolar amount of pyrrole (0.04 mol) was carried out drop wise under stirring and heating of the suspension (≈120 °C). After complete addition, the suspension was heated further to attain the reflux temperature (≈130 °C) and maintained at this temperature for *ca.* 2 h. The hot suspension was filtered and the resulting solid material washed with chloroform and tetrahydrofuran until no colored material was collected on the supernatant. The volume of supernatant was then reduced by rotoevaporation (enough volume to remove the added washing solvents). The crude was purified by silica gel column chromatography using hexane/dichloromethane (10:1) as eluent and successive precipitations. The resulting crystals were dried under vacuum (yield = 9.1%, 0.953 g).

^{1}H NMR (400 MHz, $CDCl_3$): ppm, δ −2.91 (s, 2H), 8.92 (s, 8H); ^{19}F NMR (376 MHz, $CDCl_3$) ppm, δ −160.14 to −160.28 (m, J = 22.7, 7.6 Hz, 8F), −150.06 to −150.16 (t, J = 20.8 Hz, 4F), −135.35 to −135.43 (dd, J = 23.3, 7.7 Hz, 8F); the data is in agreement with the literature [35].

4.4. Synthesis of meso-sulfonamide perfluorophenylporphyrins using Method A

In a round bottom flask containing 5,10,15,20-tetrakis(pentafluorophenyl)porphyrin (100 mg; 1.02×10^{-4} mol)(**1**) and the

desired sulfonamide (**2a–c**) (porphyrin/sulfonamide 1:6 mol) was dissolved in dioxane (20 ml) and cesium carbonate (6.15×10^{-4} mol) was added. The reaction mixture was stirred at 100 °C along 2–4 days until no further evolution reaction by TLC. The crude was washed with a saturated solution of sodium bicarbonate (6×) and then with water (6×) and dried over anhydrous Na_2SO_4. The solvent was evaporated in a rotary evaporator and the resulting solid dissolved in dichloromethane and purified by silica gel column chromatography using hexane/ethyl acetate (2:1) as eluent, followed by preparative silica gel thin layer chromatography (PrepTLC).

4.4.1. Methanesulfonamide derivatives

5-[2′,3′,5′,6′-Tetrafluoro-4′-methanesulfamoyl)phenyl]-10,15,20-tri-[(2′,3′,4′,5′,6′-pentafluoro)phenyl]porphyrin (**3a**), yield = 19% (20.3 mg).

^{1}H NMR (400 MHz, $CDCl_3$): ppm, δ −2.92 (s, 2H), 3.53 (s, 3H), 8.93 (brs, *J* = 13.5 Hz, 8H); ^{19}F NMR (376 MHz, $CDCl_3$): ppm, δ −161.26 to −161.37 (m, 6F), −151.22 (td, *J* = 20.9, 7.1 Hz, 3F), −147.82 (dd, *J* = 23.7, 10.7 Hz, 2F), −136.54 (d, *J* = 7.3 Hz, 2F), −136.47 (dd, *J* = 15.3, 7.9 Hz, 6F); MS(MALDI-TOF): *m/z* calcd. for $C_{45}H_{14}F_{19}N_5O_2S$ 1049.05593 $[M]^+$; found 1049.05487.

4.4.2. p-Toluenesulfonamide derivatives

*4.4.2.1. 5-[(2′,3′,5′,6′-Tetrafluoro-4′-p-toluenesulfamoyl)phenyl]-10,15,20-tri-[(2′,3′,4′,5′,6′-pentafluoro)phenyl]porphyrin(**3b**), yield = 4.5% (15.7 mg).* ^{1}H NMR (400 MHz, $CDCl_3$): ppm, δ −2.89 (s, 2H), 2.51 (s, 3H), 7.08 (s, 1H), 7.47 (d, *J* = 8.2 Hz, 2H), 8.05 (d, *J* = 8.2 Hz, 2H), 8.94 (s, 8H); ^{19}F NMR (376 MHz, CD_3COCD_3): ppm, δ −159.35 (td, *J* = 22.8, 7.5 Hz, 6F), −150.20 to −150.34 (m, 3F), −142.13 (dd, *J* = 67.3, 33.5 Hz, 2F), −135.45 (dd, *J* = 102.1, 51.0 Hz, 2F), −134.73 (dd, *J* = 21.8, 5.1 Hz, 6F); MS(MALDI-TOF): *m/z* calcd. for $C_{51}H_{18}F_{19}N_5O_2S$ 1125.08723 $[M]^+$; found 1125.08694.

*4.4.2.2. Mixture of 5,10-[(2′,3′,5′,6′-tetrafluoro-4′-p-toluenesulfamoyl)phenyl]-15,20-dis-[(2′,3′,4′,5′,6′-penta-fluoro)phenyl]porphyrin (**4b**) and 5,15-[(2′,3′,5′,6′-tetrafluoro-4′-p-toluenesulfamoyl)phenyl]-10,20-[(2′,3′,4′,5′,6′-penta-fluoro)phenyl]porphyrin (**5b**), yield = 0.7% (2.7 mg).* ^{1}H NMR (400 MHz, $CDCl_3$): ppm, δ −2.94 (s, 2H), 2.51 (s, 6H), 6.86 (s, 2 H), 7.46 (d, *J* = 7.9 Hz, 2H), 8.01(d, *J* = 8.1 Hz, 2H), 8.89 (s, 8H); ^{19}F NMR (376 MHz, $CDCl_3$): ppm, δ −159.34 (td, *J* = 22.3, 6.8 Hz, 4F), −150.24 (t, *J* = 20.4 Hz, 2F), −142.01 (dd, *J* = 23.3, 10.4 Hz, 4F), −135.27 (dd, *J* = 23.4, 10.4 Hz, 4F), −134.73 (dd, *J* = 23.2, 7.1 Hz, 4F); MS(MALDI-TOF): *m/z* calcd. for $C_{58}H_{26}F_{18}N_6O_4S_2$ 1276.11640 $[M]^+$; found 1276.11649.

4.4.3. N-Methyl-p-toluenesulfonamide derivatives

*4.4.3.1. 5-[(2′,3′,5′,6′-Tetrafluoro-4′-N-methyl-p-toluenesulfamoyl)-phenyl]-10,15,20-tri-[(2′,3′,4′,5′,6′-pentafluoro)phenyl]porphyrin (**3c**), yield = 3.1% (15 mg).* ^{1}H NMR (400 MHz, $CDCl_3$): ppm, δ −2.91 (s, 2H), 2.51 (s, 3H), 3.50 (s, 3H), 7.47 (d, *J* = 8.1 Hz, 2H), 7.97 (d, *J* = 8.2 Hz, 2H), 8.92 (s, 8H); ^{19}F NMR (376 MHz, $CDCl_3$): ppm, δ −160.15 to −160.26 (m, 6F), −150.12 (t, *J* = 20.6 Hz, 3F), −141.80 (dd, *J* = 23.7, 10.9 Hz, 2F), −135.69 (dd, *J* = 23.7, 10.9 Hz, 2F), −135.40 (dd, *J* = 23.2, 7.3 Hz, 6F); MS(ESI-TOF): *m/z* calcd. for $C_{52}H_{21}F_{19}N_5O_2S$ 1140.1107 $[M + H]^+$; found 1140.1078.

*4.4.3.2. Mixture of 5,10-[(2′,3′,5′,6′-tetrafluoro-4′-N-methyl-p-toluenesulfamoyl)phenyl]-15,20-dis-[(2′,3′,4′,5′,6′-pentafluoro)phenyl]-porphyrin(**4c**) and 5,15-[(2′,3′,5′,6′-tetrafluoro-4′-N-methyl-p-toluenesulfamoyl)phenyl]-10,20-[(2′,3′,4′,5′,6′-pentafluoro)phenyl]-porphyrin (**5c**), yield = 1.5% (8 mg).* ^{1}H NMR (400 MHz, $CDCl_3$): ppm, δ −2.90 (s, 2H), 2.51 (s, 3H), 3.50 (s, 6H), 7.47 (d, *J* = 7.5 Hz, 4H), 7.96 (d, *J* = 7.6 Hz, 4H), 8.85 (d, *J* = 51.6 Hz, 8H); ^{19}F NMR (376 MHz, $CDCl_3$): ppm, δ −161.25 to −161.35 (m, 4F), −151.19 (t, *J* = 20.7 Hz, 2F), −142.9 (d, *J* = 12.9 Hz, 4F), −136.79 (dd, *J* = 23.4, 10.5 Hz, 4F), −136.50 (d, *J* = 16.1 Hz, 4F); MS(MALDI-TOF): *m/z* calcd. for $C_{60}H_{30}F_{18}N_6O_4S_2$ 1304.1477 $[M]^+$; found 1304.1485.

*4.4.3.3. 5,10,15-Tri-[(2′,3′,5′,6′-tetrafluoro-4′-N-methyl-p-toluenesulfamoyl)phenyl]-20-[(2′,3′,4′,5′,6′-pentafluoro)phenyl]porphyrin(**6c**), yield = 0.6% (4 mg).* ^{1}H NMR (400 MHz, $CDCl_3$): ppm, δ −2.89 (s, 2H), 2.51 (s,9H), 3.51 (s, 9H), 7.47 (d, *J* = 8.0 Hz, 6H), 7.96 (d, *J* = 8.1 Hz, 6H), 8.96 (s, 8H); ^{19}F NMR (376 MHz, CD_3COCD_3): ppm, δ −161.14 to −161.26 (m, 2F), −152.05 (s, 1F), −141.52 (dd, *J* = 23.2, 10.0 Hz, 6F), −136.95 to −137.07 (m, 6F), −136.57 (dd, *J* = 23.2, 7.1 Hz, 2F); MS(MALDI-TOF): *m/z* calcd. for$C_{68}H_{40}F_{17}N_7O_6S_3$ 1469.1925 $[M]^+$; found 1469.1946.

4.5. Synthesis of meso-sulfonamide perfluorophenylporphyrins using Method B

In a round bottom flask, 5,10,15,20-tetrakis(pentafluorophenyl)porphyrin (30 mg; 3.07×10^{-5} mol) (**1**) and methanesulfonamide (porphyrin/sulfonamide 1:18 mol equivalents) (**2a**) were dissolved in dioxane (2 ml) and cesium carbonate (3.69×10^{-4} mol) was added. The reaction mixture was stirred at 100 °C for 2 days until complete consumption of starting material was observed by TLC. The crude was washed with acetone and the resulting precipitate was purified using the Amicon device (10 kDa membranes).

*4.5.1. 5,10,15,20-Tetra-[(2′,3′,5′,6′-tetrafluoro-4′-methanesulfamoyl)phenyl]porphyrin (**7a**), yield = 70% (27 mg).*

^{1}H NMR (400 MHz, DMSO-d_6): ppm, δ −3.01 (s, 2H), 2.94 (s, 12H), 9.08 (s, 8H); ^{19}F NMR (376 MHz, DMSO-d_6): ppm, δ −152.19 (d, 19.1, 8F), −144.71 (d, 17.7, 8F); MS(MALDI-TOF): *m/z* calcd. for $C_{48}H_{26}F_{16}N_8O_8S_4$ 1274.0496 $[M]^+$; found 1274.0478.

4.6. 1-Octanol/water partition coefficients

1-Octanol/water partition coefficients were measured following shake-flask method with minor modifications [46–48]. Equal volumes of PBS and 1-octanol were mixed and left overnight. A volume of 5 ml of 1-octanol saturated with PBS was taken from the previous mixture and used to dissolve a sample of **7a** until the solution turned into a light color. Then 5 ml of PBS saturated with 1-octanol was taken from the mixture and added to the solution of **7a** in 1-octanol saturated with PBS. The solvent mixture was then shaken vigorously. This solution was centrifuged at 3700 rpm to obtain clear phase separation. A volume of 2 ml of water part containing the compound was taken, mixed with 0.5 ml of 1-octanol and evaporated at 50 °C. After evaporation, a volume of pure 1-octanol was added keeping equal dilutions of organic and water parts containing the compound. Optical absorption of the 1-octanol and the PBS fractions were used to determine the logarithm of the partition coefficient.

4.6.1. Computational determination of the LogP

A correlation curve between experimental [10] and computational data of LogP was constructed for a family of sulfonamide-substituted porphyrins and their derivatives. The computational approach was made using the program Marvin Sketch 14.10.6.0 available in http://www.chemaxon.com. All computational data was run using the same initial conditions in the simulation. From the fitting curve given in Fig. 3, a good approximation of the LogP value can be obtained through the equation: [LogP(Theor)-0.12]/1.83.

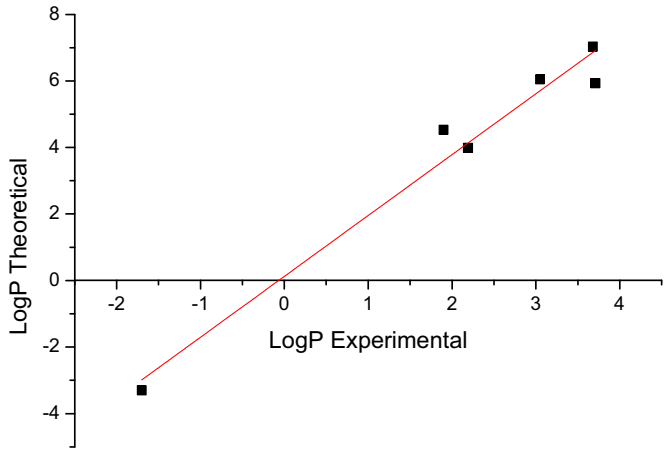


Fig. 3. Fitting curve related to the experimental and theoretical values of LogP for a family of sulfonamide-substituted porphyrins and their derivatives.

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