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Addressing subphthalocyanines and subnaphthalocyanines features relevant to fluorescence imaging

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ABSTRACT

A series of new synthetic subphthalocyanines bear structural features aimed at allowing either fluorescence activation or a bathochromic shift of the absorption band towards the near-infrared window, relevant to optical imaging. X-ray diffraction studies of four subphthalocyanines are reported. Spectrofluorimetric studies on subnaphthalocyanines and activatable subphthalocyanine pro-fluorophores are reported.

1. Introduction

Subphthalocyanines (SubPcs) are tris-isoindolic phthalocyanine analogs that were reported as synthons for ring enlargement to afford A3B phthalocyanines.[1] Their fluorescence properties place them properly in the Lavis and Raines diagram.[2] Their concave shape and the axial substituent are useful to prevent aggregation, which made SubPc interesting fluorophores for biological studies.[3] We recently reported pH-sensitive SubPc absorbing in the 570 nm window.[3] Herein, we present in the first section of the study the synthesis of SubPc species with features relevant to fluorescence imaging studies (Fig. 1): a) range of substituents for future turn-ON fluorescence at various biological pH (probes **1**–**4**), b) substituents responsible for a bathochromic shift up to the near-infrared window, i.e. the "optical window" where biological tissues are most transparent (probes **5**–**7**).[4] A hanging function X is appended to the probe for subsequent conjugation to a biomolecule or another contrast agent or therapeutic agent (bi-modality/theranostic). Subsequent characterization and examination of the optical properties (spectrofluorimetry studies) are presented in the last two sections of the study.

2. Results and discussion

2.1. Syntheses of subphthalocyanine (SubPc)

2.1.1. Activatable N-Alkylaminophenoxy subphthalocyanine (pro-fluorophores)

They were shown to be pH-sensitive and be of interest for fluorescence turn-ON at biological pH. The newer versions presented therein may afford pKa fine-tuning by adjusting the nature of the apical aniline as mentioned on other fluorescent dialkylated aminoplatforms[5] as follows: a) secondary and tertiary anilines have higher pKa than primary anilines, hence they will be more suitable for biology; b) *para* vs *meta* orientation may affect the outcome, not only because of the electronic effect of the O donor atom, but also because the meta orientation may get the donor Nitrogen atom closer to the fluorescent platform, hence facilitating the transfer; c) the lenght of the alkyl chains grafted on the aniline may also address the pKa. Herein, *N*-alkylaminophenoxy groups were introduced in apical position of the subphtalocyanine ring. Alkyl groups are either methyl or ethyl groups, leading to organosoluble SubPcs. Future studies in aqueous media will necessitate subsequent incorporation in liposomes. Two synthetic routes were examined to afford *N*-alkylaminophenoxy-substituted subphthalocyanines: direct alkylation of SubPc-NH_2 **8** or apical substitution of SubPc-Cl **9** with alkyl amine bearing phenol groups. The

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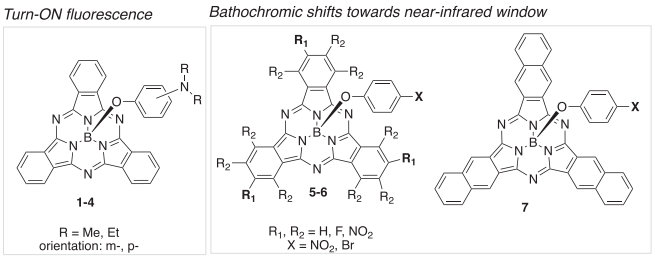


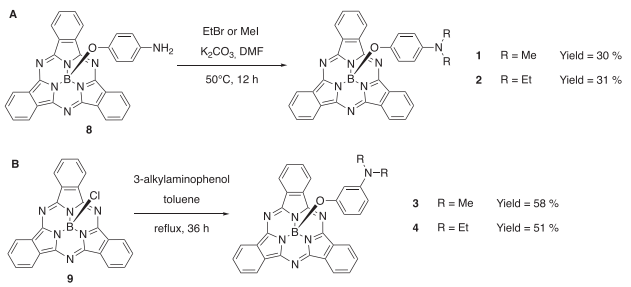
Fig. 1. Three structural modifications to adapt Subphthalocyanines to fluorescence imaging studies in biology by addressing: a) SubPc pKa and turn-ON fluorescence at various biological pHs, b) bathochromic shift to address the (near-infrared) "optical window", c) introduction of apical function **X** to future conjugation of other contrast agent or biomolecule.

first strategy allowed to get alkylated species **1** et **2** using two equiv. methyl iodide or ethylbromide in the presence of potassium carbonate in DMF (Scheme 1A). Low yields were obtained because the reactions also led to mono-alkylated products and more polar trialkylated/quaternized cationic, that were eliminated upon purification of silica column chromatography. In the second synthetic route no alkylation was achieved, commercially available *meta*-substituted phenols were used instead (Scheme 1B). The apical chlorine atom in compound **9** could be substituted with phenols using classical operating conditions. Such a reaction with meta-substituted phenols appeared to be quite long (48 h), and led to the SubPcs **3** and **4** in 58 and 51% yield, respectively.

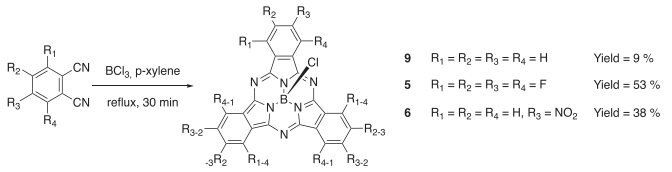
2.1.2. Bathochromically shifted subphthalocyanines

We recently studied subphthalocyanines bearing twelve H atoms (H12) at the peripheral isoindolic moieties, which absorb in the 570 nm window.[3] Although they fit well in the Lavis and Raynes diagram,[2] they still lie below the so-called "optical window".[4] Herein, a few examples report the appending of a series of electron-withdrawing nitro groups or fluorine atoms, or the extension of the conjugation on the SubPc ring to one more phenyl (Subnaphthalocyanine), which results in a *bathochromic shift* that becomes an asset for optical imaging in deeper tissues.

2.1.2.1. SubPc with peripheral EW groups. ***Cyclotrimerization*** reactions were achieved following a general procedure consisting of the stochiometric condensation of Boron trichloride (1 M in p-xylene) and dry phthalonitrile, according to a procedure reported by Claessens et al. (Scheme 2).[6] The reaction mixture was heated under refluxing conditions for 30 min under inert atmosphere. Solvent and excess BCl_3 were subsequently removed by evaporation, and the resulting residue was subjected to chromatography on silica. Three phthalonitriles were selected to examine this reaction:



Scheme 1. A: Methylation and ethylation of SubPc-NH_2 **8** to afford targets **1** and **2**. B: Syntheses of targets **3** and **4** upon substitution of the apical chlorine atom in compound **9**.



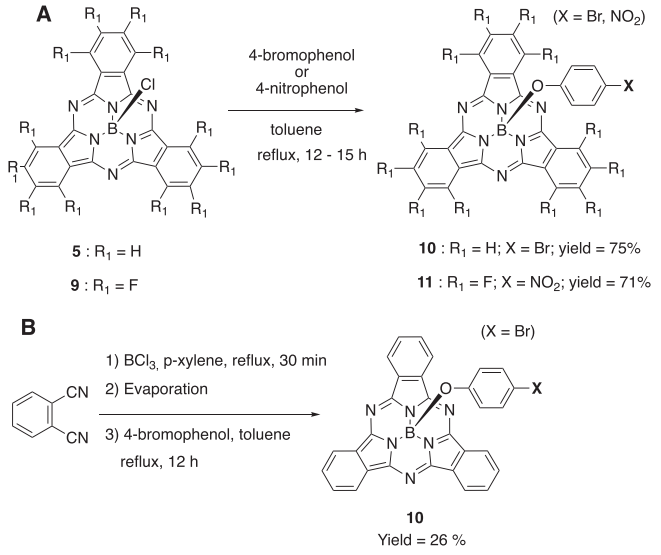
Scheme 2. Syntheses of subphthalocyanines bearing an apical chlorine atom, and various atoms/groups at the periphery: 12 Hydrogen atoms (**9**), twelve fluorine atomes (**5**), three nitro groups and nine Hydrogen atoms (**6**).

when tetrafluorophtalonitrile and 4-nitrophtalonitrile were used, subphtalocyanines **5** and **6** were obtained in satisfactory yields.[1,6] However, with non-substituted phthalonitrile, isolated yields in **9** was not greater than 9%, unlike the 82% reported yields.[6] We hypothesize that solubility issues may possibly explain such low yields: either the poor solubility of the starting phtalonitrile may not favor the reaction, or the poor solubility of subphtalocyanine **9** in common organic solvents (such as dichloromethane) may explain why its purification on column is so tricky and leads to severe loss of compound. Such a phenomenon is less an issue in the case of substituted subphtalocyanines **5** and **6**, that are much more soluble. Isolation of the subphthalocyanine by precipitation as reported in the literature, was not satisfactory in our hands.[6] Although the amount of isolated product is significantly higher, ^{1}H NMR analysis indicates mild purity even after numerous washings. A careful analysis of ^{1}H NMR and ^{19}F NMR spectra was achieved to characterize compounds **5** and **6**, showing that they are free of starting phthalonitrile.

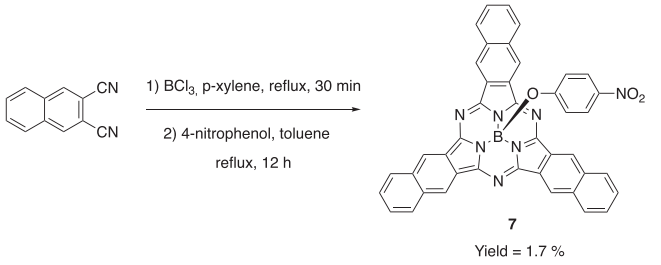
Apical substitution of the chlorine atom could be achieved on compounds **9** and **5**, upon condensation of p-substituted phenol in excess (3.3 equiv., 4-bromophenol with **9**, 4-nitrophenol with **5**) under refluxing conditions in toluene until complete consumption of the starting phthalonitrile (CCM monitoring) (Scheme 3AB). Reaction times vary and appeared to be a function of both the electron density of the SubPc aromatic platform and the nature of the phenol. The yield of apical substitution was found to be 75% (**10**) and 71% (**11**).

One pot cyclotrimerization + apical substitution Another and more straightforward method consists in the cyclo-trimerization of the subphthalocyanine ring immediately followed by evaporation of both solvents (*p*-xylene) and liquid reagents (BCl_3) in the reaction mixture without isolation of the chlorinated subphthalocyanine **9**. Both dry toluene and phenol reagent were subsequently added to the residue, and the resulting suspension was heated under reflux (Scheme 3B). The subphthalocyanine was subsequently purified by a) filtration on alumina plug (short column) that allowed the elimination of excess phenol, b) followed by chromatography column on silica, c) and recrystallization if necessary. The overall yield in compound **10** vary depending on the protocol: from 7% (two-steps procedure) to 26% (one-pot procedure). However, the overall yield droped significantly as the amount of starting phthalonitrile was raised, which hampered the larger-scale synthesis of subphthalocyanine synthons.

2.1.2.2. Extended conjugation: subnaphthalocyanine (SubNc). The « one-pot » general procedure described for synthons **10**–**11** was adapted to the synthesis of apical nitrophenoxy group bearing *naphthalocyanine* by replacing phthalonitrile for naphthalonitrile (Scheme 4). TLC analysis of the reaction mixture shows four blue spots, which were isolated by column chromatography on silica. Mass spectrometry analysis (MALDI-TOF) showed that one of these fractions corresponds to subnaphthalocyanine **7** that was obtained in a low 1.7% isolated yield (Note that the other two isolated



Scheme 3. Two-steps *vs* « one-pot » syntheses of subphthalocyanines **10** and **11** bearing Br, NO_2 – substituted apical groups for future reactions, in the H_{12} vs F_{12} series.



Scheme 4. Synthesis of naphthalocyanine SubNc-NO_2 **7.**

fractions may be assigned to the chlorinated version (SubNc-Cl) prior substitution with phenoxy group, and another resulting from hydrolysis at the apical position leading to SubNc-OH), and the last one could not be identified).

2.2. Characterization of subphthalocyanine (SubPc)

The structure of the alkylated species was assessed by ^{1}H NMR, ^{13}C NMR, ^{10}B-NMR, mass spectrometry, and X-Rays diffraction studies for compounds **3**, **4**, **10** and **11** (Fig. 2). The presence of apical substituents in bromophenoxy-substituted compound **10** was demonstrated by ^{1}H NMR spectrometry. Doublets that correspond to the protons of the phenoxy groups are quite shielded (5.27 and 6.84 ppm) compared with that of the phenol precursor (6.84 and 7.43 ppm) because these protons lie in the anisotropy cone of the aromatic subphthalocyanine. The ^{10}B-NMR spectrum shows a singlet at −15.68 ppm in the case of chlorinated species **9**, which shifts to −15.07 ppm in compound **10**. Crystals of subphthalocyanines **10** and **11** were obtained upon slow evaporation from a solution of the subphthalocyanines in dichloromethane. The conical aspect of the subphthalocyanine aromatic structure and the presence of apical *para*-bromophenoxy are clearly observed by X-ray diffraction studies (Fig. 2).

2.3. Optical properties and fluorescence activation

2.3.1. UV–vis spectroscopy

The electron-withdrawing effect of the substituents is observed

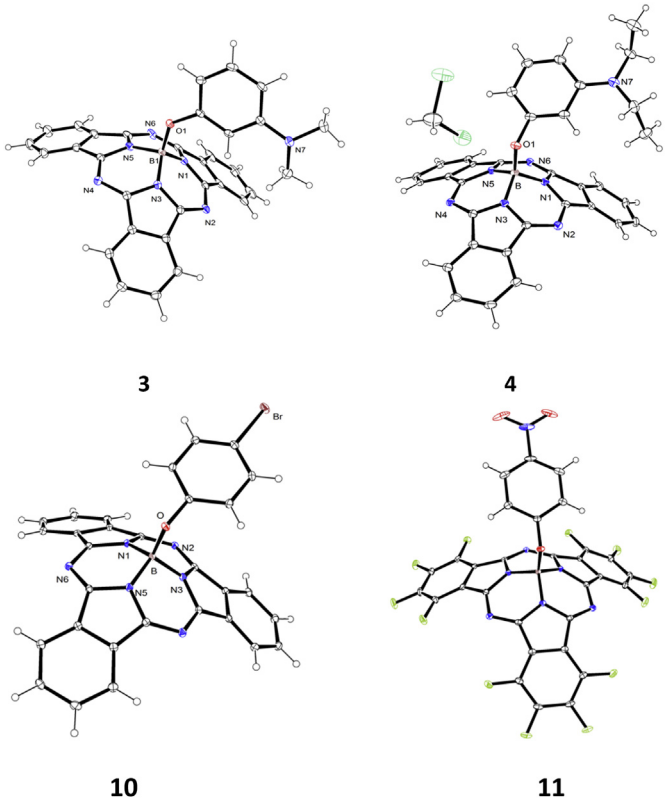


Fig. 2. Top: X-ray diffraction studies of compounds **3** (left, CCDC 1555141) and **4** (right, CCDC 1555142). Compound **4** co-crystallized with one molecule of dichloromethane. Bottom: ORTEP views of *p*-substituted-phenoxy-bearing subphthalocyanines in the H_{12} series (**10**, left, CCDC 1555143) and F_{12} series (**11**, right, CCDC 1555144).

on the UV/Vis spectra of all Subphthalocyanines and Subnaphthalocyanines (Fig. 3). Such an effect leads to a bathochromic shift of the Q bands. In the case of the trinitro-derivative **6**, the broadening of the bands and spectrum and the decrease of the epsilon may be the result of likely internal charge transfer (ICT) between the three nitro groups and the aromatic SubPc. UV/Vis absorption spectrum in SubNc **7** shows Soret band at 327 nm and Q band at 656 nm, which corresponds to a 93 nm bathochromic shift compared to the Q bands in SubPc-NO_2 **10a**. Hence, the SubNc derivative is far better than the SubPc analog in term of absorption in the « optical window » with respect to biological requirements. However, its cyclotrimerization requires optimization prior to transposing the apical substitution steps and future reactions. Subsequent fluorescence emission of the molecules occurs at 570–574 nm (SubPc **10a**) and 670 nm (SubNc **7**), respectively.

2.3.2. Activation and spectrofluorimetry

Fluorescence quantum yields of the subphthalocyanines were measured in DMF, or in DMF in the presence of H_2SO_4 (Table 1), following a procedure previously reported with other subphthalocyanines.[3a] Spectrofluorimetric studies carried out on **1** showed fluorescence turn-on upon gradual addition of acid in the medium (Fig. 4). Fluorescence quantum yields are negligible prior to protonation, and were raised to up to 4–10% upon fluorescence activation by adding sulfuric acid. The Increase Factor (F) corresponds to the ratio between the two fluorescence quantum yields (before activation (in DMF) and after activation with acid (in DMF + H_2SO_4), Table 1): it corresponds to the efficacy of the fluorophore as an activatable probe. This process is reversible: upon addition of a base to the mixture of protonated aniline-containing

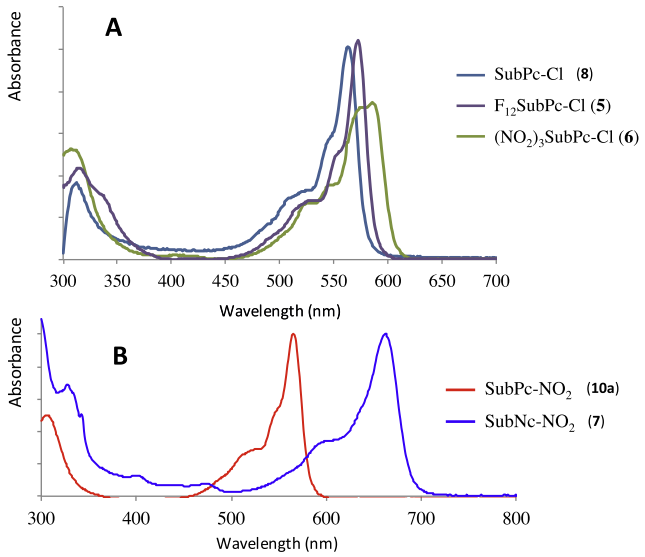


Fig. 3. Absorption spectra of: **A)** Subphthalocyanines **8**, **5** et **6** measured in chloroform (molar extinction coefficient as a fonction of wavelength); **B)** of apical nitrophenoxy-bearing subphthalocyanines **10a** *vs* nitrophenoxy-bearing naphthalocyanines **7** with fluorescence emission of the subnaphthalocyanine.

Table 1
Absorption, emission and activation properties of SubPcs **1**–**4** (298 K; Reference rhodamine 6G in MeOH, $\Phi_F = 0.96$, $\lambda_{ex} = 488$ nm; measure error: ±10%).

Compounds	Solvent	$\lambda_{abs}/\lambda_{em}$ (nm)	ε ($.10^3$ $mol^{-1}.L\,cm^{-1}$)	ϕ_F	F
1	DMF	563/572	79.6	0.009	7.4
	DMF + H_2SO_4	564/573	76.9	0.067	
2	DMF	565/572	72.4	0.008	6.8
	DMF + H_2SO_4	564/573	73.1	0.054	
3	DMF	564/570	72.1	0.002	50.5
	DMF + H_2SO_4	565/573	83.6	0.101	
4	DMF	564/570	72.1	0.003	27.7
	DMF + H_2SO_4	564/573	83.6	0.083	

SubPc, fluorescence intensity goes down. Fluorescence is OFF in compounds **1**–**4** and is turned-on upon addition of acid by protonation of the Nitrogen in the distal aniline, that results in the suppression of the photo-induced electron transfer (PeT) and/or internal charge transfer (ICT). This is unlike compounds **7**, **11** the fluorescence of which (see spectrum in the SI) is always ON, because they do not have such quenching amine moieties.

3. Conclusion

At this stage of the study two sets of conclusions may be raised, from a synthesis and properties standpoint. First, from a ***synthetic*** *standpoint*: a) Overall the cyclotrimerization reaction leading to subphthalocyanine proceeded in ca 9% yield under the general protocol developed, although it dropped to about 1–2% in the case of the subnaphthalocyanine. When no isolation of the chlorinated species was attempted subsequent substitution of the apical chlorine atom with phenol groups was achieved allowing to raise the overall yield up to 36% in the H_{12} series. When the reaction was conducted on platforms bearing electron-withdrawing fluorine atoms/groups, yields were significantly raised up to 75%. b) Bromo and nitro SubPcs/SubNc **6,7,10,11** are an entry point to future conjugations to groups relevant to biomedical studies, such as chelates for the complexation of medically relevant metals, peptides, as we previously reported[3b,8]: bromo-SubPc **7** may for instance be engaged in Sonogashira for alkyne groups and future Click conjugations. Nitro synthons **6,10,11** may be reduced into amine and subsequently acylated and engaged in peptide bond formations. The presence of nitro group and bromine atom at the para position of the apical phenoxy-group is an entry point for future reactions, which may afford conjugation to other contrast/therapeutic agents (i.e. bimodality/theranostics). Second, from a ***properties*** *standpoint*: c) Twelve fluorine atoms or three nitro groups at the isoindolic position of the SubPc ring led to modest (5–10 nm) bathochromic shifts, whereas extending the conjugation to an extra phenyl ring led to about 100 nm shift, which now brings the subsequent SubNc on the edge of the therapeutical window.[2,4] (Interestingly, it should be noted that such trinitro- and perhalogenated subphthalocyanines **5** and **6** and subnaphthalocyanine **7** are the tri-isoindolic/isobenzoindolic versions of tetraisoindolic phthalocyanines/naphthalocyanines, i.e. tetranitro- and perhalogenated phthalocyanine, naphthalocyanine).[7] E) This study also reported the syntheses of a series of dimethyl *vs* diethyl *para*-amino *vs* *meta*-amino phenoxy subphthalocyanines, which should have different pKa values suggesting turn-ON fluorescence may occur at various biological pHs. At this stage of the study, it has been demonstrated that the fluorescence of such subphthalocyanines bearing distal aniline moieties may be switched-on upon addition of small volumes of acid in the mixture, which augurs well for the activation in relevant biological systems at low pH (hypoxic tumors, lysosomes). Future studies will focus on the measurement of pKa values of dialkylaminophenoxysubphthalocyanines **1**–**4**, subphthalocyanine, encapsulation in liposome carriers and subsequent delivery and staining of living cells, as we previously reported for other subphthalocyanines/phthalocyanines[8] and the scale-up of subnaphthalocyanines.

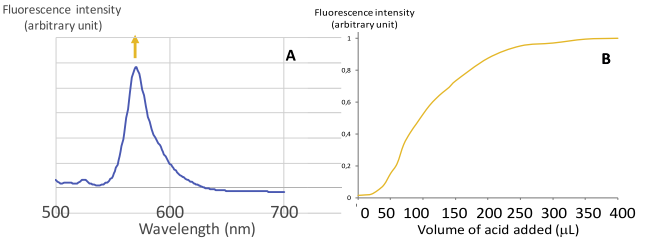


Fig. 4. A: example of spectrofluorimetry studies on Subphthalocyanine **1** in solution in DMF (emission spectra were recorded for an absorbance at 560 nm comprised between 0.03 and 0.07 (i.e. 1 µM concentration in **1**). B: SubPc **1** fluorescence intensity increases upon gradual addition of acid (H_2SO_4) until it reaches a plateau.

4. Experimental

4.1. Materials and methods

Chemicals were used as supplied. Subphthalocyanine UV/Vis spectra were recorded on a Shimadzu UV– 2550 spectrophotometer. Spectra were recorded in DMF in glass cuvettes 1 × 1x3 cm (1 cm path).

Fluorescence measurements were performed on a Jasco FP-8500 spectrofluorometer equipped with a Xe source. Fluorescence quantum yields were calculated using Rhodamine 6G methanol as a reference ($\Phi F = 0.94$). Excitation was performed at 488 nm for the reference and 560 nm for the sample. Emission spectra were recorded for an absorbance at 560 nm comprised between 0.03 and 0.07 (i.e. 1 µM). Fluorescence quantum yields (Φ_F) were determined by the comparison method, using the following equation:

$$\phi_F = \phi_F(Std) \times \left(\frac{\eta}{\eta(Std)}\right)^2 \times \left(\frac{1-10^{Abs}}{1-10^{-Abs(Std)}}\right) \times \left(\frac{A(Std)}{A}\right)$$

Std corresponds to the standard fluorophore (Rhodamine 6G); Φ_F and Φ_F(Std): fluorescence quantum yields; η and η(Std): refractive index of the solvent (MeOH for standard; DCM, DMF or water for samples); Abs and Abs(Std): absorbances at excitation wavelength (560 nm) A and A(Std): areas under the fluorescence curves.

4.2. B-(4-(N,N-dimethyl)aminophenoxy)[subphthalocyaninato] boron(III) (**1**)

To a solution of compound **8** (50 mg, 0.1 mmol) in DMF (5 mL) was added potassium carbonate (59 mg, 0.4 mmol), then methyl iodide (12.3 μL, 0.2 mmol). The reaction mixture was stirred at 50 °C for 12 h, then filtered off on clarcel® and finally evaporated under reduced pressure. The residue was subjected to silica gel column chromatography (eluent: DCM/MeOH 99:1) and dried under reduced pressure (12 mg, 37%).

^{1}H NMR (300 MHz, $CDCl_3$, 300 K): δ (ppm) = 2.67 (s, 6H); 5.32 (d, ^{3}J = 8.9, Hz, 2H); 6.17 (d, ^{3}J = 8.9 Hz, 2H); 7.90 (m, 6H); 8.84 (m, 6H). MS MALDI-TOF: m/z = 531.77 $[M+H]^+$ (calcd for $C_{32}H_{23}BN_7O^+$: 532.21). UV–Vis (DMF): λ_{max} (nm) ($\varepsilon \times 10^3$ L mol^{-1} cm^{-1}) = 307 (33.3), 563 (79.7).

4.3. B-(4-(N,N-diethyl)aminophenoxy)[subphthalocyaninato] boron(III) (**2**)

To a solution of *B*-(4-aminophenoxy)[subphthalocyaninato] boron(III) **8** (50 mg, 0.1 mmol) in DMF (5 mL) was added potassium carbonate (59 mg, 0.4 mmol), then bromoethane (12.3 μL, 0.2 mmol). The reaction mixture was stirred at 50 °C for 12 h, then filtered off on clarcel® and evaporated under reduced pressure. The residue was subjected to silica gel column chromatography (eluent: DCM/MeOH 99:1) and the isolated product was dried under reduced pressure (19 mg, 31%).

^{1}H NMR (300 MHz, $CDCl_3$, 300 K): δ (ppm) = 0.95 (s, 6H); 3.42 (q, 4H); 5.29 (d, ^{3}J = 8.9, Hz, 2H); 6.15 (d, ^{3}J = 8.9 Hz, 2H); 7.90 (m, 6H); 8.85 (m, 6H). MS MALDI-TOF: m/z = 559.80 $[M+H]^+$ (calcd for $C_{34}H_{27}BN_7O^+$: 560.24). UV–Vis (DMF): λ_{max} (nm) ($\varepsilon \times 10^3$ L mol^{-1} cm^{-1}) = 308 (39.1), 565 (72.1).

4.4. B-(3-(N,N-dimethyl)aminophenoxy)[subphthalocyaninato] boron(III) (**3**)

B-Chloro[subphthalocyaninato]boron(III) **9** (50 mg, 0.12 mmol) and 3-(N,N-dimethyl)aminophenol (247 mg, 1.8 mmol) dissolved in toluene (5 mL) were heated to reflux for 36 h. After evaporation of the solvent, the residue was subjected to alumina gel column chromatography (eluent: DCM/MeOH, gradient from 100:0 to 99:1) and then to silica gel column chromatography (eluent: DCM/MeOH 99:1) to give the desired subphthalocyanine **19** (36 mg, 58%).

^{1}H NMR (300 MHz, $CDCl_3$, 300 K): δ (ppm) = 2.64 (s, 6H); 4.81 (m, 2H); 6.10 (m, 1H); 6.63 (m, 1H); 7.87 (m, 6H); 8.84 (m, 6H). MS MALDI-TOF: m/z = 531.78 $[M+H]^+$ (calcd for $C_{32}H_{23}BN_7O^+$: 532.21). HR-MS ESI: m/z = 532.20509 $[M+H]^+$ (calcd for $C_{32}H_{23}BN_7O^+$: 532.20573). UV–Vis (DMF): λ_{max} (nm) ($\varepsilon \times 10^3$ L mol^{-1} cm^{-1}) = 309 (31.3), 565 (72.4). CCDC 1555141.

4.5. B-(3-(N,N-diethyl)aminophenoxy)[subphthalocyaninato] boron(III) (**4**)

A mixture of chloro[subphthalocyaninato]boron(III) **9** (50 mg, 0.12 mmol) and 3-(N,N-diethyl)aminophenol (297 mg, 1.8 mmol) in toluene (5 mL) was heated under reflux for 36 h. After evaporation of the solvent, the residue was subjected to alumina gel column chromatography (eluent: DCM) and then to silica gel column chromatography (eluent: DCM/MeOH 99:1), to afford the desired subphthalocyanine **20** (33 mg, 51%).

^{1}H NMR (300 MHz, $CDCl_3$, 300 K): δ (ppm) = 0.91 (t, ^{3}J = 6.8 Hz, 6H); 3.30 (q, ^{3}J = 6.8 Hz, 4H); 4.68 (m, 2H); 5.94 (m, 1H); 6.57 (m, 1H); 7.88 (m, 6H); 8.84 (m, 6H). MS MALDI-TOF: m/z = 559.88 $[M+H]^+$ (calcd for $C_{34}H_{27}BN_7O^+$: 560.24).

HR-MS ESI: m/z = 560.23497 $[M+H]^+$ (calcd for $C_{34}H_{27}BN_7O^+$: 560.23706). UV–Vis (DMF): λ_{max} (nm) ($\varepsilon \times 10^3$ L mol^{-1} cm^{-1}) = 309 (36.2), 564 (73.6). CCDC 1555142.

4.6. B-chloro[1,2,3,4,7,8,9,10,15,16,17,18-dodecafluorosubphthalocyaninato]boron(III) (**5**)

BCl_3 (4 mL, 1 M solution in *p*-xylene) was added to dry tetrafluorophthalonitrile (800 mg, 4 mmol under an argon atmosphere. The vessel was placed in a preheated oil bath (150 °C) and the mixture was stirred and left to reflux for 30 min. The solvent was removed under reduced pressure and the resulting solid was subjected to silica gel column chromatography (eluent: DCM) (455 mg, 53%).

^{19}F NMR (282 MHz, $CDCl_3$, 300 K): δ (ppm) = −146.95 (m, 6F); −136.65 (m, 6F). ^{11}B NMR (96 MHz, $CDCl_3$, 300 K): δ (ppm) = −14.20 (s, 1B). UV–Vis ($CHCl_3$): λ_{max} (nm) ($\varepsilon \times 10^3$ L mol^{-1} cm^{-1}) = 307 (43.0), 573 (100.2).

4.7. B-chloro[2,9(10),16(17)-trinitrosubphthalocyaninato] boron(III) (**6**)

BCl_3 (4 mL, 1 M solution in *p*-xylene) was added to dry 4-nitrophthalonitrile (690 mg, 4 mmol), under an argon atmosphere. The vessel was placed in a preheated oil bath (150 °C) and the mixture was stirred and left to reflux for 30 min. The solvent was removed under reduced pressure and the resulting solid was subjected to silica gel column chromatography (eluent: DCM) (287 mg, 38%).

^{1}H NMR (300 MHz, $CDCl_3$, 300 K): δ (ppm) = 8.83 (m, 3H); 9.06 (m, 3H); 9.73 (m, 3H). ^{11}B NMR (96 MHz, $CDCl_3$, 300 K): δ (ppm) = −14.00 (s, 1B). UV–Vis ($CHCl_3$): λ_{max} (nm) ($\varepsilon \times 10^3$ L mol^{-1} cm^{-1}) = 311 (52.0), 586 (74.9).

4.8. B-(4-nitrophenoxy)[subnaphthalocyaninato]boron(III) (**7**)

BCl_3 (5,61 mL, 1 M solution in *p*-xylene, 5.61 mmol) was added to dry naphthalonitrile (1 g, 5.61 mmol), under an argon atmosphere. The vessel was pourred in a preheated oil bath (150 °C), stirring and left to reflux for 30 min. The solvent and the excess of boron trichloride were removed under reduced pressure and the resulting solid was resuspended in toluene (30 mL). An excess of 4-nitrophenol (2.34 g, 16.83 mmol) was added and the mixture was heated under reflux for 15 h. After evaporation to dryness, the residue was subjected to alumina gel column chromatography (eluent: DCM) and then to silica gel column chromatography (eluent: DCM/Heptane, gradient from 70:30 to 100:0) (16 mg, 1.3%).

^{1}H NMR (300 MHz, $CDCl_3$, 300 K): δ (ppm) = 5.63 (d, ^{3}J = 9.2 Hz, 2H); 7.72 (d, ^{3}J = 9.2 Hz, 2H); 7.74 (m, 6H); 8.34 (m, 6H); 9.39 (m, 6H). MS MALDI-TOF: m/z = 682.77 $[M+H]^+$ (calcd for $C_{42}H_{22}BN_7O_3^+$: 683.19). UV–Vis (DCM): λ_{max} (nm) ($\varepsilon \times 10^3$ L mol^{-1} cm^{-1}) = 327 (43.2), 656 (63.1).

4.9. B-(4-nitrophenoxy)[1,2,3,4,7,8,9,10,15,16,17,18-dodecafluorosubphthalocyaninato]boron(III) (**11**)

A mixture of *B*-chloro[dodecafluorosubphthalocyaninato] boron(III) (100 mg, 0.15 mmol) and 4-nitrophenol (209 mg, 1.5 mmol) in toluene (5 mL) was heated under reflux for 15 h. After

evaporation of the solvent, the residue was subjected to alumina gel column chromatography (eluent: DCM) and dried under reduced pressure (80 mg, 71%).

^{1}H NMR (300 MHz, $CDCl_3$, 300 K): δ (ppm) = 5.17 (d, ^{3}J = 9.1 Hz, 2H); 7.47 (d, ^{3}J = 9.1 Hz, 2H). ^{19}F NMR (282 MHz, $CDCl_3$, 300 K): δ (ppm) = −147.14 (m, 6F); −136.88 (m, 6F). CCDC 1555144.

*4.9.1. B-(4-bromophenoxy)[subphthalocyaninato]boron(III) (**7**)*

*Method A:*A mixture of *B*-chloro[subphthalocyaninato]boron(III) **3** (50 mg, 0.12 mmol) and 4-bromophenol (208 mg, 1.2 mmol) in toluene (5 mL) was brought to reflux for 12 h. After evaporation of the solvent, the residue was subjected to alumina gel column chromatography (eluent: DCM) and then recrystallized in a 50:50 DCM/heptane mixture by slow evaporation of DCM, to afford *B*-(4-bromophenoxy)(subphthalocyaninato)boron(III) **7** as a bronze cristalinae solid (51 mg, 75%). *Method B:* BCl_3 (4 mL, 1 M solution in p-xylene) was added to dry phthalonitrile (500 mg, 4 mmol), under an argon atmosphere. The vessel was placed in a preheated oil bath (150 °C) and the mixture was stirred and left to reflux for 30 min. The solvent was removed under reduced pressure and the resulting solid resuspended in toluene (30 mL). Excess of 4-bromophenol (2.08 g, 12 mmol) was added and the mixture was heated to reflux during 15 h. After evaporation to dryness, the residue was subjected to alumina gel column chromatography (eluent: dichloromethane) to remove the excess of phenol and then to silica gel column chromatography (eluent: DCM), to afford the desired subphthalocyanine **7** (200 mg, 26%). **^{1}**H NMR (300 MHz, DMSO-d_6, 300 K): δ (ppm) = 5.27 (d, ^{3}J = 8.8 Hz, 2H); 6.84 (d, ^{3}J = 8.8 Hz, 2H); 7.91 (m, 6H); 8.85 (m, 6H). ^{11}B NMR (96 MHz, $CDCl_3$, 300 K): δ (ppm) = −15.07 (s, 1B). UV–Vis (DCM): λ_{max} (nm) ($\varepsilon \times 10^3$ L mol^{-1} cm^{-1}) = 305 (42.3), 564 (61.7). CCDC 1555143.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.tet.2018.01.029.

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