TÜBİTAK

Turkish Journal of Chemistry

http://journals.tubitak.gov.tr/chem/

Research Article

Turk J Chem
(2013) 37: 394 – 404

doi:10.3906/kim-1207-61

A phthalocyanine–fluorescein conjugate

İlker ÜN,[‡] Yunus ZORLU,[‡] Hanife İBİŞOĞLU, Fabienne DUMOULIN,[*] Vefa AHSEN
Department of Chemistry, Gebze Institute of Technology, Kocaeli, Turkey

Received: 26.07.2012 • **Accepted:** 13.03.2013 • **Published Online:** 10.06.2013 • **Printed:** 08.07.2013

Abstract: A phthalocyanine–fluorescein conjugate was designed and prepared. Its photophysical properties (electronic absorption and fluorescence) were determined and compared with those of an analogous derivative functionalized by a simple triazole without chromophore. It is likely to be used as a theranostic agent in photodynamic therapy.

Key words: Phthalocyanine, fluorescein, electronic absorption, fluorescence, theranostic agent, third-generation photosensitizer

1. Introduction

Theranostics are treatment strategies that associate diagnostics and therapeutics, mainly against cancer.[1] Imaging techniques, treatment monitoring, precise molecule delivery, and/or personalized adaptation of the medication are combined and optimized. These expanding medical approaches take place in several cancer treatment procedures: surgery[2] and cell screening[3,4] among others. While nanotheranostics integrating these imaging and treatment features on nanoparticles of various types[5–8] are being developed fast, molecular theranostic agents are scarcely described.

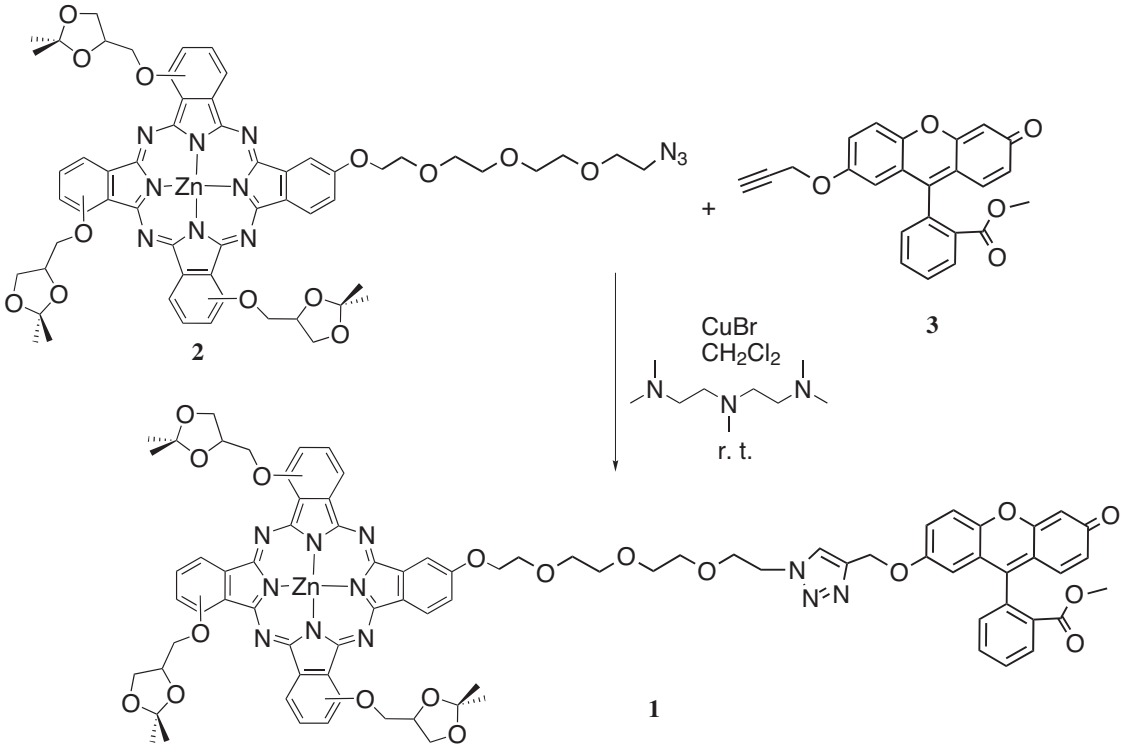
Photodynamic therapy (PDT) is an alternative cancer treatment based on the oxidative destruction of tumors via the local generation of singlet oxygen by a photosensitizer excited by appropriate wavelength.[9] In the last 4 decades, extensive chemical research on photosensitizers dramatically optimized their efficiency, with the successive development of several generations of molecules.[10] Recent research focuses on the development of theranostic agents combining imaging and photosensitizing properties.

Phthalocyanines have an original electronic structure based on 18 π delocalization, resulting in near-infrared absorption around 700 nm and possibly up to 1000 nm by increasing the electronic delocalization.[11] Subsequent electronic, photophysical, and photochemical properties are desired for many applications.[12] Phthalocyanines are broadly employed as sensors,[13] oxidation catalysts,[14] and photocatalysis,[15] as well as for their nonlinear properties.[16] Their use as photosensitizers of second and third generation for photodynamic therapy[17] remains a major one. Among the various types of phthalocyanines used in PDT, possibly water-soluble,[18] we focus on the development of glycerol-substituted derivatives[19] with enhanced properties thanks to various functionalizations: carbohydrates,[20] tailored amphiphilicity,[21] or different metalation.[22]

Fluorescein is used for fluorescence-based applications.[23] As a fluorescence probe, it has been widely functionalized to allow versatile coupling to molecules for their labeling: oligonucleotides,[24] nanoparticles,[25]

[*]Correspondence: fdumoulin@gyte.edu.tr
[‡]These 2 authors contributed equally to this work

pH sensitive moieties,[26] etc. Bioorthogonal approaches have been developed as well.[27] Azaphthalocyanines conjugated to various fluorophores—including fluorescein—behave as dark quenchers[28] of DNA polymerization monitoring. Keeping the glycerol substitution basis, we designed the fluorescein–phthalocyanine conjugate **1** (Scheme), likely to combine the photoproperties of both derivatives: the fluorescence imaging provided by the fluorescein moiety at its own excitation wavelengths and the photodynamic activity of the phthalocyanine part, resulting in enhanced flexibility for the imaging excitation wavelengths.



Scheme. Preparation of phthalocyanine–fluorescein conjugate **1**.

2. Results and discussion

2.1. Syntheses and characterizations

The powerful role of click chemistry in the preparation of functionalized tetrapyrrolic derivatives[29] is a useful tool for such purposes thank to its flexibility, enhancing the design and synthesis of alkynyl-functionalized fluorescein derivatives. Phthalocyanine–fluorescein conjugate **1** was obtained by a click reaction between phthalocyanine **2**[20a] and fluorescein **3**[30] (Scheme).

The alkynylfluorescein derivative (**3**) was prepared following a described procedure[30] and crystallized from chloroform–hexane. Available analytic data[30] were completed by its crystallographic structure (Figure 1) and 2-dimensional HSQC NMR (Figures 2a–d).

Single-crystal X-ray diffraction of **3** (Figure 1a) reveals that the crystal asymmetric unit consists of one independent molecule. The 3 rings in the xanthene moiety have a high degree of planarity. The benzene moiety was almost perpendicular to the xanthene moiety. The dihedral angle between the 2 extended aromatic ring systems is 66.40(2)° and comparable to that observed for *p*-methoxycarbonylphenyl fluorone (64.9(2)°).[31]

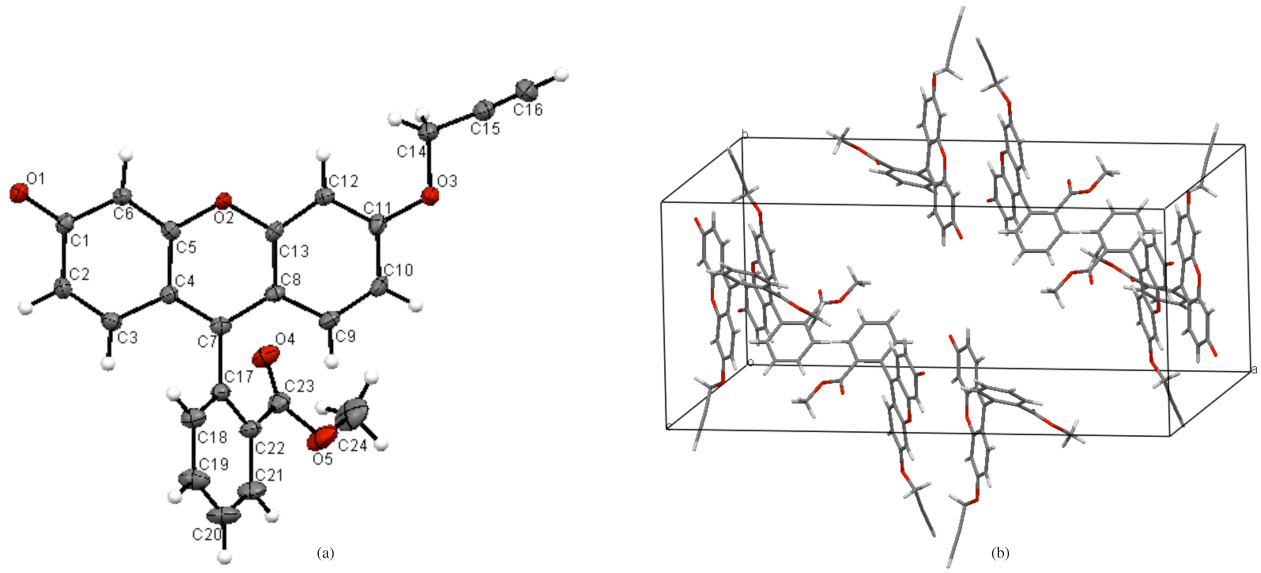


Figure 1. a) Structure of fluorescein derivative **3**. Displacement ellipsoids are drawn at the 50% probability level. H-atoms are shown as small spheres of arbitrary radii; b) Crystal packing of **3.**

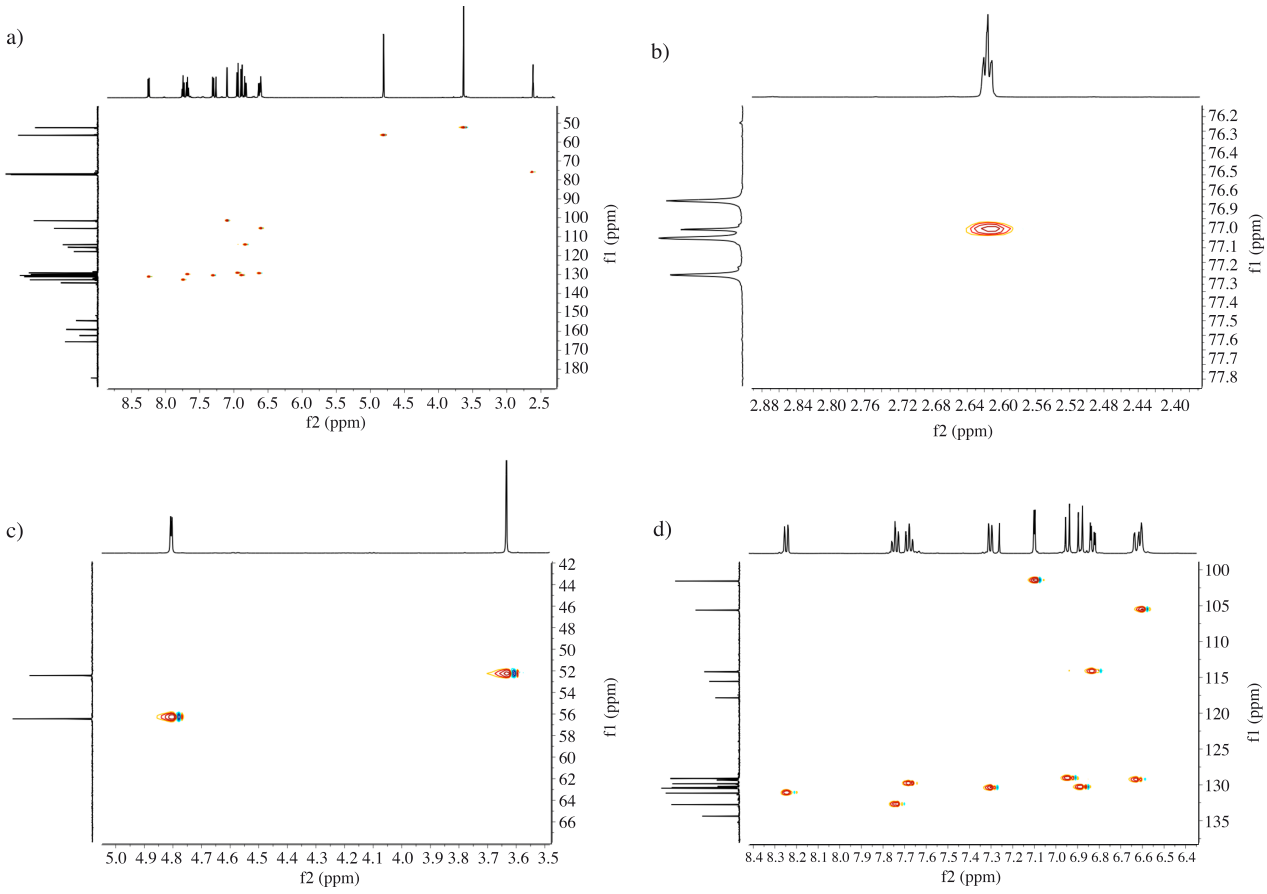


Figure 2. Full HSQC NMR spectrum of **3** (a), magnifications corresponding to the alkynyls (b), to the CH_2 and CH_3 protons (c), and to the aromatic area (d).

Bond lengths and angles may be regarded as normal. Hydrogen bond distances and angles of this compound are presented in Table 1. Crystal data and experimental crystallographic details are presented in Table 2. Crystal packing is stabilized by intermolecular C-H$\cdots$O hydrogen bond and $\pi \cdots \pi$ stacking interactions (Figure 1b).

Table 1. Hydrogen bond distances [Å] and angles [°] for fluorescein derivative **3**.

D-H$\cdots$A	D-H	H$\cdots$A	D$\cdots$A	D-H$\cdots$A
C6-H6$\cdots$O2^{i}	0.95	2.60	3.499(3)	158
C9-H9$\cdots$O4^{ii}	0.95	2.39	3.109(3)	132
C12-H12$\cdots$O1^{i}	0.95	2.45	3.362(3)	160
C14-H14A$\cdots$O1^{ii}	0.99	2.42	3.221(3)	137
C16-H16$\cdots$O1^{iii}	0.95	2.21	3.141(3)	165
C12-H12$\cdots$O1^{iv}	0.95	2.40	3.337(3)	171

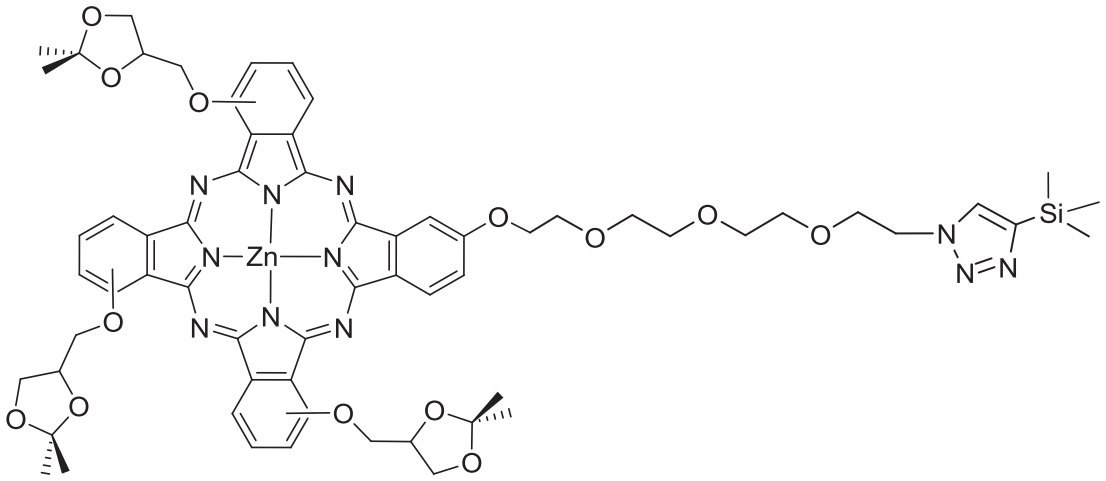
Symmetry codes: (i) 1 – x, 2 – y, 1 – z; (ii) x, 2 – y, –1/2 + z; (iii) 1 – x, 1 + y, 1/2 – z; (iv) 1 – x, y, 1/2 – z

Table 2. Crystal data and experimental crystallographic details for **3**.

Empirical formula	$C_{24}H_{16}O_5$
Formula weight	384.37
Temperature	120(2) K
Radiation, wavelength	Mo-$K\alpha$, 0.71073 Å
Crystal system, space group	Monoclinic, C2/c
Habit, color	Needle, orange
Unit cell dimensions	
a	28.3554(12) Å
b	13.7108(6) Å
c	10.4106(5) Å
α	90°
β	110.608(3)°
γ	90°
Volume	3788.4(3) Å^3
Crystal size	0.030 × 0.050 × 0.570 mm
Z	8
Calculated density	1.348 Mg/cm^3
Absorption coefficient	0.095 mm^{-1}
$F(000)$	1600
θ range for data collection	1.53 to 25.03°
Limiting indices	–33 $\leq$ h $\leq$ 33, –16 $\leq$ k $\leq$16, –12 $\leq$ l $\leq$ 12
Reflections collected	26,257
Absorption correction	multiscan
Independent reflections	3357
Max. and min. transmission	0.9969 and 0.9482
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	3357/0/264
Goodness-of-fit on F^2	1.073
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0456$, $wR_2 = 0.1091$
R indices (all data)	$R_1 = 0.0737$, $wR_2 = 0.1215$
Largest diff. peak and hole	0.239 and –0.251 e Å^{-3}

The click reaction between **2** and **3** was conducted using copper(I) bromide and *N*,*N*,*N*',*N*",*N*" pentamethyldiethylenetriamine (PMDETA) in dichloromethane and led to the expected compound **1** in high yield (83%). For comparative purposes, commercial ethynyltrimethylsilane was simply clicked to azidophthalocyanine **2**, giving the conjugate **4** (Figure 3). This close analogue of **1** has no fluorescein moiety but includes the same phthalocyanine and a triazole ring, in order to be able to attribute the observed behavior variations only to the presence of the fluorescein part. Thanks to photoinerty of the TMS function, its cleavage is not required for this study.

Conjugates **1** and **4** were characterized by mass spectrometry, ATR-IR, and ^{1}H and ^{13}C NMR, their purity being ascertained by HPLC (Figures 4a and 4b).



4

Figure 3. Structure of analogous **4**.

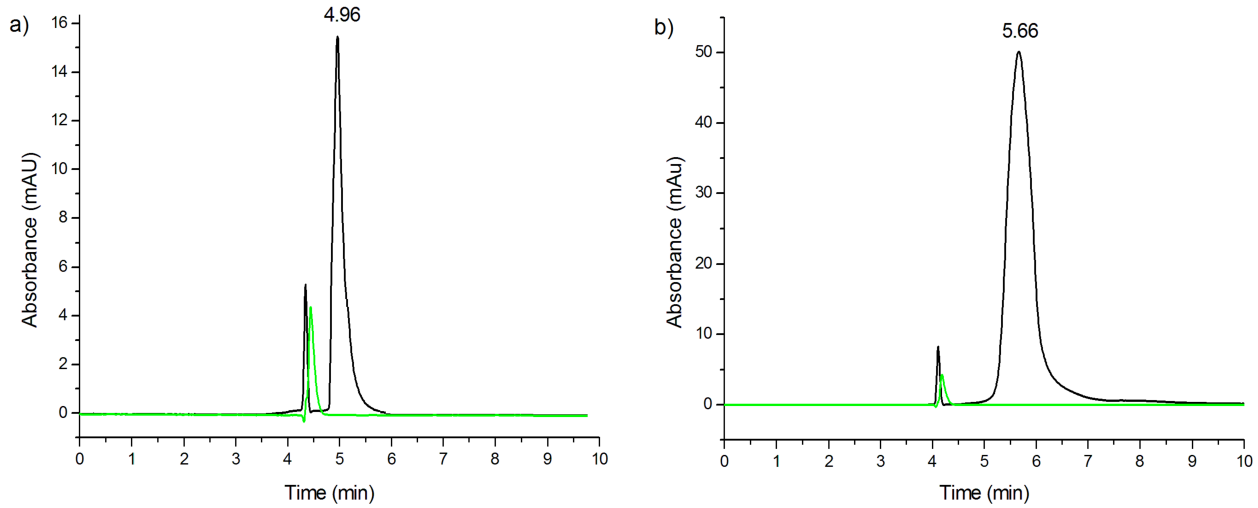


Figure 4. HPLC profile of (a) **1** and (b) **4**.

Comparative analysis of the FT-IR spectra of **1** and **4** evidences the stronger intensity of peaks due to aromatic bonds in **1**, attributable to the presence of the fluorescein moiety. Sharp carbonyl peaks at 1722 and 1641 cm^{-1} in the spectrum of **1** are due as well to the fluorescein part. Peaks centered at 3070 cm^{-1} in the

spectrum of both compounds are due to the aromatic stretchings of the triazole and phthalocyanine macrocycle bonds.[29b] Phthalocyanine derivatives prepared in these works are isomeric mixtures. For this reason, their NMR spectra present overlapping peaks of tedious interpretation. Characteristic peaks can be observed, such as carbonyl peaks resonating at low fields in the ^{13}C NMR spectrum of **1**, whereas no peaks are present in the same area of the spectrum of **4**. A characteristic peak of the methyl carbons attached to the silicon atom in the spectrum of **4** is observed at –0.98 ppm.

2.2. Photophysical measurements

Photophysical measurements were conducted in DMSO, a solvent suitable for fluorescein-containing molecules,[32] as well as in ethanol and chloroform. Electronic absorption spectra of the derivatives **1**, **3**, and **4** in DMSO are presented in Figure 5. Table 3 summarizes the values observed depending on the solvent for the Q band of phthalocyanine derivatives **1** and **4**. Maximum absorption wavelengths corresponding respectively to the phthalocyanine and the fluorescein moiety are not modified by the coupling, but Q band intensity is synergistically increased by its presence in all solvents tested (Table 3). Absorption due to fluorescein moiety is clearly additive, as seen in the conjugate spectrum between 400 and 520 nm, with perfectly superimposed curves in this area for **1** and **3**.

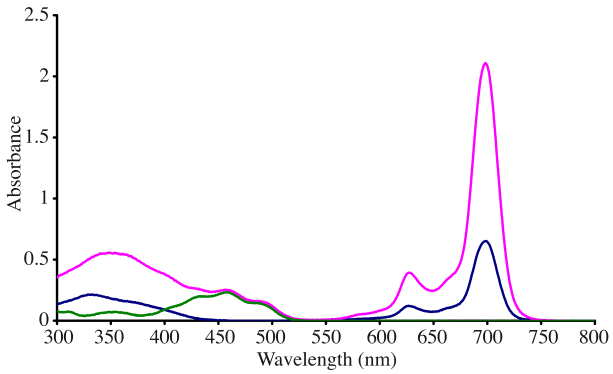


Figure 5. UV-vis spectra of phthalocyanine-fluorescein conjugate **1** (pink), fluorescein **3** (green), and reference **4** (blue) in DMSO (10 μM).

Table 3. Electronic absorption data of **1** and **4**.

Compound	Solvent	Q band λ_{max} (nm)	log ε
1	DMSO	699	5.32
	$CHCl_3$	696	5.32
	EtOH	695	5.20
4	DMSO	699	4.81
	$CHCl_3$	697	4.86
	EtOH	690	4.92

Fluorescence measurements were recorded by exciting **1**, **3**, and **4** at 450 nm (Figure 6a), and **1** and **4** at 664 nm (Figure 6b). Fluorescence quantum yields, Stokes shifts for the Q band, and maximum emission wavelengths are summarized in Table 4. A Förster resonance energy transfer is observable when exciting at 450 nm: the emission of **1** compared to **4** is much stronger (Figure 6). This FRET effect is due to the excitation

of the phthalocyanine Q band by the fluorescence emission of the fluorescein moiety, and is not observed on control conjugate **4**. The presence of the fluorescein moiety on **1** allows generation of fluorescein by excitation at various wavelengths, a desirable flexibility for imaging purposes.

Table 4. Fluorescence data of **1** and **4** (λ_{exc} 664 nm).

Compound	Solvent	Emission	Stokes shift	Φ_F
		λ_{em} (nm)	Δ_{Stokes} (nm)	
1	DMSO	710	11	0.11
	$CHCl_3$	709	13	0.03
	EtOH	702	7	0.02
4	DMSO	705	6	0.14
	$CHCl_3$	709	12	0.14
	EtOH	700	10	0.13

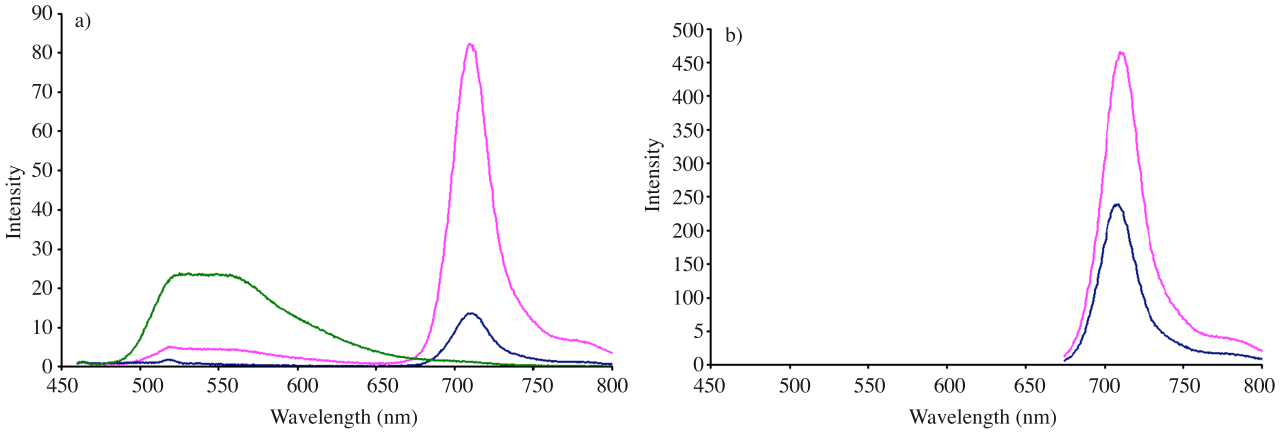


Figure 6. Normalized emission spectra of phthalocyanine–fluorescein conjugate **1** (pink), fluorescein **3** (green), and reference **4** (blue) in DMSO. λ_{exc} 450 nm in a), λ_{exc} 664 nm in b).

3. Experimental part

3.1. Materials and methods

Optical spectra in the UV-visible region were recorded with a Shimadzu 2001 UV spectrophotometer using a 1-cm path length cuvette at room temperature. Mass spectra were recorded on a MALDI (matrix assisted laser desorption ionization) BRUKER Microflex LT using 2,5-dihydroxybenzoic acid as matrix. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ solutions on a Varian 500 MHz spectrometer. The HPLC system is an Agilent 1100 series HPLC system (ChemStation software) equipped with a G1311A pump and G1315B diode array detector monitoring the range 254–900 nm. A normal phase column Lichrosorb-SI-60 (250 × 4.6 mm) from Alltech Associates, Inc. was used. The mobile phase was a 50/50 (v/v) mixture of chloroform/THF. The column temperature was maintained at 28 °C. The flow-rate was set at 0.8 mL min^{-1} and the sample was dissolved in chloroform at a concentration of 0.2 mg mL^{-1}.

3.2. Synthesis of 1

Azidophthalocyanine **2** (20 mg, 16.9 μmol) and methyl 2-(3-oxo-6-(prop-2-ynyloxy)xanthen-9-yl)benzoate **3** (10 mg, 25.4 μmol, 1.5 equiv.) were dissolved in degassed CH_2Cl_2 (10 mL) under argon. *N*,*N*,*N*',*N*",*N*"

pentamethyldiethylenetriamine (5 mg, 25.4 μmol) was added and the solution was purged for 5 min with argon. Then copper(I) bromide (4 mg, 25.4 μmol) was added and the mixture was purged with argon for 5 min more. The reaction mixture was stirred at room temperature for 48 h, then diluted with CH_2Cl_2, and washed with water (10 mL). The organic phase was dried on Na_2SO_4 and concentrated. **1** was purified by silica gel column chromatography. Elution with ethyl acetate removed most of the impurities; then the column was equilibrated with CH_2Cl_2 and eluted by a gradient ending with CH_2Cl_2/THF 5/1. **1** was obtained pure after a last purification by preparative silica gel thin layer chromatography, elution CH_2Cl_2/THF 3/1. Yield 83% (22 mg). $C_{82}H_{77}N_{11}O_{18}Zn$, MW 1569.96. MALDI-TOF-MS m/z: 1568.70. FTIR (KBr): n_{max} (cm^{-1}) 3068, 2984, 2932, 2874, 1722, 1641, 1592, 1505, 1486, 1452, 1379, 1335, 1269, 1238, 1207, 1104, 1081, 1049, 1027, 1006, 962, 934, 918, 877, 839, 800, 740 709, 664. ^{1}H NMR (DMSO-d_6, δ, ppm): 9.3–6.3 (m, 23H, Ar, triazole), 5.5–4.2 (m, 15H, $3CH_2CHCH_2$, 2H, CCH_2O), 4.1–3.4 (m, 19H, $4OCH_2CH_2O$, OCH_3), 1.65–1.39 (m, 18H, 6 CH_3). ^{13}C NMR (DMSO-d_6, δ, ppm): (overlapping signals) 182.89, 167.10, 164.77, 156.99, 156.41, 153.05, 141.97, 137.83, 137.06, 134.12, 133.44, 131.01, 126.56, 125.83, 125.25, 117.21, 115.75, 114.13, 114.13, 109.59, 109.33, 78.00, 75.11, 74.70, 72.21, 70.58, 70.36, 70.07, 69.11, 68.54, 66.55, 62.27, 52.60, 49.96, 39.80, 27.36, 27.15, 26.19, 25.85. HPLC t_R: 4.96 min.

3.3. Synthesis of 4

Azidophthalocyanine **2** (20 mg, 16.9 μmol, 1 equiv.) and ethynyltrimethylsilane (2.54 mg, 25.4 μmol, 1.5 equiv) were dissolved in degassed CH_2Cl_2 (10 mL) under argon. N,N,N',N'',N''pentamethyldiethylenetriamine (8.8 mg, 50.7 μmol, 3 equiv.) was added and the solution was purged for 5 min with argon. Then copper(I) bromide (7.27 mg, 50.7 μmol, 3 equiv.) was added and the mixture was purged with argon for 5 min more. The reaction mixture was stirred at room temperature for 48 h; only one new product was observed and no starting material **2** was detected by TLC. Then it was diluted with CH_2Cl_2 and washed with water (10 mL). The organic phase was dried on Na_2SO_4 and concentrated. **5** was purified by chromatography on silica gel (CH_2Cl_2/THF 3/1). Yield: 19 mg, (87.7%). $C_{63}H_{71}N_{11}O_{13}SiZn$, MW 1283.80. MALDI-TOF-MS m/z: 1282.52. FTIR (KBr): n_{max} (cm^{-1}) 3072, 2983, 2933, 2877, 1769, 1726, 1650, 1606, 1542, 1487, 1453, 1371, 1336, 1278, 1242, 1219, 1157, 1083, 1051, 1035, 992, 974, 930, 839, 801, 800, 772, 744, 675. ^{1}H NMR (DMSO-d_6, δ, ppm): 9.2–7.0 (m, 13H, Ar, triazole), 5.35–4.05 (m, 15H, 3 CH_2CHCH_2), 4.0–3.45 (m, 16H, 4 OCH_2CH_2O), 1.65–1.35 (m, 18H, 6 CH_3), 0.30 (m, 9H, $Si(CH_3)_3$). ^{13}C NMR (DMSO-d_6, δ, ppm): (overlapping signals) 177.84, 168.82, 168.77, 167.42, 163.53, 155.44, 144.51, 136.44, 135.22, 134.73, 130.72, 124.74, 124.50, 120.41, 119.69, 117.82, 115.13, 114.85, 109.12, 108.96, 108.90, 108.25, 74.65, 74.30, 73.61, 73.32, 70.19, 69.92, 69.75, 69.65, 69.56, 69.33, 68.79, 68.74, 68.67, 68.27, 66.16, 65.40, 57.98, 48.74, 27.41, 26.92, 26.73, 26.43, 25.74, 25.55, 25.42, 24.90, 21.74, –0.98. HPLC t_R: 5.66 min.

3.4. X-ray data collection and structure refinement for 3

Molecular geometry calculations were performed with PLATON v 1.16,[33] and molecular graphics were prepared using CCDC-Mercury.[34] Crystal of methyl 2-(3-oxo-6-(prop-2-ynyloxy)xanthen-9-yl)benzoate was grown from chloroform–hexane. A clear orange needle-like specimen of $C_{24}H_{16}O_5$, approximate dimensions 0.030 mm × 0.050 mm × 0.570 mm, was used for the X-ray crystallographic analysis. Unit cell measurements and intensity data collection was performed at 120(2) K on a Bruker Smart APEXII difractometer using monochromatized Mo $K\alpha$ X-radiation (λ = 0.71073 Å). The data reduction included correction for Lorentz and polarization effects,

with applied multiscan absorption correction (SADABS).[35] The structure was solved using the direct methods procedure in SHELXS-97 and then refined by full-matrix least-squares refinements on F^2 using SHELXL-97.[36] All nonhydrogen atoms were refined anisotropically using all reflections with $I > 2\sigma(I)$ and the hydrogen atoms were included riding on the respective parent atom with isotropic thermal displacement factors fixed at 1.2 times the U(eq) of the parent atoms (1.5 times for methyl groups).

3.5. Fluorescence quantum yield

Fluorescence quantum yields (Φ_F) were determined by the comparative method using Eq. 1 [1]:

$$\Phi F = \Phi_F(Std)\frac{F \cdot A_{Std}}{F_{Std} \cdot A}, \quad (1)$$

where F and F_{Std} are the areas under the fluorescence emission curves of the studied molecules and the standard, respectively. A and A_{Std} are the respective absorbances (which was $\sim$0.05) of the sample and standard at the excitation wavelengths. Unsubstituted ZnPc ($\Phi_F = 0.20$) [2] was employed as the standard.

4. Conclusion

The photophysical properties of phthalocyanine–fluorescein conjugate **1** compared to **4** reveal its potential as a theranostic agent. The effect of the presence of the fluorescein on the singlet oxygen generation as well as on biological photodynamic activity is currently under investigation. Furthermore, water-soluble derivatives are being prepared. Other fluorophores will be grafted as well.

Supplementary data

CCDC-840034 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre (CCDC), 12 Union Road, Cambridge CB2 1EZ, UK; fax: + 44(0)1223-336033; email: deposit@ccdc.cam.ac.uk).

References

1. Kelkar, S. S.; Reineke, T. M. *Bioconjugate Chem.* **2011**, *22*, 1879–1903.
2. Manthe, R. L.; Foy, S. P.; Krishnamurthy, N.; Sharma, B.; Labhasetwar, V. *Mol. Pharm.* **2010**, *7*, 1880–1898.
3. Stasinopoulos, I.; Penet, M. F.; Chen, Z.; Kakkad, S.; Glunde, K.; Bhujwalla, Z. M. *NMR Biomed.* **2011**, *24*, 636–647.
4. Paterlini-Bréchot, P. *Futur. Oncol.* **2011**, *7*, 849–871.
5. Lammers, T.; Kiessling, F.; Hennink, W. E.; Storm, G. *Mol. Pharm.* **2010**, *7*, 1899–1912.
6. Ho, Y.-P.; Leong, K. W. *Nanoscale* **2010**, *2*, 60–68.
7. Pan, D.; Caruthers, S. D.; Chen, J.; Winter, P. M.; Senpan, A.; Schmieder, A. H.; Wickline, S. A.; Lanza, G. M. *Future Med. Chem.* **2010**, *2*, 471–490.
8. Garcia-Bennett, A. E. *Nanomed.* **2011**, *6*, 867–877.
9. (a) Pandey, R. K. *J. Porphyr. Phthalocya.* **2000**, *4*, 368–373; (b) Macdonald, I. J.; Dougherty, T. J. *J. Porphyr. Phthalocya.* **2001**, *5*, 105–129; (c) Josefsen, L. B.; Boyle, R. W. *Met.-Based Drugs* **2008**, 1–24; (d) Ali, H.; van Lier, J. E. *Chem. Rev.* **1999**, *99*, 2379–2450.

10. (a) Hudson, R.; Boyle, R. W. *J. Porphyr. Phthalocya.* **2004**, *8*, 954–975; (b) Taquet, J.-P.; Frochot, C.; Manneville, V.; Barberi-Heyob, M. *Curr. Med. Chem.* **2007**, *14*, 1673–1687; (c) Bugaj, A. M. *Photochem. Photobiol. Sci.* **2011**, *10*, 1097–1109; (d) Bullous, A. J.; Alonso, C. M. A.; Boyle, R. W. *Photochem. Photobiol. Sci.* **2011**, *10*, 721–750.

11. (a) Makarov, S.; Litwinski, C.; Ermilov, E. A.; Suvorova, O.; Röder, B.; Wöhrle, D. *Chem. Eur. J.* **2006**, *12*, 1468–1474; (b) Kobayashi, N.; Furuyama, T.; Satoh, K. *J. Am. Chem. Soc.* **2011**, *133*, 19642–19645; (c) Köç, M.; Gürek, A. G.; Dumoulin, F.; Ahsen, V. *Turk. J. Chem.* **2012**, *36*, 493–502.

12. Garcia, J.; Gonzalez, A.; Gouloumis, A.; Maya, E. M.; Perez, M. D.; Rey, B. D.; Vazquez, P.; Torres, T. *Turk. J. Chem.* **1998**, *22*, 23–31.

13. (a) Guillaud, G.; Simon, J.; Germain, J. P. *Coord. Chem. Rev.* **1998**, *178–180*, 1433–1484; (b) Zhou R.; Josse F.; Göpel, W.; Öztürk, Z. Z.; Bekaroğlu, Ö. *Applied Organomet. Chem.* **1996**, *10*, 557–577; (c) Rodriguez-Méndez, M. L.; Gaya, M.; Antonio de Saja, J. *J. Porphyr. Phthalocya.* **2009**, *13*, 1159–1167.

14. (a) Simonneaux, G.; Tagliatesta, P. *J. Porphyr. Phthalocya.* **2004**, *8*, 1166–1171; (b) Zagal, J. H.; Griveau, S.; Silva, J. F.; Nyokong, T.; Bedioui, F. *Coord. Chem. Rev.* **2010**, *254*, 2755–2791; (c) İşci, Ü.; Afanasiev, P.; Millet, J.-M. M.; Kudrik, E. V.; Ahsen, V.; Sorokin, A. B. *Dalton Trans.* **2009**, 7410–7420.

15. Bressan, M.; d'Alessandro, N.; Liberatore, L.; Morvillo, A. *Coord. Chem. Rev.* **1999**, *385*, 185–186.

16. (a) Ayhan, M. M.; Singh, A.; Hirel, C.; Gürek, A. G.; Ahsen, V.; Jeanneau, E.; Ledoux-Rak, I.; Zyss, J.; Andraud, C.; Bretonnière, Y. *J. Am. Chem. Soc.* **2012**, *8*, 3655–3658; (b) Dini, D.; Barthel, M.; Hanack, M. *Eur. J. Org. Chem.* **2001**, 3759–3769; (c) de la Torre, G.; Vázquez, P.; Agulló-López, F.; Torres, T. *Chem. Rev.* **2004**, *104*, 3723–3750.

17. Dumoulin, F.; Durmuş, M. *In Photosensitizers in Medicine, Environment, and Security*; Nyokong, T.; Ahsen, V., Eds; Springer, New York, 2012.

18. Dumoulin, F.; Durmuş, M.; Ahsen, V.; Nyokong, T. *Coord. Chem. Rev.* **2010**, *254*, 2792–2847.

19. (a) Pashkovskaya, A.; Kotova, E.; Zorlu, Y.; Dumoulin, F.; Ahsen, V.; Agapov, I.; Antonenko, Y. *Langmuir* **2010**, *26*, 5726–5733; (b) Zorlu, Y.; Ermeydan, M. A; Dumoulin, F.; Ahsen, V.; Savoie, H.; Boyle, R. W. *Photochem. Photobiol. Sci.* **2009**, *8*, 312–318; (c) Giuntini, F.; Dumoulin, F.; Daly, R.; Ahsen, V.; Scanlan, E. M.; Lavado, A.; Aylott, J. W.; Rosser, G.; Beeby, A.; Boyle, R. W. *Nanoscale* **2012**, *4*, 2034–2045.

20. (a) Zorlu, Y.; Dumoulin, F.; Bouchu, D.; Ahsen V.; Lafont, D. *Tetrahedron Lett.* **2010**, *51*, 6615–6618; (b) Lafont, D.; Zorlu, Y.; Savoie, H.; Albrieux, F.; Ahsen, V.; Boyle, R. W.; Dumoulin, F. *Photodiag. Photodyn. Ther.*, **2013**, in press http://dx.doi.org/10.1016/j.pdpdt.2012.1.

21. (a) Dumoulin, F.; Ali, H.; Ahsen, V.; van Lier, J. E. *Tetrahedron Lett.* **2011**, *52*, 4395–4397; (b) Ermeydan, M. A.; Dumoulin, F.; Basova, T. V.; Bouchu, D.; Gürek, A. G.; Ahsen, V.; Lafont, D. *New. J. Chem.* **2010**, *34*, 1153–1162.

22. Zorlu, Y.; Dumoulin, F.; Durmuş, M.; Ahsen, V. *Tetrahedron* **2010**, *66*, 3248–3258.

23. Thielbeer, F. *Synlett* **2012**, *23*, 1703–1704

24. Seo, T. S.; Li, Z.; Ruparel, H.; Ju, J. *J. Org. Chem.* **2003**, *68*, 609–612.

25. Tanaka, K.; Kitamura, N.; Chujo, Y. *Bioconjugate Chem.* **2011**, *22*, 1484–1490.

26. Kim, H. N.; Swamy, K. M. K.; Yoon, J. *Tetrahedron Lett.* **2011**, *52*, 2340–2343.

27. Kele, P.; Li X.; Link, M.; Nagy, K.; Herner, A.; Lőrincz, K.; Béni, S.; Wolfbeis, O. S. *Org. Biomol. Chem.* **2009**, *7*, 3486–3490.

28. (a) Kopecky, K.; Novakova, V.; Miletin, M.; Kučera, R.; Zimcik, P.; *Tetrahedron* **2011**, *67*, 5956–5963; (b) Kopecky, K.; Novakova, V.; Miletin, M.; Kučera, R.; Zimcik, P. *Bioconjugate Chem.* **2010**, *21*, 1872–1879.

29. (a) Dumoulin, F.; Ahsen, V. *J. Porphyr. Phthalocya.* **2011**, *15*, 481–504; (b) Yılmaz, Y.; Şener, M. K.; Erden, İ.; Avcıata, U. *Polyhedron* **2009**, *28*, 3419–3424.

30. Daugaard, A. E.; Hvilsted, S.; Hansen, T. S.; Larsen, N. B.; *Macromolecules* **2008**, *41*, 4321–4327.

31. Kamino, S.; Kawamae, Y.; Ijyuin, M.; Takada, S.; Yamaguchi, T.; Doi, M.; Fujita, Y. *Chem. Pharm. Bull.* **2009**, *57*, 1405–1408.

32. Cook, A.; Le, A. *J. Phys. Chem. Lab* **2006**, *10*, 44–49.

33. Spek, A. L. *J. Appl. Crystallogr.* **2003**, *36*, 7–13.

34. Macrae, C. F.; Edgington, P. R.; McCabe, P.; Pidcock, E.; Shields, G. P.; Taylor, R.; Towler, M.; van de Streek, J. *J. Appl. Cryst.* **2006**, *39*, 453–457.

35. Bruker, *SADABS*, Bruker AXS Inc., Madison, Wisconsin, USA, 2005.

36. Sheldrick, G. M. *Acta Cryst.* **2008**, *A64*, 112–122.