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Synthesis of porphyrin–quinolone conjugates

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ABSTRACT

meso-Tetrakis(pentafluorophenyl)porphyrin reacts with propargyl alcohol to afford porphyrins substituted with one, two, three or four prop-2-yn-1-yloxy groups in the 4-position of the *meso*-aryl groups. These new porphyrin derivatives react with a 6-azidoquinolone under 'click-chemistry' conditions to give porphyrin–quinolone conjugates linked by 1,2,3-triazole units.

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1. Introduction

Since the discovery of nalidixic acid, the parent compound of the quinolone antibiotics, the molecular structures of quinolones have been extensively modified to improve their pharmacological properties and pharmacokinetic profiles.[1–4] Quinolones are easily synthesized, have a broad antimicrobial spectrum, are orally and parenterally active and, apart from a few exceptions, are non-toxic compounds. Therefore, they are important agents against microbial pathogens. Ciprofloxacin and levofloxacin, two quinolones introduced in 1986 and 1993, respectively, are the most successful (economically and clinically) of all the totally synthetic antimicrobial drugs.[1] Quinolones are also being considered for the treatment of fungal and viral[5] infections and for cancer chemotherapy.[6] The antimicrobial activity of the quinolone derivatives is due to the inhibition of DNA synthesis by targeting two essential topoisomerases: DNA gyrase and topoisomerase IV.[1]

Porphyrin derivatives are also exhibiting several medicinal applications, namely as photosensitizers in the photodynamic therapy (PDT) of cancer diseases, in the treatment of age-related macular degeneration, and in the diagnosis of neoplastic diseases.[7] Porphyrins are also very effective against bacteria and viruses and are currently being studied for the photodynamic inactivation of pathogenic microorganisms.[8,9] For example, porphyrins are highly active against viral diseases such as herpes simplex viruses[10] and fungal infections.[11]

The emergence of antibiotic resistance among pathogenic bacteria has led to a major research effort to find alternative antibacterial therapeutics. In this context, the synthesis of molecules with dual functions may be a good strategy for the discovery of new drugs. Those molecules can be achieved by coupling entities containing well-established pharmacological activities. Frequently, the resulting dyad systems have improved biochemical characteristics relatively to their components or even new biological properties.[12] With this in mind, we have designed a synthetic route to porphyrin–quinolone conjugates which involves the 1,3-dipolar cycloaddition of an azidoquinolone to porphyrins bearing alkynyl groups. It is expected that the new conjugates will display interesting biological activities.

This Letter describes the synthesis of five novel porphyrin–quinolone conjugates (**5a**–**d**) linked by 1,2,3-triazole units. Four novel porphyrins bearing one to four prop-2-yn-1-yloxy groups in the 4-position of the *meso*-aryl substituents (**2a**–**d**) were prepared and their reaction with 6-azidoquinolone **4**, under 'click-chemistry' conditions, afforded the corresponding new porphyrin–triazole–quinolones **5a**–**d**. Typically this type of reaction leads to a mixture of isomeric 1,4- and 1,5-disubstituted 1,2,3-triazoles[13] but the copper(I)-catalyzed variant affords selectively the 1,4-disubstituted derivatives.[14–16] This 'click-chemistry'[17] reaction is especially interesting, since it can be conducted under mild conditions, in various solvents, and generally affords high yields of the expected triazoles.

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2. Results and discussion

For the synthesis of the new porphyrin derivatives we started with the simple and symmetric *meso*-tetrakis(pentafluorophenyl)porphyrin (**1**), easily obtained from pentafluorobenzaldehyde and pyrrole under microwave irradiation.[18] The reaction of porphyrin **1** with an excess (10 equiv.) of propargyl alcohol in DMSO, in the presence of potassium carbonate, for 24 h at 80 °C, affords the tetrasubstituted porphyrin **2d** in 65% yield along with a mixture of the di- and tri-substituted porphyrins **2b–c** (Scheme 1). These compounds were separated by column chromatography (silica gel) using chloroform/petroleum ether (1:3) as the eluent.[19] The formation of the mono-substituted derivative **2a** was optimized to 86% yield by using an excess of porphyrin **1** relatively to propargyl alcohol (3:1 molar equiv.). In this case, the reaction was carried out at 50 °C for 4 h; minor amounts of disubstituted products were also formed.

All porphyrin derivatives **2a–d** were fully characterized by ^{1}H and ^{19}F NMR and high resolution mass spectrometry. The ^{1}H NMR spectra of these compounds show typically two singlets at δ 5.23 and 2.82 ppm corresponding to the resonances of the –OCH_2– and –C≡CH protons, respectively.

The formation of the porphyrin–quinolone conjugates involves the 1,3-dipolar cycloaddition reaction of the propynyloxy groups in derivatives **2a–d** with the 6-azidoquinolone **4**[20,21] under 'click-chemistry' conditions, that is, using copper sulfate and ascorbic acid as catalyst.[15] However, since free-base porphyrins are metallated by copper, it was necessary to prepare, previously, the zinc complexes **3a–d**. These complexes were obtained in quantitative yields from the reaction of **2a–d** with zinc acetate in a 2:1 mixture of chloroform/methanol at 50 °C for 15 min.

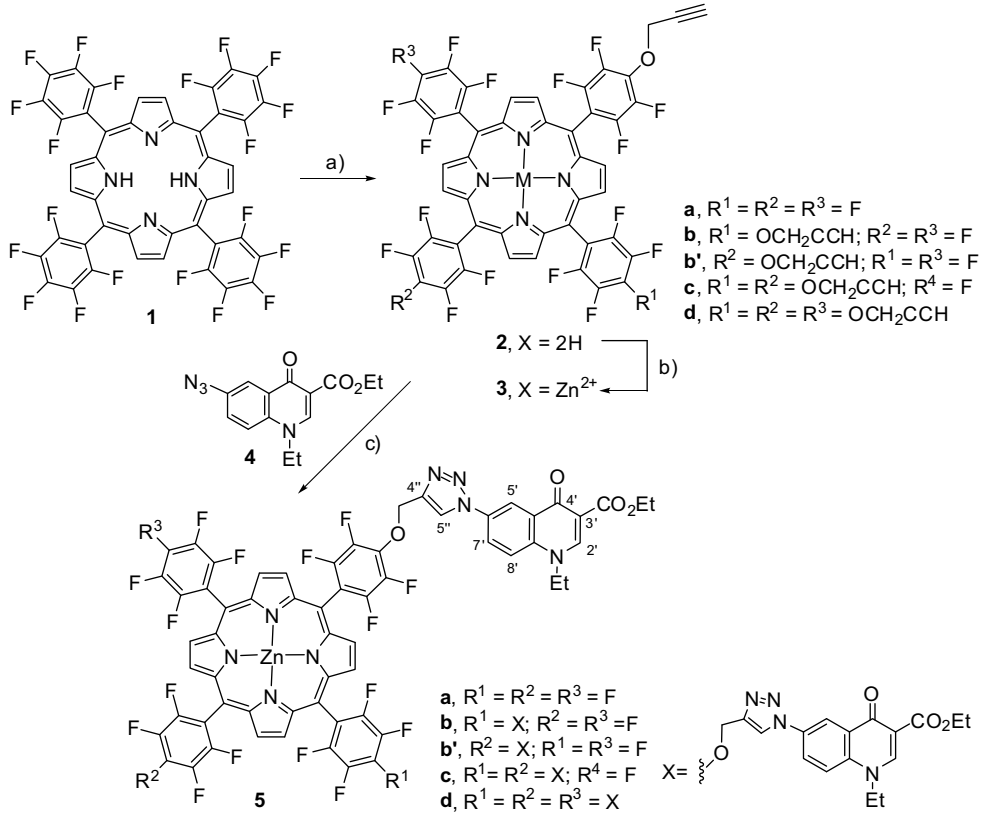
The cycloaddition reactions were carried out in DMF, at 50 °C, for 4–48 h, using 2 equiv. of 6-azidoquinolone **4** for each propynyloxy group (Table 1).[22] The cycloadducts were purified by preparative TLC. The isolated yields of the triazole derivatives are in the range 53–93%, being the best result for the monotriazole derivative. Ditriazole derivatives were obtained in a global 88% yield as a mixture of isomers **5b** and **5b′**, which could be separated by preparative TLC. As expected, the slowest reaction, and the lowest yield (53%), was for the formation of the tetratriazole derivative **5d**.[23]

Table 1
Synthesis of triazoles **5a–d**

Alkyne	Azidoquinolone **4** (number of equiv)	Reaction time (h)	Triazole **5** (isolated yields, %)
3a	2	8	93
3b + **3b′**	4	48	88
3c	6	48	62
3d	8	72	53

The structures of compounds **5a–d** were confirmed by their mass, ^{1}H and ^{19}F NMR spectra.[24] Compound **5a** was also characterized by ^{13}C NMR. Typically, their ^{1}H NMR spectra (in DMSO-d_6) show multiplets in the range of δ 9.22–9.17 ppm corresponding to the β-pyrrolic protons. The quinolone protons H-2′ and H-5′ appear as broad signals in the range of δ 8.82–8.79 ppm, while the proton of the triazole ring (H-5″) appears as a singlet in the range of δ 9.48–9.47 ppm. This pattern is observed for all compounds **5a–d**. The ESI mass spectra of compounds **5a–c** show the $[M+Na]^+$ ion while the spectrum of **5d** shows the $[M+2Na]^{2+}$ ion.

In conclusion, a versatile route to new porphyrin–triazole–quinolone derivatives **5a–d** is described. It involves the nucleophilic displacement of fluorine atoms in porphyrin **1** by reaction with propargyl alcohol, metallation with zinc acetate, and reaction with the 6-azidoquinolone **4** under 'click-chemistry' conditions. Further



Scheme 1. Reagents and conditions: (a) propargyl alcohol, K_2CO_3, DMSO, 50 °C or 80 °C; (b) $Zn(OAc)_2{\cdot}5H_2O$, $CHCl_3$/MeOH 2:1, 50 °C (100%); (c) $CuSO_4{\cdot}5H_2O$, ascorbic acid, DMF, 50 °C, 8–72 h.

studies on the properties of these new porphyrin derivatives are currently under investigation in our laboratories.

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19. It was not possible to separate isomers **2b** and **2b′**. The mixture was used in the cycloaddition reaction with the azidoquinolone **4**, yielding a mixture of ditriazole derivatives **5b** and **5b′**, which were separated by preparative TLC. However, due to the similarity of their NMR spectra, it was not possible to differentiate these two isomers.
20. Azidoquinolone **4** was obtained from the reaction of the corresponding quinolone diazonium salt with sodium azide. The experimental details of this synthesis will be published elsewhere.
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22. General procedure for the 1,3-dipolar cycloadditions: each of metalloporphyrin **3a–d** (0.03 mmol) and the 6-azidoquinolone **4** (2–8 equiv.) were dissolved in DMF (3 mL) and $CuSO_4{\cdot}5H_2O$ (0.03–0.12 mmol) and ascorbic acid (0.06–0.24 mmol) were added. The reaction mixture was stirred at 50 °C until the disappearance of the starting porphyrin (8–72 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 residue was purified by preparative TLC using dichloromethane/ethanol (20:1) as the eluent. Compounds **5a–d** were crystallized from ethanol.
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24. Compound **5a**: mp >300 °C; ^{1}H NMR (300.13 MHz, DMSO-d_6, internal standard: Me_4Si): δ = 1.31 (t, J = 7.1 Hz, 3H, $CO_2CH_2CH_3$), 1.42 (t, J = 6.8 Hz, 3H, NCH_2CH_3), 4.27 (q, J = 7.1 Hz, 2H, $CO_2CH_2CH_3$), 4.51 (q, J = 6.8 Hz, 2H, NCH_2CH_3), 5.82 (s, 2H, OCH_2-triazole), 8.16 (d, J = 9.2 Hz, 1H, H-8′), 8.47 (dd, J = 2.0 and 9.2 Hz, 1H, H-7′), 8.82 (br s, 2H, H-2′ and H-5′), 9.22 (m, 8H, H-β), 9.48 (s, 1H, H-5″); ^{19}F NMR (282.38 MHz, DMSO-d_6, external standard: C_6F_6 at −163 ppm): δ = −185.51 to −185.44 (m, 6F, F-*meta*), −179.57 to −179.50 (m, 2F, F-*meta*), −175.75 (t, J = 22.6 Hz, 3F, F-*para*), −161.78 (dd, J = 7.6 and 23.1 Hz, 2F, F-*ortho*), −160.28 (dd, J = 7.6 and 23.1 Hz, 6F, F-*ortho*); UV–vis (DMSO): λ_{max} ($\log\varepsilon$) = 324 (4.3), 422 (5.3), 551 (4.1) nm; HRMS (ESI) m/z calcd for $C_{61}H_{25}F_{19}N_8O_4ZnNa$ [M+Na]$^+$ 1381.0885, found 1381.0834.
Compound **5b**: mp >300 °C; ^{1}H NMR (300.13 MHz, DMSO-d_6, internal standard: Me_4Si): δ = 1.30 (t, J = 7.1 Hz, 6H, $CO_2CH_2CH_3$), 1.42 (t, J = 7.0 Hz, 6H, NCH_2CH_3), 4.26 (q, J = 7.1 Hz, 4H, $CO_2CH_2CH_3$), 4.50 (q, J = 7.0 Hz, 4H, NCH_2CH_3), 5.81 (s, 4H, OCH_2-triazole), 8.15 (d, J = 9.0, 2H, H-8′), 8.45 (dd, J = 2.5 and 9.0 Hz, 2H, H-7′), 8.81 (br s, 4H, H-2′ and H-5′), 9.22 and 9.18 (d, J = 3.4 Hz, 8H, H-β), 9.47 (s, 2H, H-5″); ^{19}F NMR (282.38 MHz, DMSO-d_6, external standard: C_6F_6 at −163 ppm): δ = −186.69 (dd, J = 5.6 and 28.2 Hz, 4F, F-*meta*), −180.10 (dd, J = 8.5 and 28.2 Hz, 4F, F-*meta*), −177.99 (t, J = 22.6 Hz, 2F, F-*para*), −164.13 (dd, J = 5.6 and 25.4 Hz, 4F, F-*ortho*), −162.78 (dd, J = 5.6 and 28.2 Hz, 4F, F-*ortho*); UV–vis (DMSO): λ_{max} ($\log\varepsilon$) = 325 (4.5), 421 (5.4), 551 (4.1) nm; HRMS (ESI) m/z calcd for $C_{78}H_{42}F_{18}N_{12}O_8ZnNa$ [M+Na]$^+$ 1703.2145, found 1703.2098.
Compound **5b′**: mp >300 °C; ^{1}H NMR (300.13 MHz, DMSO-d_6, internal standard: Me_4Si): δ = 1.31 (t, J = 7.0 Hz, 6H, $CO_2CH_2CH_3$), 1.42 (t, J = 6.9 Hz, 6H, NCH_2CH_3), 4.27 (q, J = 7.0 Hz, 4H, $CO_2CH_2CH_3$), 4.51 (q, J = 6.9 Hz, 4H, NCH_2CH_3), 5.81 (s, 4H, OCH_2-triazole), 8.16 (d, J = 9.1 Hz, 2H, H-8′), 8.45 (dd, J = 2.8 and 9.1 Hz, 2H, H-7′), 8.81 (br s, 4H, H-2′ and H-5′), 9.23 and 9.18 (d, J = 4.7 Hz, 8H, H-β), 9.47 (s, 2H, H-5″); ^{19}F NMR (282.38 MHz, DMSO-d_6, external standard: C_6F_6 at −163 ppm): δ = −186.69 (dd, J = 5.6 and 28.2 Hz, 4F, F-*meta*), −180.10 (dd, J = 8.5 and 28.2 Hz, 4F, F-*meta*), −177.99 (t, J = 22.6 Hz, 2F, F-*para*), −164.13 (dd, J = 5.6 and 25.4 Hz, 4F, F-*ortho*), −162.78 (dd, J = 5.6 and 28.2 Hz, 4F, F-*ortho*); UV–vis (DMSO): λ_{max} ($\log\varepsilon$) = 327 (4.5), 421 (5.5), 551 (4.1) nm; HRMS (ESI) m/z calcd for $C_{78}H_{42}F_{18}N_{12}O_8ZnNa$ [M+Na]$^+$ 1703.2145, found 1703.2077.
Compound **5c**: mp >300 °C; ^{1}H NMR (300.13 MHz, DMSO-d_6, internal standard: Me_4Si): δ = 1.30 (t, J = 7.1 Hz, 9H, $CO_2CH_2CH_3$), 1.42 (t, J = 6.8 Hz, 9H, NCH_2CH_3), 4.27–4.24 (m, 6H, $CO_2CH_2CH_3$), 4.51–4.49 (m, 6H, NCH_2CH_3), 5.82 (s, 6H, OCH_2-triazole), 8.14 (d, J = 9.2 Hz, 3H, H-8′), 8.45 (dd, J = 2.4 and 9.2 Hz, 3H, H-7′), 8.79 (br s, 6H, H-2′ and H-5′), 9.21–9.17 (m, 8H, H-β), 9.47 (s, 3H, H-5″); ^{19}F NMR (282.38 MHz, DMSO-d_6, external standard: C_6F_6 at −163 ppm): δ = −186.69 (dd, J = 8.5 and 31.0 Hz, 2F, F-*meta*), −180.09 (dd, J = 8.5 and 31.0 Hz, 6F, F-*meta*), −178.00 (t, J = 22.6 Hz, 1F, F-*para*), −164.13 (dd, J = 8.5 and 31.0 Hz, 6F, F-*ortho*), −162.77 (dd, J = 8.5 and 31.0 Hz, 2F, F-*ortho*); UV–vis (DMSO): λ_{max} ($\log\varepsilon$) = 340 (4.6), 422 (5.5), 551 (4.1) nm; HRMS (ESI) m/z calcd for $C_{95}H_{59}F_{17}N_{16}O_{12}ZnNa$ [M+Na]$^+$ 2025.3411, found 2025.3376.
Compound **5d**: mp >300 °C; ^{1}H NMR (300.13 MHz, DMSO-d_6, internal standard: Me_4Si): δ = 1.30 (t, J = 7.1 Hz, 12H, $CO_2CH_2CH_3$), 1.42 (t, J = 7.0 Hz, 12H, NCH_2CH_3), 4.26 (q, J = 7.1 Hz, 8H, $CO_2CH_2CH_3$), 4.51–4.49 (m, 8H, NCH_2CH_3), 5.83 (s, 8H, OCH_2-triazole), 8.14 (d, J = 9.2, 4H, H-8′), 8.45 (dd, J = 2.6 and 9.2 Hz, 4H, H-7′), 8.79 (br s, 8H, H-2′ and H-5′), 9.17 (s, 8H, H-β), 9.48 (s, 4H, H-5″); ^{19}F NMR (282.38 MHz, DMSO-d_6, external standard: C_6F_6 at −163 ppm) δ = −179.15 (dd, J = 11.3 and 25.4 Hz, 8F, F-*meta*), −161.82 (dd, J = 11.3 and 25.4 Hz, 8F, F-*ortho*); UV–vis (DMSO): λ_{max} ($\log\varepsilon$) = 337 (4.5), 423 (5.3), 553 (3.9) nm; HRMS (ESI) m/z calcd for $C_{112}H_{76}F_{16}N_{20}O_{16}ZnNa_2$ [M+2Na]$^{2+}$ 1185.2284, found 1185.2321.