Microwave-Enhanced Synthesis of Novel Pyridinone-Fused Porphyrins

Ana M. G. Silva,*[a] Baltazar Castro,[a] Maria Rangel,[b] Artur M. S. Silva,[c] Paula Brandão,[d] Vítor Felix,[d] José A. S. Cavaleiro*[c]

[a] REQUIMTE, Departamento de Química, Faculdade de Ciências, Universidade do Porto, 4169-007 Porto, Portugal
Fax +351(22)0402659; E-mail: ana.silva@fc.up.pt

[b] REQUIMTE, Instituto de Ciências Biomédicas de Abel Salazar, Universidade do Porto, 4099-003 Porto, Portugal

[c] Department of Chemistry, QOPNA, University of Aveiro, 3810-193 Aveiro, Portugal
Fax +351(23)370084; E-mail: jcavaleiro@ua.pt

[d] Department of Chemistry, CICECO, University of Aveiro, 3810-193 Aveiro, Portugal

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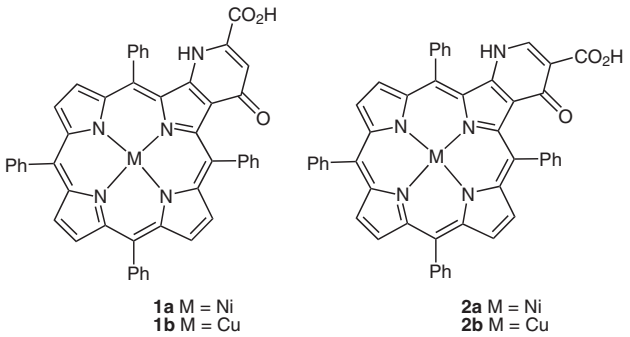
Dedicated to Professor Henk van der Plas on the occasion of his 80th birthday

Abstract: Condensation adducts of the Ni(II) and Cu(II) complexes of β-amino-*meso*-tetraphenylporphyrin with dimethyl acetylenedicarboxylate (DMAD) and diethyl ethoxymethylenemalonate were converted into the corresponding esters of pyridinone-fused porphyrins by using three different cyclization protocols: conventional heating, microwave irradiation, and Eaton's reagent. High yields in a short period of time were obtained by using the microwave-irradiation protocol under closed-vessel conditions. The structure of the copper(II) complex of pyridinone-fused porphyrin was confirmed by X-ray crystallography.

Key words: porphyrins, cyclizations, microwave irradiations



1a M = Ni
1b M = Cu

2a M = Ni
2b M = Cu

Figure 1 Structures of pyridinone-fused porphyrins **1** and **2**

The development of new transformation methods of porphyrins, particularly those which provide the introduction of an additional heterocyclic fused ring and/or a functionalized group in a peripheral position of the macrocycle, is of great interest in order to access new porphyrinic systems.[1,2]

β-Amino-substituted porphyrins have been widely used as versatile starting materials for the synthesis of highly functionalized porphyrins.[3] Recent examples include the three-component reaction of β-amino-*meso*-tetraphenylporphyrin, aromatic aldehydes and enol ethers,[4] and the two-component reaction of β-amino-*meso*-tetraphenylporphyrin and enol ethers,[5] both providing the synthesis of pyrido[2,3-*b*]porphyrin derivatives. On the other hand, the condensations of β-aminoporphyrin with α,β-unsaturated carbonyl compounds[6] and also with quinones,[7] afford a range of different π-extended heterocyclic fused porphyrin derivatives.

Herein, we report the synthesis of two novel pyridinone-fused porphyrins (**1a** and **2a**; Figure 1) obtained from condensation of the nickel(II) complex of β-amino-*meso*-tetraphenylporphyrin with dimethyl acetylenedicarboxylate (DMAD) and diethyl ethoxymethylenemalonate, followed by cyclization and subsequent ester hydrolysis. Such porphyrins and their free bases can have promising applications in photoelectronics, namely for being used as dyes for solar cells and in medicine as photosensitizers for cancer therapy (PDT).[8a–8e]

Nitrogen-containing heterocycles, particularly 4-quinolone derivatives, are present in a large number of biologically active compounds such as ciprofloxacin and levofloxacin, which has been described to exhibit potent antimicrobial activity.[9] In order to improve the quinolone pharmacological activity, the molecular structure of the parent compound has been extensively modified. For instance, the synthesis of dyad systems containing both quinolone and other pharmacologically active molecule has been described as a good strategy to discover new drugs.[2c,10] Considering the medicinal applications already known for porphyrins and for quinolones, one might anticipate that a porphyrin–pyridinone fused system could bring significant improvements to such applications. Several methodologies to prepare 4-quinolone derivatives have been reported;[11] however, the classical and most popular method employs the well-known Gould–Jacobs reaction.[12] This reaction involves the condensation of anilines with ethylenemalonate analogues followed by thermal cyclization, at high temperatures, to give rise to the desired quinolones. Owing to the increasing interest on this family of compounds, important improvements to promote the cyclization step have been reported. For instance, the condensation adduct of 3-chloro-4-fluoroaniline with diethyl ethoxymethylenemalonate was successfully cyclized using polyphosphoric acid or acidic alumina, under microwave irradiation.[13] Also, a mixture

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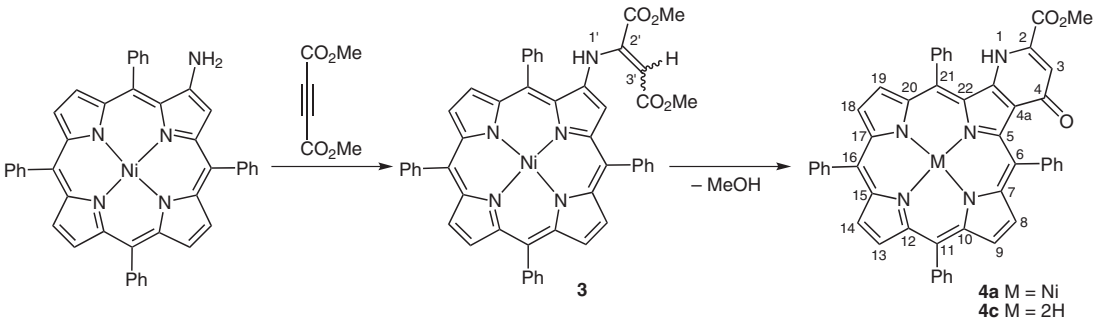


Scheme 1 Condensation–cyclization reaction of β-amino-*meso*-tetraphenylporphyrin with DMAD

of P_2O_5 and $MeSO_3H$, known as Eaton's reagent, allowed the cyclization of a range of different anilines, producing 4-quinolones in high yields and under mild conditions.[14]

Based on such methodologies, three different protocols were employed to access pyridinone-fused porphyrins **1a** and **2a**: (a) cyclization under conventional heating (oil bath), (b) cyclization under microwave irradiation, and (c) acidic cyclization using Eaton's reagent.

The initial condensation of the nickel(II) complex of β-amino-*meso*-tetraphenylporphyrin with DMAD was performed in toluene at 85 °C during 150 minutes, affording the expected porphyrin **3** in good yield (78%, Scheme 1).[15,16] With porphyrin **3** in hand, the first attempt to perform the cyclization was carried out by heating, in an oil bath, a nitrobenzene solution of **3**, at 200 °C. The reaction progress was monitored by TLC and reached its completion after 6 hours.[17] The pyridinone-fused porphyrin **4a** was then obtained in 74% of yield (entry 1, Table 1).

Table 1 Results Obtained in Cyclization of Porphyrin **3**

Entry	Method	Temp (°C)	Time	Yield (%)
1	oil bath	200	6 h	74
2[a]	MW open vessel	180	40 min	93
3[b]	MW closed vessel	220	4 min	88
4	Eaton's reagent	50	2 h	84

[a] Multimode reactor.
[b] Monomode reactor.

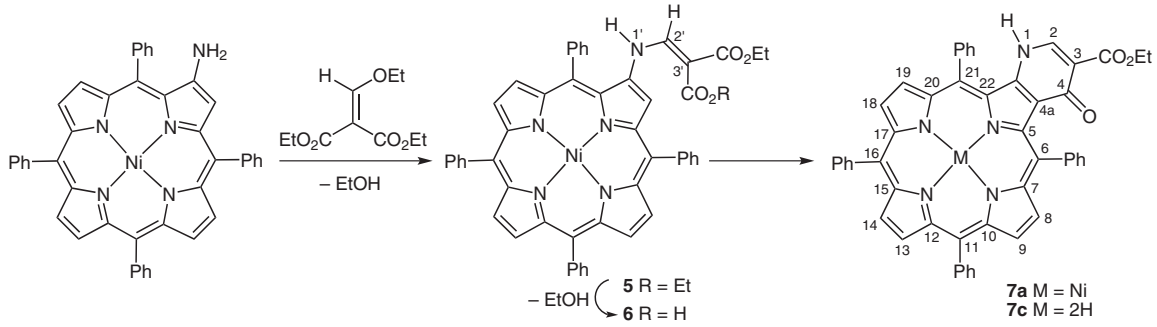
Although the 4-quinolones may exist in two tautomeric forms (enol and keto forms),[18] in the present case the NMR analysis shows that porphyrin **4a** exists exclusively in the keto form.[19] In fact, the ^1H NMR spectrum showed the presence of a broad singlet at δ = 9.10 ppm corresponding to the resonance of the NH proton which is in agreement with the ^{13}C NMR spectrum that showed a signal at δ = 173.7 ppm corresponding to the resonance of the ketone carbonyl group.

Aiming to improve the cyclization reaction outcome (mainly by reducing the reaction time), we explored the benefits of microwave irradiation. All microwave experiments were performed in nitrobenzene since it is a good microwave absorbing solvent (tan δ = 0.589).[20] Two microwave apparatus were available: multimode and monomode reactors. Using open vessel microwave irradiation in a multimode reactor, the cyclization was complete after 40 minutes at 180 °C, leading to the expecting porphyrin **4a** in an excellent yield of 93%.[21a] Switching the microwave platform to a single-mode reactor using closed vessel conditions and increasing reaction temperature to 220 °C, the complete cyclization took place in only 4 minutes (88% yield of **4a**).[21b] Comparing the results obtained in the microwave-enhanced cyclizations using the multimode and monomode reactors, it is remarkable the significant reduction of reaction times achieved when the monomode reactor is used (entries 2 and 3, Table 1).

When the reaction was performed with Eaton's reagent (P_2O_5 and $MeSO_3H$) at moderate temperatures (50 °C, 2 h), instead of the expected porphyrin **4a**, the reaction provides the metal-free cyclized porphyrin **4c**, in 84% yield (entry 4, Table 1).[22,23] This is due to the strong acidic character of the Eaton's reagent.

The same experimental methodology using the three different protocols was applied to the synthesis of the pyridinone-fused porphyrin **7a** analogue (Scheme 2). The starting porphyrin **5** was prepared in high yield (85%) from the condensation of the nickel(II) complex of β-amino-*meso*-tetraphenylporphyrin with diethyl ethoxymethylenemalonate, in refluxing toluene for 150 minutes. Subsequent cyclization in nitrobenzene under classical heating conditions (oil bath, 200 °C, 2 h), afforded the expected pyridinone-fused porphyrin **7a** in 50% yield (entry 1, Table 2). Besides porphyrin **7a**, a second product was isolated and it was identified as porphyrin **8** (Figure 2); this is presumably formed by hydrolysis and subsequent decarboxylation of porphyrin **7a**. We noticed that a longer reaction time (6 h) leads to a dramatic decrease in the yield of porphyrin **7a**, promoting the formation of **8**. In order to avoid the hydrolysis and decarboxylation of **7a**, the reaction time was reduced to 1 hour; however, under these conditions, the cyclization was not complete, and a 1:1 mixture of cyclized and uncyclized porphyrins **7a** and **6** is obtained.

Surprisingly, when such a reaction was conducted under open vessel microwave heating conditions in a multimode reactor at 180 °C, the cyclization did not reach completion



Scheme 2 Condensation–cyclization reactions of β-amino-*meso*-tetraphenylporphyrin with diethyl ethoxymethylenemalonate

Table 2 Results Obtained in Cyclization of Porphyrin **5**

Entry	Method	Temp (°C)	Time	Yield (%)
1	oil bath	200	2 h	50
2[a]	MW open vessel	180	1 h	50
3[b]	MW closed vessel	220	4 min	83
4	Eaton's reagent	80	2–5 h	not obtained

[a] Multimode reactor.
[b] Monomode reactor.

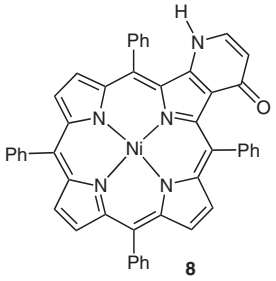


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Figure 2 Structure of pyridinone-fused porphyrin **8**

even after 1 hour of continuous irradiation. Also in this case, a mixture of uncyclized and cyclized porphyrins **6** and **7a** is obtained. However, when the cyclization is performed at higher temperatures (220 °C) in a monomode reactor using closed-vessel conditions, the reaction is complete in 4 minutes, providing the pyridinone-fused porphyrin **7a** in good yield (83%). Under these conditions, the formation of the derivative **8** could be almost suppressed. We also observed that extending the reaction time for more than 6 minutes an immediate decrease in the yield of porphyrin **7a** in benefit of **8** was observed. Thus, microwave cyclization under sealed-vessel conditions using a monomode reactor was found to be the method that gives higher yields of porphyrin **7a** (entries 2 and 3, Table 2).

To our surprise all attempts using Eaton's reagent as an alternative method for cyclizing porphyrin **5** were unsuccessful (entry 4, Table 2). In a series of experiments performed at 50 °C during 2–7 hours, a mixture of metal-free porphyrins **5** and **6** are the only isolated products; at higher temperatures (80 °C, 2–5 hours) the metal-free porphyrin **8** is the isolated product.

We were pleased to observe that such condensation–cyclization reactions can be successfully extended to the corresponding Cu(II) porphyrin complexes. The behavior of these complexes is similar to that observed with the Ni(II) ones.

The molecular structure of the Cu(II) complex of pyridinone-fused porphyrin **4c** was determined by single-crystal X-ray diffraction,[24] and is presented in Figure 3; it confirms the presence of an α,β-unsaturated carbonyl group. Indeed, the carbonyl and α-carbon atoms are connected by a C–C single bond of 1.464(12) Å. The C=O and C_{α}=C_{β} bonds have distances of 1.235(11) Å and 1.347(10) Å, respectively, which are typical of double bonds. The Cu(II) centre is bonded to four nitrogen donors of the porphyrin macrocycle in a distorted square planar coordination environment (see Figure 3, right) with Cu–N distances ranging from 1.982(5) to 2.021(6) Å. The N4 coordination plane displays a slight tetrahedral distortion of ± 0.056(3) Å. These distances compare well with those found for other related Cu(II) porphyrin derivatives.[25] Furthermore, the pyrrole rings are tilted relatively to each other with dihedral angles between consecutive rings varying between 16.50(6) and 19.65(5)°. Comparable geometric arrangements were found for other porphyrin metal complexes containing fused groups such as in Ni(II) benzoporphyrin derivatives.[26]

Finally, the methyl and ethyl esters of the pyridinone-fused porphyrins **4a** and **7a** were hydrolyzed with NaOH aqueous solutions to afford quantitatively the corresponding carboxylic acid derivatives **1a** and **2a** (Figure 1).

In conclusion, we have established efficient synthetic methodologies leading to novel porphyrin derivatives and further studies on their properties are currently under investigation in our laboratories.

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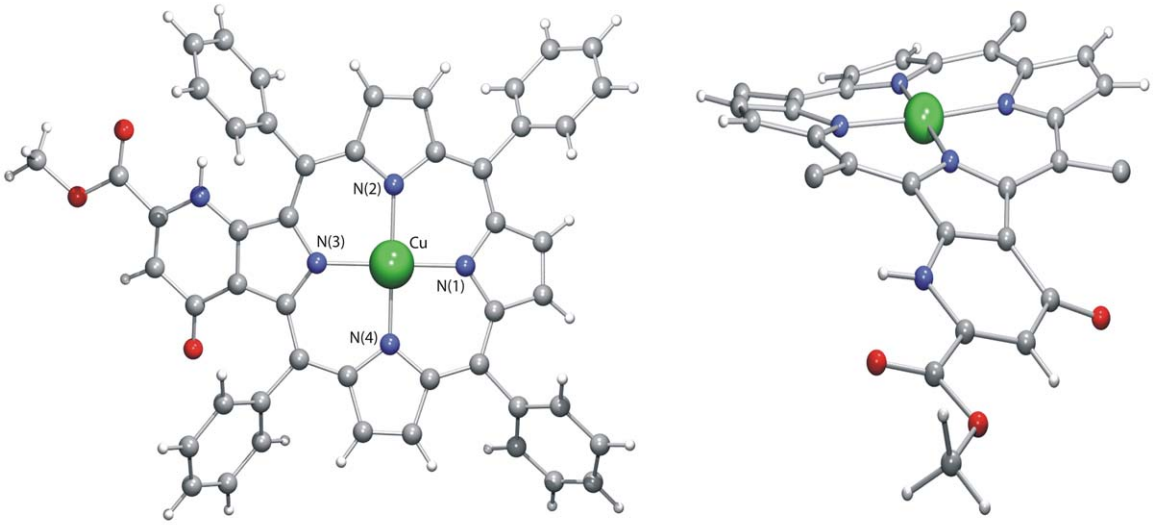

Figure 3 Molecular structure of Cu(II) complex of pyridinone-fused porphyrin **4c** in two different views; top view showing the overall structure of the complex and a side view emphasizing the absence of planarity between the pyrrole rings. In this later view the phenyl rings have been omitted for clarity.

References and Notes

(1) For a review: Fox, S.; Boyle, R. W. *Tetrahedron* **2006**, *62*, 10039.

(2) For recent examples,see: (a) Lacerda, P. S. S.; Silva, A. M. G.; Tomé, A. C.; Neves, M. G. P. M. S.; Silva, A. M. S.; Cavaleiro, J. A. S.; Llamas-Saiz, A. L. *Angew. Chem. Int. Ed.* **2006**, *45*, 5487. (b) Kadish, K. M.; Wenbo, E.; Sintic, P. J.; Ou, Z.; Shao, J.; Ohkubo, K.; Fukuzumi, S.; Govenlock, L. J.; McDonald, J. A.; Try, A. C.; Cai, Z.-L.; Reimers, J. R.; Crossley, M. J. *J. Phys. Chem. B* **2007**, *111*, 8762. (c) Santos, F. C.; Cunha, A. C.; Souza, M. C. B. V.; Tomé, A. C.; Neves, M. G. P. M. S.; Ferreira, V. F.; Cavaleiro, J. A. S. *Tetrahedron Lett.* **2008**, *49*, 7268.

(3) Jaquinod, L. In *The Porphyrin Handbook*, Vol. 1; Kadish, K. M.; Smith, K. M.; Guilard, R., Eds.; Academic Press: San Diego, **2000**, Chap. 5, 212.

(4) Alonso, C. M. A.; Neves, M. G. P. M. S.; Tomé, A. C.; Silva, A. M. S.; Cavaleiro, J. A. S. *Tetrahedron Lett.* **2001**, *42*, 8307.

(5) Alonso, C. M. A.; Serra, V. I. V.; Neves, M. G. P. M. S.; Tomé, A. C.; Silva, A. M. S.; Paz, F. A. A.; Cavaleiro, J. A. S. *Org. Lett.* **2007**, *9*, 2305.

(6) Alonso, C. M. A.; Neves, M. G. P. M. S.; Silva, A. M. S.; Cavaleiro, J. A. S.; Hombrecher, H. K. *Tetrahedron Lett.* **1997**, *38*, 2757.

(7) Alonso, C. M. A.; Neves, M. G. P. M. S.; Tomé, A. C.; Silva, A. M. S.; Cavaleiro, J. A. S. *Tetrahedron* **2005**, *61*, 11866.

(8) For recent examples. see: (a) Campbell, W. M.; Jolley, K. W.; Wagner, P.; Wagner, K.; Walsh, P. J.; Gordon, K. C.; Schmidt-Mende, L.; Nazeeruddin, M. K.; Wang, Q.; Grätzel, M.; Officer, D. L. *J. Phys. Chem. C* **2007**, *111*, 11760. (b) Eu, S.; Hayashi, S.; Umeyama, T.; Matano, Y.; Araki, Y.; Imahori, H. *J. Phys. Chem. C* **2008**, *112*, 4396. (c) Park, J. K.; Lee, H. R.; Chen, J.; Shinokubo, H.; Osuka, A.; Kim, D. *J. Phys. Chem. C* **2008**, *112*, 16691. (d) Mozer, A. J.; Wagner, P.; Officer, D. L.; Wallace, G. G.; Campbell, W. M.; Miyashita, M.; Sunahara, K.; Mori, S. *Chem. Commun.* **2008**, 4741. (e) Bonnett, R. *Chemical Aspects of Photodynamic Therapy*; Gordon and Breach Science Publishers: Amsterdam, **2000**.

(9) Mitscher, L. A. *Chem. Rev.* **2005**, *105*, 559.

(10) (a) Srivastava, B. K.; Solanki, M.; Mishra, B.; Soni, R.; Jayadev, S.; Valani, D.; Jain, M.; Patel, P. R. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 1924. (b) Rivault, F.; Liébert, C.; Burger, A.; Hoegy, F.; Abdallah, M. A.; Schalk, I. J.; Mislin, G. L. A. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 640. (c) Wang, Z.; Vince, R. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 1293.

(11) For recent examples, see: (a) Jones, C. P.; Anderson, K. W.; Buchwald, S. L. *J. Org. Chem.* **2007**, *72*, 7968. (b) Huang, J.; Chen, Y.; King, A. O.; Dilmeghani, M.; Larsen, R. D.; Faul, M. M. *Org. Lett.* **2008**, *10*, 2609; and references therein.

(12) Gould, R. G.; Jacobs, W. A. *J. Am. Chem. Soc.* **1939**, *61*, 2890.

(13) (a) Kidwai, M.; Misra, P.; Kumar, R.; Saxena, R. K.; Gupta, R.; Bradoo, S. *Monatsh. Chem.* **1998**, *129*, 961. (b) Kidwai, M.; Misra, P.; Dave, B.; Bhushan, K. R.; Saxena, R. K.; Singh, M. *Monatsh. Chem.* **2000**, *131*, 1207.

(14) (a) Dorow, R. L.; Herrinton, P. M.; Hohler, R. A.; Maloney, M. T.; Mauragis, M. A.; McGhee, W. E.; Moeslein, J. A.; Strohbach, J. W.; Veley, M. F. *Org. Process Res. Dev.* **2006**, *10*, 493. (b) Zewge, D.; Chen, C. Y.; Deer, C.; Dormer, P. G.; Hughes, D. L. *J. Org. Chem.* **2007**, *72*, 4276.

(15) **Condensation Reaction**
To a solution of (β-amino-*meso*-tetraphenylporphyrinato)-nickel(II) (50 mg, 0.073 mmol) in toluene (5 mL), DMAD (0.02 mL, 0.15 mmol) was added, and the resulting mixture was heated at 85 °C under argon atmosphere for 150 min. The reaction mixture was cooled to r.t. and purified by flash chromatography using a 1:2 mixture of hexane–CH_2Cl_2 as eluent. The first fraction to be collected was a small amount of starting porphyrin, followed by porphyrin **3**, which was collected and crystallized from $CHCl_3$–MeOH to give 47 mg (78% yield) of red crystals.

(16) **Spectroscopic Data for [2-(2,3-Dimethoxycarbonyl-2-en-1-yl)amino-5,10,15,20-tetraphenylporphyrinato]nickel (II) (3)**
^{1}H NMR (500.13 MHz, $CDCl_3$): δ = 3.57 (s, 3 H, 2′-OCH_3), 3.66 (s, 3 H, 3′-OCH_3), 5.24 (s, 1 H, 3′-H), 7.63–7.69 (m, 12 H, $PhH_{meta+para}$), 7.90–7.91 (m, 3 H, 3-H and PhH_{ortho}), 7.96–8.00 (m, 6 H, PhH_{ortho}), 8.57 (d, *J* = 4.9 Hz, 1 H, β-H), 8.66 (d, *J* = 4.9 Hz, 1 H, β-H), 8.69–8.71 (m, 4 H, β-H), 9.01 (s, 1 H, 1′-NH) ppm. ^{13}C NMR (125.77 MHz, $CDCl_3$): δ = 51.1

(2′-OCH_3), 52.7 (3′-OCH_3), 94.1 (C-3′), 117.3, 117.7, 118.8, 119.7, 120.5 (C-3), 126.81, 126.84, 126.90, 126.91, 127.5, 127.6, 127.66, 127.74, 127.8, 127.9, 128.12, 128.18, 131.71, 131.84, 132.04, 132.08, 132.13, 132.17, 132.6, 132.7, 133.0, 133.41, 133.45, 133.54, 133.6, 133.7, 139.1, 140.6, 140.7, 142.0, 142.28, 142.33, 142.6, 142.8, 143.4, 143.5, 146.9, 165.0 (2′ -C=O), 168.4 (3′ -C=O) ppm. UV/vis ($CHCl_3$): λ_{max} (log ε) 422 (5.07), 537 (4.14), 567 (3.89) nm. MS–FAB$^+$: *m/z* = 828 [M + H], 827 [M]$^+$. Anal. Calcd for $C_{50}H_{35}N_5O_4Ni$: C, 72.48; H, 4.26; N, 8.45. Found: C, 72.66; H, 4.06; N, 8.37.

(17) **Cyclization Reaction Using an Oil Bath**
A solution of porphyrin **3** (29 mg, 0.035 mmol) in nitrobenzene (1.5 mL) was heated at 200 °C under argon atmosphere for 6 h. The reaction mixture was then purified by flash chromatography [CH_2Cl_2, then CH_2Cl_2–acetone (95:5)] to remove the nitrobenzene and the product pyridinone-fused porphyrin **4a**. Porphyrin **4a** was further crystallized from CH_2Cl_2–MeOH to give the pure compound (20 mg, 74% yield).

(18) The 4-quinolones could exist in two different forms: enol and keto forms, however, usually these compounds exist primarily in the keto form. For more information, see: Mphahlele, M. J.; El-Hahas, A. M. *J. Mol. Struct.* **2004**, *688*, 129.

(19) **Spectroscopic Data for (2-Methoxycarbonyl-6,11,16,21-tetraphenyl-1*H*-pyrido-4-one[2,3-*b*]porphyrinato)-nickel (4a)**
^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 3.94 (s, 3 H, OCH_3), 7.01 (d, *J* = 1.6 Hz, 1 H, 3-H), 7.63–7.71 and 7.88–8.08 (2 m, 20 H, PhH), 8.51 (d, *J* = 5.0 Hz, 1 H, β-H), 8.59–8.70 (m, 5 H, β-H), 9.10 (br s, 1 H, 1-NH) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 53.4 (OCH_3), 114.9, 117.7 (C-3), 119.3, 120.1, 120.5, 126.6, 127.1, 127.5, 128.0, 128.3, 128.6, 129.3, 129.8, 131.2, 131.8, 132.3, 132.5, 132.7, 133.3, 133.65, 133.73, 133.83, 133.92, 137.9, 138.2, 140.04, 140.06, 142.29, 142.31, 142.49, 142.54, 142.7, 143.6, 146.1, 146.8, 162.8 (2 -C=O), 173.7 (4 -C=O) ppm. UV/vis ($CHCl_3$): λ_{max} (log ε) = 433 (5.25), 546 (4.17) nm. MS–FAB$^+$: *m/z* = 796 [M + H]$^+$, 795 [M]$^+$. HRMS–FAB: *m/z* calcd for $C_{49}H_{31}N_5O_3Ni$ [M + H]$^+$: 796.1859; found: 796.1855. Anal. Calcd for $C_{49}H_{31}N_5O_3Ni·3/2H_2O$: C, 71.46; N, 8.50; H, 4.16. Found: C, 71.66; N, 8.40; H, 3.61.

(20) Kappe, C. O. *Angew. Chem. Int. Ed.* **2004**, *43*, 6250.

(21) **Cyclization Reaction**
(a) **Using a Multimode Reactor**
A solution of porphyrin **3** (21 mg, 0.025 mmol) in nitrobenzene (3.5 mL) under argon atmosphere was irradiated at atmospheric pressure in a Milestone MicroSynth microwave reactor (5 min ramp up to 180 °C and 35 min hold at 180 °C, using 400 W maximum power). The reaction mixture was then purified by flash chromatography using a 1:2 mixture of hexane–CH_2Cl_2 as eluent to give porphyrin **4a** (19 mg, 93% yield).
(b) **Using a Monomode Reactor**
A solution of porphyrin **3** (28 mg, 0.034 mmol) in nitrobenzene (1.5 mL) was placed in a 10 mL reaction vial, which was then sealed under argon atmosphere and placed in the cavity of a CEM microwave reactor. The reaction vial was irradiated at 220 °C (1 min ramp to 220 °C and 3 min hold at 220 °C, using 200 W maximum power). The reaction mixture was then purified by flash chromatography using a 1:2 mixture of hexane–CH_2Cl_2 as eluent to give porphyrin **4a** (24 mg, 88% yield).

(22) **Cyclization Reaction Using Eaton's Reagent**
A mixture of porphyrin **3** (50 mg, 0.060 mmol) and Eaton's reagent (0.4 mL) was heated at 50 °C for 150 min. The reaction mixture was neutralized with an aq sat. soln of Na_2CO_3. The aqueous layer was extracted three times with CH_2Cl_2, and the organic layer was dried (anhyd Na_2SO_4) and evaporated under vacuum to dryness. The resulting residue was purified by flash chromatography using $CHCl_3$ as eluent and crystallized from CH_2Cl_2–*n*-hexane to give porphyrin **4c** (37 mg, 84% yield) as purple crystals.

(23) **Spectroscopic Data for 2-Methoxycarbonyl-6,11,16,21-tetraphenyl-1*H*-pyrido-4-one[2,3-*b*]porphyrin (4c)**
^{1}H NMR (300.13 MHz, $CDCl_3$): δ = –2.71 and –2.57 (2 s, 2 H, NH), 3.95 (s, 3 H, OCH_3), 7.09 (d, *J* = 1.4 Hz, 1 H, 3-H), 7.74–7.79, 7.98–8.11, and 8.19–8.34 (3 m, 20 H, PhH), 8.69–8.74 (m, 3 H, β-H), 8.83, 8.87, and 9.01 (3 d, *J* = 5.0 Hz, 3 H, β-H), 9.24 (br s, 1 H, 1-NH) ppm. UV/vis ($CHCl_3$): λ_{max} (log ε) = 425 (5.16), 523 (4.28), 556 (3.76), 596 (3.76), 651 (3.44) nm. MS–FAB$^+$: *m/z* = 740 [M + H]$^+$, 839 [M]$^+$. Anal. Calcd for $C_{51}H_{39}N_5O_4·EtOH$: C, 77.94; N, 8.91; H, 5.00. Found: C, 77.62; N, 8.70; H, 5.41.

(24) **X-ray Single-Crystal Determination**
The X-ray data of porphyrin **4c**–Cu(II) complex was collected on a CCD Bruker APEX II using graphite monochromatized Mo Kα radiation (λ = 0.71073 Å) with the crystal positioned at 35 mm from the CCD, and the spots were measured using a counting time of 80 s. Data reduction and empirical absorption were carried out using SAINT-NT from Bruker aXS. The structure was solved by direct methods and by subsequent difference Fourier syntheses and refined by full matrix least squares on F^2 using the SHELX-97 system programs.[27] The CH_2Cl_2 solvent molecule was found disordered over three tetrahedral positions with occupation factors of 0.333. In addition, the chlorine atoms of one disorder component are also disordered occupying two alternative positions with occupation factors of 0.166. Anisotropic thermal parameters were used for all nonhydrogen atoms excluding the atoms of CH_2Cl_2, which were refined with group isotropic temperature factors. The hydrogen atoms of this molecule was not inserted in the structure refinement while the hydrogen atoms of the copper porphyrin derivative complex were included in refinement in calculated positions with isotropic parameters equivalent 1.2 times those of the atom to which they are attached. Crystal structure has been deposited with the Cambridge Crystallographic Data Center and allocated with the deposit number CCDC 710189.

(25) Allen, F. H. *Acta Crystallogr., Sect. B: Struct. Sci.* **2002**, *58*, 380.

(26) Silva, A. M. G.; Oliveira, K. T.; Faustino, M. A. F.; Neves, M. G. P. M. S.; Tomé, A. C.; Silva, A. M. S.; Cavaleiro, J. A. S.; Brandão, P.; Felix, V. *Eur. J. Org. Chem.* **2008**, 704.

(27) Sheldrick, G. M. *SHELX-97*; University of Göttingen: Germany, **1997**.