Synthesis of Methyl Derivatives of 4*H*-Furo[2,3-*h*]quinolin-4-one and 5*H*-Furo[3,2-*g*]quinolin-5-one

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Synthesis of the linear and angular furoquinolin-4-one derivatives **6** and **12** was performed, using nitrobenzofurans **3** and **9** as key intermediates. These compounds were reduced to the corresponding aminobenzofurans **4** and **10**, which were condensed in two steps to yield, the linear furoquinolin-4-ones **6a,b** and the angular ones **12a,b**.

The antiproliferative activity of psoralens, which is due to their ability to photobind to DNA[1], is today well known and exploited in PUVA therapy for various skin diseases[2] and in photopheresis[3]. In order to eliminate adverse effects attributed to the capacity to form crosslinks[4], a number of furocoumarin isosters have been prepared[5], including linear[6] and angular[7] furoquinolin-2-ones. The angular isosters show not only remarkable photoinduced antiproliferative activity but, unexpectedly, they also block macromolecular synthesis in the dark, probably through topoisomerase II inhibition[7].

With the aim of increasing activity in the dark and possibly also eliminating or reducing photoreactivity, we planned the synthesis of two different series of derivatives with structural modifications at one or other of the two reactive sites of the molecule, i.e. the double bond of the lactamic ring, or the double bond of the furan ring. In this connection, we now describe the synthesis of new linear and angular furoquinolin-4-one derivatives, in which the lactamic moiety is modified with respect to previously reported furoquinolin-2-ones.

In essence, the synthetic method involves building the benzofuran nucleus as a first step, followed by condensing the γ-lactamic ring on it. The alternative pathway, i.e. preparation of the quinolin-4-one moiety and cyclization of the furan ring on it, was not feasible. Attempts to cyclize the furan ring by etherification of 7-hydroxyquinolin-4-one with the appropriate alkyl chloride, resulted in simultaneous reaction at both the O and N atoms, owing to the great reactivity of the lactamic moiety of the quinolinone nucleus. We therefore planned our synthetic route according to Schemes 1 and 2, with different strategies for 4′- and 5′-methyl derivatives.

The commercially available nitrocresols **1** and **7** were condensed with propargyl chloride to give the corresponding *O*-propargyl ethers **2a** and **8a** which, submitted to Claisen rearrangement in the presence of CsF[8], furnished 2,7-dimethyl-6-nitrobenzofuran (**3a**) and 2,7-dimethyl-4-nitrobenzofuran (**9a**), respectively.

For the synthesis of our second series of derivatives, the nitrocresols **1** and **7** were condensed with chloroacetone to give ethers **2b** and **8b**, which were cyclized in acidic medium to yield 3,7-dimethyl-6-nitrobenzofuran (**3b**) and 3,7-dimethyl-4-nitrobenzofuran (**9b**), respectively.

The use of these cresols, i.e. methyl derivatives of *m*-nitrophenol, in the Claisen rearrangement and the acid-induced cyclization, ensured that ring closure of the furan ring occurred regiospecifically at the free *ortho* position.

Reduction of the nitrobenzofuran intermediates **3** and **9** by catalytic hydrogenation gave the corresponding aminobenzofurans **4** and **10**. The Conrad–Limpach method was used for γ-lactamic ring formation[9]. Compounds **4** and **10** were therefore submitted to condensation with ethyl acetoacetate at 80 °C, and the aminocrotonate derivatives **5** and **11** thus obtained were cyclized by heating at 215 °C to ac-

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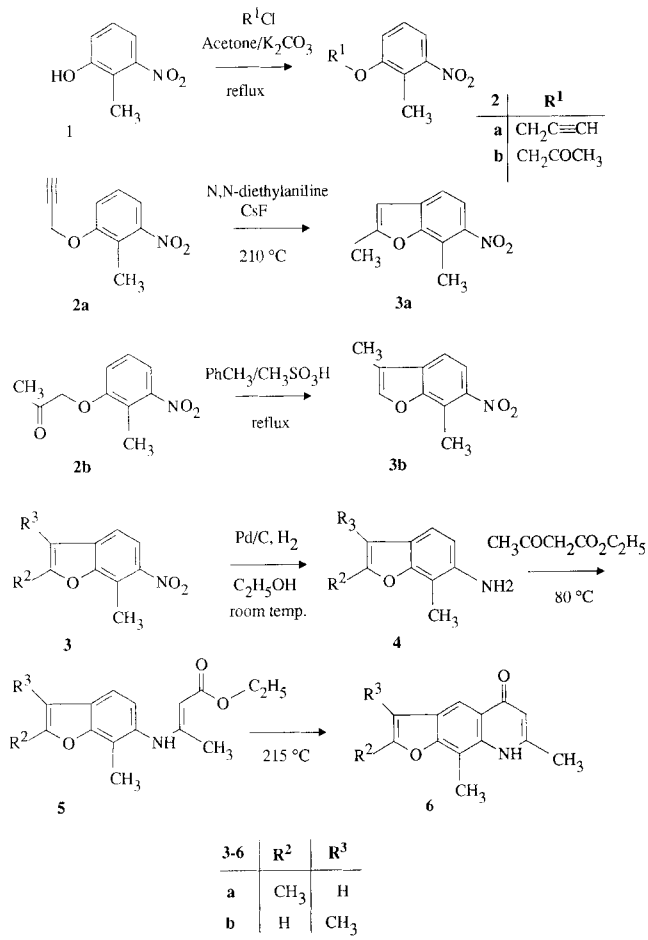
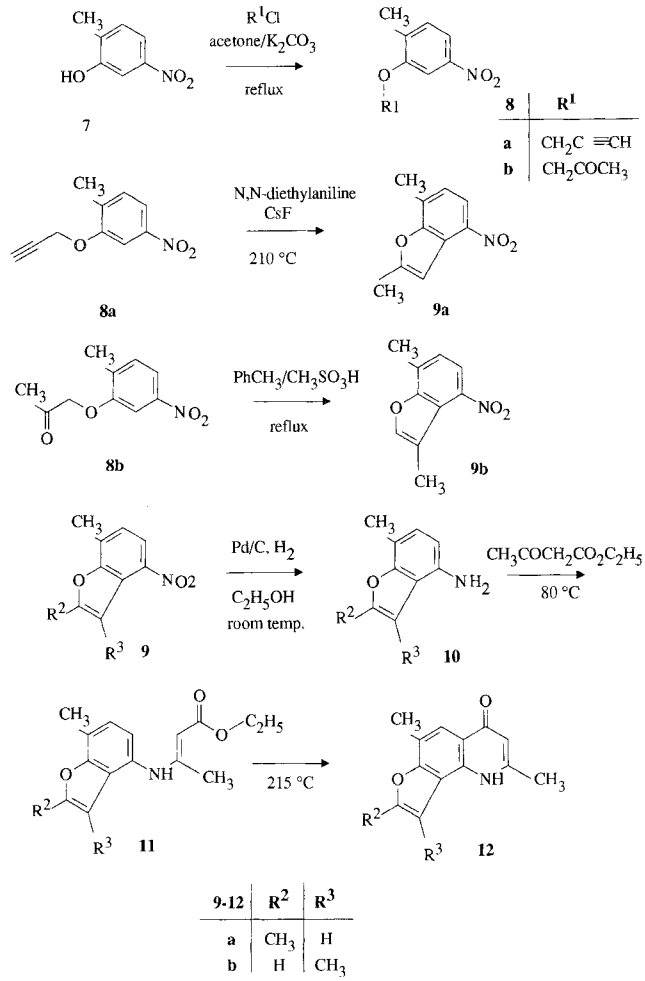
Scheme 1



Scheme 2



complish the synthesis of the desired 5*H*-furo[3,2-*g*]quinolin-5-ones **6a**, **b** and 4*H*-furo[2,3-*h*]quinolin-4-ones **12a**, **b**.

Experimental Section

Melting points (uncorrected): Gallenkamp MFB-595-010M melting point apparatus. – Thin-layer chromatography (TLC): 60 F_{254} precoated silica gel plates (Merck, 0.2 mm), eluting with an ethyl acetate/cyclohexane mixture (3:7). – Column chromatography (CC): Silica gel 60 (Merck, 0.063–0.100 mm). – ^{1}H NMR: Varian Gemini 200 MHz. – Elemental analyses were carried out by the Microanalytical Laboratory of the Department of Pharmaceutical Sciences of the University of Padova under the direction of A. Pietrogrande.

2-Methyl-1-nitro-3-propargyloxybenzene (**2a**): To a solution of **1** (8.3 g, 54.4 mmol) in acetone (200 ml), propargyl chloride (6.1 g, 5.2 ml, 81.6 mmol) and anhydrous K_2CO_3 (25.0 g) were added and the mixture was refluxed until **1** was completely consumed (12 h; TLC). After cooling, the K_2CO_3 was filtered off and washed with fresh acetone. The solvent was evaporated from the pooled filtrate and washings, affording a solid which was crystallized from cyclohexane to give **2a** (7.9 g, 77%), m.p. 63 °C. – ^{1}H NMR ($CDCl_3$): δ = 7.47 (dd, *J* = 8.0 Hz, *J* = 1.4 Hz, 1 H, 6-H), 7.29 (dd, *J* = 8.2 Hz, *J* = 8.0 Hz, 1 H, 5-H), 7.19 (dd, *J* = 8.2 Hz, *J* = 1.4 Hz, 1 H, 4-H), 4.79 (d, *J* = 2.4 Hz, 2 H, 1′-H), 2.55 (t, *J* = 2.4 Hz, 1 H, 3′-H), 2.39 (s, 3 H, 2-Me). – $C_{10}H_9NO_3$ (191.2): calcd. C 62.82, H 4.75, N 7.33; found C 62.62, H 4.68, N 7.17.

4-Methyl-1-nitro-3-propargyloxybenzene (**8a**): This compound was prepared from **7** in an analogous manner to **2a**. The solid was crystallized from cyclohexane to give **8a** (95%), m.p. 75 °C. – ^{1}H NMR ($CDCl_3$): δ = 7.82 (dd, *J* = 8.8 Hz, *J* = 2.2 Hz, 1 H, 6-H), 7.81 (d, *J* = 2.2 Hz, 1 H, 2-H), 7.29 (d, *J* = 8.8 Hz, 1 H, 5-H), 4.82 (d, *J* = 2.4 Hz, 2 H, 1′-H), 2.58 (t, *J* = 2.4 Hz, 1 H, 3′-H), 2.33 (s, 3 H, 4-Me). – $C_{10}H_9NO_3$ (191.2): calcd. C 62.82, H 4.75, N 7.33; found C 62.72, H 4.61, N 7.09.

2-Methyl-1-nitro-3-(2′-oxopropyloxy)benzene (**2b**): To a solution of **1** (15.0 g, 98.0 mmol) in acetone (1 l), chloroacetone (10.9 g, 9.4 ml, 117.6 mmol) and anhydrous K_2CO_3 (60 g) were added and the mixture was refluxed until **1** was completely consumed (15 h; TLC). The mixture was worked up as previously described, affording a solid which was crystallized from cyclohexane to give **2b** (20.1 g, 98%), m.p. 78 °C. – ^{1}H NMR ($CDCl_3$): δ = 7.42 (dd, *J* = 8.5 Hz, *J* = 1.1 Hz, 1 H, 6-H), 7.23 (dd, *J* = 8.2 Hz, *J* = 8.5 Hz, 1 H, 5-H), 6.87 (dd, *J* = 8.2 Hz, *J* = 1.1 Hz, 1 H, 4-H), 4.61 (s, 2 H, 1′-H), 2.42 (s, 3 H, 2-Me), 2.30 (s, 3 H, 3′-H). – $C_{10}H_{11}NO_4$ (209.2): calcd. C 57.41, H 5.30, N 6.70; found C 57.28, H 5.15, N 6.61.

4-Methyl-1-nitro-3-(2′-oxopropyloxy)benzene (**8b**): This compound was prepared from **7** in an analogous manner to **2b**. The solid was crystallized from cyclohexane to give **8b** (98%), m.p. 98 °C. – ^{1}H NMR ($CDCl_3$): δ = 7.82 (dd, *J* = 8.5 Hz, *J* = 2.1 Hz, 1 H, 6-H), 7.51 (d, *J* = 2.1 Hz, 1 H, 2-H), 7.32 (d, *J* = 8.5 Hz, 1 H, 5-H), 4.68 (s, 2 H, 1′-H), 2.40 (s, 3 H, 4-Me), 2.34 (s, 3 H, 3′-H). –

$C_{10}H_{11}NO_4$ (209.2): calcd. C 57.41, H 5.30, N 6.70; found C 57.21, H 5.10, N 6.58.

2,7-Dimethyl-6-nitrobenzofuran (**3a**): To a solution of **2a** (7.7 g, 40.4 mmol) in *N,N*-diethylaniline (20 ml), cesium fluoride (4.1 g, 26.8 mmol) was added and the suspension was heated at 210°C until **2a** was completely consumed (2 h; TLC). After cooling, the suspension was diluted with ethyl acetate (100 ml) and washed with dil. HCl (3 × 50 ml). The dried (Na_2SO_4) organic phase was concentrated under reduced pressure and the residue was crystallized from *n*-hexane to give **3a** (6.9 g, 93%), m.p. 84–85°C. – ^{1}H NMR ($CDCl_3$): δ = 7.97 (d, *J* = 8.6 Hz, 1H, 5-H), 7.37 (d, *J* = 8.6 Hz, 1H, 4-H), 6.47 (q, *J* = 1.1 Hz, 1H, 3-H), 2.80 (s, 3H, 7-Me), 2.53 (d, *J* = 1.1 Hz, 3H, 2-Me). – $C_{10}H_9NO_3$ (191.2): calcd. C 62.82, H 4.75, N 7.33; found C 62.59, H 4.62, N 7.21.

2,7-Dimethyl-4-nitrobenzofuran (**9a**): This compound was prepared from **8a** in an analogous manner to **3a**. The residue was crystallized from cyclohexane to give **9a** (88%), m.p. 92–94°C. – ^{1}H NMR ($CDCl_3$): δ = 8.05 (d, *J* = 8.3 Hz, 1H, 5-H), 7.13 (q, *J* = 1.1 Hz, 1H, 3-H), 7.10 (d, *J* = 8.3 Hz, 1H, 6-H), 2.58 (s, 3H, 7-Me), 2.55 (d, *J* = 1.1 Hz, 2-Me). – $C_{10}H_9NO_3$ (191.2): calcd. C 62.82, H 4.75, N 7.33; found C 62.68, H 4.65, N 7.19.

3,7-Dimethyl-6-nitrobenzofuran (**3b**): A solution of **2b** (15.0 g, 71.8 mmol) in toluene (500 ml) was refluxed for 40 h, while methanesulfonic acid (15 ml, 22.2 g, 231.2 mmol) was added in small portions. After cooling, the solution was washed with water and the dried (Na_2SO_4) organic phase concentrated under reduced pressure. Purification by CC (CH_2Cl_2) of the residue yielded **3b** (8.9 g, 65%), m.p. 104°C. – ^{1}H NMR ($CDCl_3$): δ = 8.00 (d, *J* = 8.5 Hz, 1H, 5-H), 7.64 (q, *J* = 1.2 Hz, 1H, 2-H), 7.42 (d, *J* = 8.5 Hz, 1H, 4-H), 2.80 (s, 3H, 7-Me), 2.28 (d, *J* = 1.2 Hz, 3H, 3-Me). – $C_{10}H_9NO_3$ (191.2): calcd. C 62.82, H 4.75, N 7.33; found C 62.70, H 4.60, N 7.15.

3,7-Dimethyl-4-nitrobenzofuran (**9b**): This compound was prepared from **8b** in an analogous manner to **3b**. Purification by CC (CH_2Cl_2) of the residue yielded **9b** (43%), m.p. 92°C. – ^{1}H NMR ($CDCl_3$): δ = 7.95 (d, *J* = 8.2 Hz, 1H, 5-H), 7.58 (q, *J* = 1.2 Hz, 1H, 2-H), 7.15 (d, *J* = 8.2 Hz, 1H, 6-H), 2.58 (s, 3H, 7-Me), 2.41 (d, *J* = 1.2 Hz, 3H, 3-Me). – $C_{10}H_9NO_3$ (191.2): calcd. C 62.82, H 4.75, N 7.33; found C 62.64, H 4.62, N 7.20.

6-Amino-2,7-dimethylbenzofuran (**4a**): To a solution of **3a** (3.1 g, 16.1 mmol) in absolute ethanol (100 ml), a catalytic amount of 10% Pd/C was added and the reaction mixture was kept at room temp. under a low pressure of hydrogen. After stirring for 7 h the catalyst was filtered off and the solution was concentrated under reduced pressure. The residue was chromatographed by CC (CH_2Cl_2) to give **4a** (2.3 g, 87%) as a gummy product. – ^{1}H NMR ($CDCl_3$): δ = 7.10 (d, *J* = 8.2 Hz, 1H, 4-H or 5-H), 6.61 (d, *J* = 8.2 Hz, 1H, 4-H or 5-H), 6.23 (q, *J* = 1.1 Hz, 1H, 3-H), 3.58 (br. s, 2H, $-NH_2$), 2.42 (d, *J* = 1.1 Hz, 3H, 2-Me), 2.31 (s, 3H, 7-Me). – $C_{10}H_{11}NO$ (161.2): calcd. C 74.51, H 6.88, N 8.69; found C 74.38, H 6.81, N 8.56.

6-Amino-3,7-dimethylbenzofuran (**4b**): This compound was prepared from **3b** in an analogous manner to **4a**. The crude product was chromatographed by CC (CH_2Cl_2) to give **4b** (90%) as a gummy product. – ^{1}H NMR ($CDCl_3$): δ = 7.26 (q, *J* = 1.2 Hz, 1H, 2-H), 7.15 (d, *J* = 8.1 Hz, 1H, 4-H or 5-H), 6.67 (d, *J* = 8.1 Hz, 1H, 4-H or 5-H), 3.75 (br. s, 2H, $-NH_2$), 2.31 (s, 3H, 7-Me), 2.18 (d, *J* = 1.2 Hz, 3H, 2-Me). – $C_{10}H_{11}NO$ (161.2): calcd. C 74.51, H 6.88, N 8.69; found C 74.71, H 6.68, N 8.61.

4-Amino-2,7-dimethylbenzofuran (**10a**): This compound was prepared from **9a** in an analogous manner to **4a**. The crude product was chromatographed by CC (CH_2Cl_2) to give **10a** (90%) as a gummy product. – ^{1}H NMR ($CDCl_3$): δ = 6.80 (dq, *J* = 7.8 Hz, *J* = 0.7 Hz, 1H, 6-H), 6.41 (d, *J* = 7.8 Hz, 1H, 5-H), 6.29 (q, *J* = 1.1 Hz, 1H, 3-H), 3.70 (br. s, 2H, $-NH_2$), 2.45 (d, *J* = 1.1 Hz, 3H, 2-Me), 2.38 (d, *J* = 0.7 Hz, 3H, 7-Me). – $C_{10}H_{11}NO$ (161.2): calcd. C 74.51, H 6.88, N 8.69; found C 74.41, H 6.90, N 8.66.

4-Amino-3,7-dimethylbenzofuran (**10b**): This compound was prepared from **9b** in an analogous manner to **4a**. The crude product was chromatographed by CC (CH_2Cl_2) to give **10b** (95%) as a gummy product. – ^{1}H NMR ($CDCl_3$): δ = 7.27 (q, *J* = 1.3 Hz, 1H, 2-H), 6.84 (d, *J* = 7.7 Hz, 1H, 5-H or 6-H), 6.37 (d, *J* = 7.7 Hz, 1H, 5-H or 6-H), 3.89 (br. s, 2H, $-NH_2$), 2.43 (d, *J* = 1.3 Hz, 3H, 3-Me), 2.38 (s, 3H, 7-Me). – $C_{10}H_{11}NO$ (161.2): calcd. C 74.51, H 6.88, N 8.69; found C 74.63, H 6.61, N 8.71.

Ethyl 3-(2,7'-Dimethyl-6'-benzofurylamino)but-2-enoate (**5a**): A mixture of **4a** (1.3 g, 8.1 mmol) and ethyl acetoacetate (1.1 g, 8.1 mmol) was heated at 80°C for 4 h. The reaction mixture was chromatographed by CC (CH_2Cl_2) to give **5a** (1.9 g, 86%), m.p. 85°C. – ^{1}H NMR ($CDCl_3$): δ = 10.08 (br. s, 1H, NH), 7.24 (d, *J* = 8.2 Hz, 1H, 4'-H or 5'-H), 6.94 (d, *J* = 8.2 Hz, 1H, 4'-H or 5'-H), 6.34 (q, *J* = 1.0 Hz, 1H, 3'-H), 4.70 (s, 1H, 2-H), 4.16 (q, *J* = 7.2 Hz, 2H, $-OCH_2CH_3$), 2.46 (d, *J* = 1.0 Hz, 3H, 2'-Me), 2.41 (s, 3H, 7'-Me), 1.79 (s, 3H, 4-H), 1.31 (t, *J* = 7.2 Hz, 3H, $-OCH_2CH_3$). – $C_{16}H_{19}NO_3$ (273.3): calcd. C 70.31, H 7.01, N 5.13; found C 70.17, H 6.89, N 5.09.

Ethyl 3-(3',7'-Dimethyl-6'-benzofurylamino)but-2-enoate (**5b**): This compound was prepared from **4b** in an analogous manner to **5a**. The reaction mixture was chromatographed by CC (CH_2Cl_2) to give **5b** (59%) as a gummy product. – ^{1}H NMR ($CDCl_3$): δ = 10.15 (br. s, 1H, –NH), 7.43 (q, *J* = 1.2 Hz, 1H, 2'-H), 7.27 (d, *J* = 8.3 Hz, 1H, 4'-H or 5'-H), 7.01 (d, *J* = 8.3 Hz, 1H, 4'-H or 5'-H), 4.72 (s, 1H, 2-H), 4.17 (q, *J* = 7.1 Hz, 2H, $-OCH_2CH_3$), 2.42 (s, 3H, 7'-Me), 2.23 (d, *J* = 1.2 Hz, 3H, 3'-Me), 1.80 (s, 3H, 4-H), 1.30 (t, *J* = 7.1 Hz, 3H, $-OCH_2CH_3$). – $C_{16}H_{19}NO_3$ (273.3): calcd. C 70.31, H 7.01, N 5.13; found C 70.27, H 6.99, N 5.10.

Ethyl 3-(2',7'-Dimethyl-4'-benzofurylamino)but-2-enoate (**11a**): This compound was prepared from **10a** in an analogous manner to **5a**. The reaction mixture was chromatographed by CC (CH_2Cl_2) to give **11a** (86%) as an oil. – ^{1}H NMR ($CDCl_3$): δ = 10.37 (br. s, 1H, –NH), 6.95 (d, *J* = 7.8 Hz, 1H, 5'-H or 6'-H), 6.83 (d, *J* = 7.8 Hz, 1H, 5'-H or 6'-H), 6.43 (q, *J* = 1.0 Hz, 1H, 3'-H), 4.71 (br. s, 1H, 2-H), 4.18 (q, *J* = 7.1 Hz, 2H, $-OCH_2CH_3$), 2.48 (s, 3H, 7'-Me), 2.47 (d, *J* = 1.0 Hz, 3H, 2'-Me), 1.94 (s, 3H, 4-H), 1.31 (t, *J* = 7.1 Hz, 3H, $-OCH_2CH_3$). – $C_{16}H_{19}NO_3$ (273.3): calcd. C 70.31, H 7.01, N 5.13; found C 70.28, H 7.00, N 5.07.

Ethyl 3-(3',7'-Dimethyl-4'-benzofurylamino)but-2-enoate (**11b**): This compound was prepared from **10b** in an analogous manner to **5b**. The reaction mixture was chromatographed by CC (CH_2Cl_2) to give **11b** (59%) as an oil. – ^{1}H NMR ($CDCl_3$): δ = 10.28 (br. s, 1H, –NH), 7.37 (q, *J* = 1.2 Hz, 1H, 2'-H), 7.00 (d, *J* = 7.9 Hz, 1H, 5'-H or 6'-H), 6.85 (d, *J* = 7.9 Hz, 1H, 5'-H or 6'-H), 4.71 (s, 1H, 2-H), 4.16 (q, *J* = 7.2 Hz, 2H, $-OCH_2CH_3$), 2.48 (s, 3H, 7'-Me), 2.27 (d, *J* = 1.2 Hz, 3H, 3'-Me), 1.83 (s, 3H, 4-H), 1.30 (t, *J* = 7.1 Hz, 3H, $-OCH_2CH_3$). – $C_{16}H_{19}NO_3$ (273.3): calcd. C 70.31, H 7.01, N 5.13; found C 70.19, H 6.88, N 5.06.

2,7,9-Trimethyl-5H-furo[3,2-g]quinolin-5-one (**6a**): Compound **5a** (0.3 g, 1.1 mmol) was heated at 215°C for 2 h. After cooling, the reaction mixture was chromatographed by CC ($CHCl_3$/EtOH, 9:1) to give **6a** (0.14 g, 56%), m.p. >300°C. – ^{1}H NMR (CD_3OD): δ = 8.17 (s, 1H, 4-H), 6.58 (q, *J* = 1.2 Hz, 1H, 3-H), 6.17 (q, *J* =

0.7 Hz, 1H, 6-H), 2.68 (d, J = 0.7 Hz, 3H, 7-Me), 2.55 (s, 3H, 9-Me), 2.51 (d, J = 1.2 Hz, 3H, 2-Me). – $C_{14}H_{13}NO_2$ (227.3): calcd. C 73.99, H 5.77, N 6.16; found C 73.75, H 5.70, N 6.11.

3,7,9-Trimethyl-5H-furo[3,2-g]quinolin-5-one (**6b**): This compound was prepared from **5b** in an analogous manner to **6a**. The residue was chromatographed by CC ($CHCl_3$/EtOH, 9:1) to give **6b** (56%), m.p. >300°C. – ^{1}H NMR (CD_3OD): δ = 8.27 (s, 1H, 4-H), 7.67 (q, J = 1.3 Hz, 1H, 2-H), 6.19 (q, J = 0.7 Hz, 1H, 6-H), 2.69 (d, J = 0.7 Hz, 3H, 7-Me), 2.56 (s, 3H, 9-Me), 2.31 (d, J = 1.3 Hz, 3H, 3-Me). – $C_{14}H_{13}NO_2$ (227.3): calcd. C 73.99, H 5.77, N 6.16; found C 73.83, H 5.70, N 6.04.

2,6,8-Trimethyl-4H-furo[2,3-h]quinolin-4-one (**12a**): This compound was prepared from **11a** in an analogous manner to **6a**. The residue was chromatographed by CC ($CHCl_3$/EtOH, 9:1) to give **12a** (58%), m.p. >300°C. – ^{1}H NMR (CD_3OD): δ = 7.79 (q, J = 1.0 Hz, 1H, 5-H), 6.95 (q, J = 1.1 Hz, 1H, 9-H), 6.19 (q, J = 0.6 Hz, 1H, 3-H), 2.53 (d, J = 1.1 Hz, 3H, 8-Me), 2.52 (d, J = 1.0 Hz, 3H, 6-Me), 2.49 (d, J = 0.6 Hz, 3H, 2-Me). – $C_{14}H_{13}NO_2$ (227.3): calcd. C 73.99, H 5.77, N 6.16; found C 73.77, H 5.72, N 6.09.

2,6,9-Trimethyl-4H-furo[2,3-h]quinolin-4-one (**12b**): This compound was prepared from **11b** in an analogous manner to **6a**. The residue was chromatographed by CC ($CHCl_3$/EtOH, 9:1) to give **12b** (30%), m.p. >300°C. – ^{1}H NMR (CD_3OD): δ = 7.92 (q, J = 1.0 Hz, 1H, 5-H), 7.71 (q, J = 1.2 Hz, 1H, 8-H), 6.26 (br. s, 1H, 3-H), 2.65 (d, J = 1.2 Hz, 3H, 9-Me), 2.57 (br. s, 3H, 2-Me), 2.55 (d, J = 1.0 Hz, 3H, 6-Me). – $C_{14}H_{13}NO_2$ (227.3): calcd. C 73.99, H 5.77, N 6.16; found C 73.83, H 5.70, N 6.04.

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