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Synthesis of some benzo[*c*][2,6]naphthyridin-5-ones and new tetracyclic benzofuro[4,5-*c*]-2,6-naphthyridin-5(6*H*)-ones

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Abstract—A series of novel methylbenzofuro[4,5-*c*]-2,6-naphthyridin-5(6*H*)-ones were synthesized, first building the pyridine nucleus on the appropriated quinolin-2-ones, and then condensing the furan ring on the preconstituted benzonaphthyridinones. The benzo[*c*][2,6]naphthyridinic nucleus was also interesting for its known pharmacological properties, as well as intermediate for the synthesis of natural product analogues. © 2002 Elsevier Science Ltd. All rights reserved.

1. Introduction

In the last few years we have been working in the field of furocoumarins, well known photochemotherapeutic agents,[1,2] and furoquinolinones,[3,4] furocoumarin isosters, with the aim to investigate and compare their antiproliferative activity. In this way, we have been interested in synthesizing other correlated and more complex structures to achieve improved biological activities of the parent compounds.

During these studies, we often dealt with nitrogen heterocycles and with straightforward synthetic methods to built them profitably. So we developed a useful synthetic strategy to prepare a new tetracyclic nucleus, namely benzofuro-[4,5-*c*]-2,6-naphthyridin-5(6*H*)-one. This novel heterocyclic structure was prepared to obtain novel DNA intercalating photochemotherapeutic agents;[5] in addition, this synthetic route may prove very useful to afford benzonaphthyridinone intermediates, interesting for their known pharmacological properties,[6,7] as well as for the synthesis of marine alkaloids analogues, widely studied for its significant and diverse biological activities.[8–10]

For these reasons, we are now reporting a convenient synthesis of some methylbenzofuro[4,5-*c*]-2,6-naphthyridin-5(6*H*)-ones and a general procedure leading to benzo-[*c*][2,6]naphthyridine nucleus.

2. Results and discussion

The synthetic approach to benzofuronaphthyridinones (**7a–d**) consisted of first building the pyridine nucleus on the appropriate quinolin-2-ones by the Pomeranz–Fritsch reaction,[11] and then condensing the furan ring on the preconstituted benzonaphthyridinones. Since the final compounds carried methyl substituents in various positions of the tetracyclic nucleus, for the known positive effects of these groups on biological activity,[12] the introduction of these substituents was carried out at different steps of the synthetic pathway. So the final 10-methyl group was present from the beginning of the synthesis, while *N*-methyl group (when present) was introduced in a further step, and the methyl substituents on the furan ring were introduced using specific synthetic routes.

As outlined in Scheme 1, starting materials were methyl-7-hydroxyquinolin-2-ones **1a** and **b**,[13] which were acetylated with acetic anhydride; acetylation was necessary for the following *N*-methylation and to help the next oxidative step. Compound **2b** was methylated at the *N*-position with dimethyl sulphate and the methyl-7-acetoxyquinolin-2-ones **2a–c** were then reacted with selenium dioxide in dioxane solution. This step was completely chemoselective, because SeO_2 enabled oxidation only of allylic methyl groups and not of aromatic methyl functions.[14]

Formylquinolinones **3a–c** were condensed with amino-acetaldehyde dimethyl acetal to give the corresponding Schiff bases **4a–c**; during this step, deacetylation also occurred. Compounds **4a–c** were submitted to cyclization in concentrated sulphuric acid at 60°C, yielding the benzo-[*c*][2,6]naphthyridin-5-ones **5a–c**, which were then condensed

Keywords: synthesis; benzonaphthyridone; benzofuronaphthyridone; biological activity.

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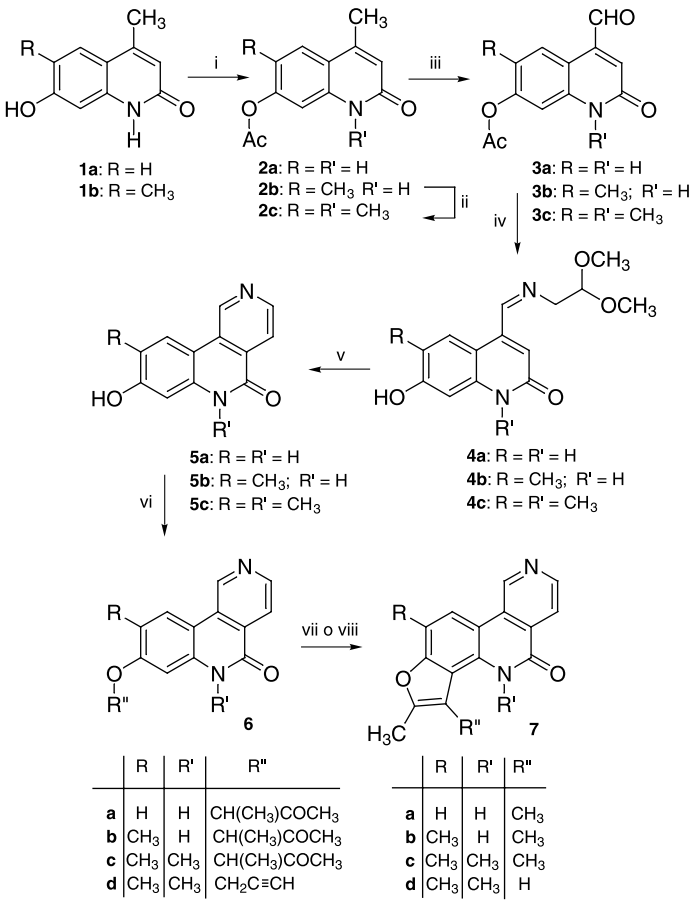
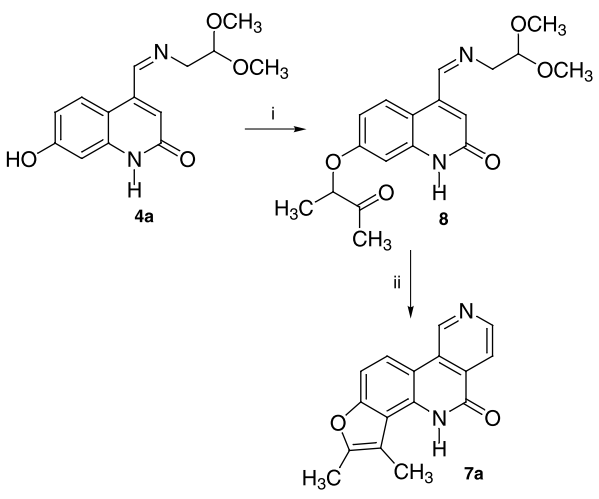


Scheme 1. (i) Ac_2O, AcONa, reflux, 68% (**2a**), and 74% (**2b**); (ii) Me_2SO_4, acetone, K_2CO_3, reflux, 55%; (iii) SeO_2, dioxane, molecular sieves, reflux, 65% (**3a**), 79% (**3b**), and 40% (**3c**); (iv) $NH_2CH_2CH(OMe)_2$, toluene, reflux, 80% (**4a**), 67% (**4b**), and 73% (**4c**); (v) conc. H_2SO_4, 60°C, 54% (**5a**), 70% (**5b**), and 70% (**5c**); (vi) 3-chloro-2-butanone or propargyl chloride, DMF, K_2CO_3, 40°C, 55% (**6a**), 43% (**6b**), 63% (**6c**), and 68% (**6d**); (vii) conc. H_2SO_4, room temperature, 63% (**7a**), 76% (**7b**), and 33% (**7c**); (viii) *N*,*N*-diethylaniline, CsF, reflux, 42%.

with 3-chloro-2-butanone. The resulting 7-*O*-ethers **6a**–**c** were cyclized in concentrated sulphuric acid at room temperature, yielding the corresponding benzofuro[4,5-*c*]-2,6-naphthyridin-5(6*H*)-ones **7a**–**c**. This cyclization proved to be highly regioselective, even if the 6-position was free from substituent, since only one of the two possible isomers was found.



Scheme 2. (i) 3-Chloro-2-butanone, DMF, K_2CO_3, 40°C, 80%; (ii) conc. H_2SO_4, room temperature, 10%.

Compound **5c** was also condensed with propargyl chloride to give **6d**, which was submitted to cyclization in the presence of CsF,[15] affording benzofuro[4,5-*c*]-2,6-naphthyridin-5(6*H*)-one **7d**.

Since both the cyclizations of the pyridine and furan rings were accomplished in concentrated sulphuric acid, synthesis of **7a** was attempted cyclizing at the same time the two rings, as shown in Scheme 2. The Schiff base **4a** was condensed with 3-chloro-2-butanone and the resulting 7-*O*-ether **8** was cyclized in concentrated sulphuric acid at room temperature, yielding the desired benzofuronaphthyridinone **7a**, but with very low yield.

3. Conclusion

A convenient and easy route to benzofuro[4,5-*c*]-2,6-naphthyridin-5(6*H*)-one is described, which allows the synthesis of both methyl derivatives of the tetracyclic nucleus and benzonaphthyridinone intermediates useful as natural product precursors.

4. Experimental

Melting points were determined on a Gallenkamp

MFB-595-010M melting point apparatus and are uncorrected. Analytical TLC was performed on pre-coated 60 F_{254} silica gel plates (0.25 mm; Merck) eluting with a $CHCl_3$/MeOH mixture (9:1) unless otherwise indicated. Preparative column chromatography was performed using silica gel 60 (0.063–0.100 mm; Merck), eluting with $CHCl_3$. UV spectra were recorded on a Perkin–Elmer Lambda 20 UV–VIS spectrophotometer. IR spectra were recorded on a Perkin–Elmer 1600 FT-IR spectrometer. ^1H NMR and ^{13}C NMR spectra were recorded at 300.13 and 75.47 MHz, respectively, on a Bruker AMX300 spectrometer with TMS as internal standard. Mass spectra were recorded on a Varian MAT112 spectrometer. Elemental analyses were obtained on all intermediates and were within ±0.4% of theoretical values. Starting 7-hydroxy-4-methylquinolin-2-one (**1a**) and 7-hydroxy-4,6-dimethylquinolin-2-one (**1b**) were prepared according to literature methods.[13]

4.1. General procedure for 7-acetoxyquinolin-2-ones (2a,b)

A mixture of **1** (70.0 mmol) and anhydrous AcONa (5.0 g) in acetic anhydride (130 mL) was refluxed for 2 h. The mixture was cautiously diluted with water (130 mL) and poured into cold water (600 mL). The precipitate was collected, washed with water, and crystallized from MeOH to give **2**.

4.1.1. 7-Acetoxy-4-methylquinolin-2-one (2a). Yield 68%; mp 261°C; IR (KBr) cm^{-1} 2930, 2850, 1750, 1680, 1560, 1400, 1360, 1230, 1160, 1020, 910, 850; ^1H NMR ($CDCl_3$) δ 11.55 (1H, broad s, NH), 7.69 (1H, d, J=8.7 Hz, 5-H), 7.08 (1H, d, J=2.5 Hz, 8-H), 7.01 (1H, dd, J=8.7, 2.5 Hz, 6-H), 6.54 (1H, q, J=1.1 Hz, 3-H), 2.50 (3H, d, J=1.1 Hz, 4-Me), 2.34 (3H, s, 7-OAc). Anal. calcd for $C_{12}H_{11}NO_3$: C, 66.35; H, 5.10; N, 6.45. Found: C, 66.44; H, 5.07; N, 6.50.

4.1.2. 7-Acetoxy-4,6-dimethylquinolin-2-one (2b). Yield 74%; mp 260°C; IR (KBr) cm^{-1} 2930, 2820, 1750, 1660, 1550, 1410, 1370, 1200, 1130, 1070, 910, 860; ^1H NMR ($CDCl_3$) δ 11.72 (1H, broad s, NH), 7.52 (1H, q, J=0.9 Hz, 5-H), 7.05 (1H, s, 8-H), 6.52 (1H, q, J=1.1 Hz, 3-H), 2.48 (3H, d, J=1.1 Hz, 4-Me), 2.36 (3H, s, 7-OAc), 2.26 (3H, d, J=0.9 Hz, 6-Me). Anal. calcd for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.67; N, 6.06. Found: C, 67.48; H, 5.64; N, 6.02.

4.2. 7-Acetoxy-1,4,6-trimethylquinolin-2-one (2c)

A mixture of **2b** (11.0 g, 47.5 mmol), dimethyl sulfate (6.7 mL, 71.3 mmol) and anhydrous K_2CO_3 (20.0 g) in acetone (500 mL) was refluxed until starting material disappeared (72 h, TLC). After cooling, the solid was filtered off and washed with fresh acetone. The solvent was evaporated under reduced pressure from the combined filtrate and washings. The residue was purified by column chromatography to give **2c** (6.4 g, 55%): mp 118°C; IR (KBr) cm^{-1} 2930, 2810, 1710, 1650, 1560, 1450, 1390, 1240, 1060, 850; ^1H NMR ($CDCl_3$) δ 7.51 (1H, s, 5-H), 7.01 (1H, s, 8-H), 6.52 (1H, q, J=1.1 Hz, 3-H), 3.61 (3H, s, N–Me), 2.36 (3H, s, 6-Me or 7-OAc), 2.24 (3H, s, 6-Me or 7-OAc). Anal. calcd for $C_{14}H_{15}NO_3$: C, 68.56; H, 6.16; N, 5.71. Found: C, 68.55; H, 6.13; N, 5.75.

4.3. General procedure for methyl-4′-(7′-acetoxy-2′-oxoquinoline)carboxaldehydes (3)

A mixture of **2** (30.0 mmol), selenium dioxide (13.3 g, 120.0 mmol) and molecular sieves (5A, 8–12 mesh) in dioxane (200 mL) was refluxed until starting material disappeared (72 h, TLC). After cooling, the solid was filtered off and washed with fresh dioxane. The solvent was evaporated from the combined filtrate and washings and the residue was purified by column chromatography to give **3**.

4.3.1. 7-Acetoxy-2-oxoquinoline-4-carboxaldehyde (3a). Yield 65%; mp 256°C; IR (KBr) cm^{-1} 2930, 2850, 2760, 1760, 1660, 1540, 1420, 1210, 1170, 1130, 1060, 870; ^1H NMR ($CDCl_3$) δ 10.16 (1H, s, CHO), 8.81 (1H, d, J=8.8 Hz, 5-H), 7.15 (1H, d, J=2.2 Hz, 8-H), 7.13 (1H, s, 3-H), 7.09 (1H, dd, J=8.8, 2.2 Hz, 6-H), 2.36 (3H, s, 7-OAc). Anal. calcd for $C_{12}H_9NO_4$: C, 62.34; H, 3.92; N, 6.06. Found: C, 62.37; H, 3.98; N, 6.04.

4.3.2. 7-Acetoxy-6-methyl-2-oxoquinoline-4-carboxaldehyde (3b). Yield 79%; mp 258°C; IR (KBr) cm^{-1} 2990, 2850, 2760, 1750, 1710, 1660, 1560, 1430, 1370, 1210, 1120, 1060, 920, 860; ^1H NMR ($CDCl_3$) δ 10.14 (1H, s, CHO), 8.64 (1H, q, J=0.9 Hz, 5-H), 7.11 (1H, s, 3-H), 7.06 (1H, s, 8-H), 2.38 (3H, s, 7-OAc), 2.28 (3H, d, J=0.9 Hz, 6-Me). Anal. calcd for $C_{13}H_{11}NO_4$: C, 63.67; H, 4.52; N, 5.71. Found: C, 63.67; H, 4.50; N, 5.65.

4.3.3. 7-Acetoxy-1,6-dimethyl-2-oxoquinoline-4-carboxaldehyde (3c). Yield 40%; mp 170°C; IR (KBr) cm^{-1} 2940, 2760, 1760, 1690, 1660, 1580, 1430, 1370, 1260, 1130, 1030, 890, 850; ^1H NMR ($CDCl_3$) δ 10.10 (1H, s, CHO), 8.75 (1H, q, J=0.8 Hz, 5-H), 7.13 (1H, s, 3-H or 8-H), 7.11 (1H, s, 3-H or 8-H), 3.71 (3H, s, N–Me), 2.39 (3H, s, 7-OAc), 2.28 (3H, d, J=0.8 Hz, 6-Me). Anal. calcd for $C_{14}H_{13}NO_4$: C, 64.86; H, 5.05; N, 5.40. Found: C, 64.85; H, 5.03; N, 5.42.

4.4. General procedure for methyl-7-hydroxy-4-(2′,2′-dimethoxyethylimino)methylquinolin-2-ones (4)

A mixture of **3** (15.0 mmol) and aminoacetaldehyde dimethyl acetal (4.7 g, 45.0 mmol) in toluene (500 mL) was refluxed with a Dean–Stark apparatus until starting material disappeared (20 h, TLC). After cooling, the solid was collected and washed with fresh toluene to give **4**.

4.4.1. 7-Hydroxy-4-(2′,2′-dimethoxyethylimino)-methylquinolin-2-one (4a). Yield 80%; mp 220°C; IR (KBr) cm^{-1} 3410, 3100, 2940, 2830, 1650, 1540, 1410, 1250, 1120, 1060, 910, 830; ^1H NMR (acetone-d_6) δ 10.74 (1H, broad s, OH or NH), 9.17 (1H, broad s, OH or NH), 8.66 (1H, d, J=8.9 Hz, 5-H), 8.60 (1H, t, J=1.4 Hz, CH=N), 6.89 (1H, d, J=2.4 Hz, 8-H), 6.76 (1H, dd, J=8.9, 2.4 Hz, 6-H), 6.62 (1H, s, 3-H), 4.74 (1H, t, J=5.4 Hz, $CH(OMe)_2$), 3.84 (2H, dd, J=5.4, 1.4 Hz, N–CH_2), 3.38 (6H, s, –OMe). Anal. calcd for $C_{14}H_{16}N_2O_4$: C, 60.86; H, 5.84; N, 10.14. Found: C, 60.80; H, 5.87; N, 10.10.

4.4.2. 7-Hydroxy-4-(2′,2′-dimethoxyethylimino)methyl-6-methylquinolin-2-one (4b). Yield 67%; mp 244°C; IR (KBr) cm^{-1} 3420, 3070, 2920, 2850, 1650, 1540, 1420, 1250, 1130, 1020, 910, 830; ^1H NMR (acetone-d_6) δ 10.60

(1H, broad s, OH or NH), 9.16 (1H, broad s, OH or NH), 8.64 (1H, t, J=1.4 Hz, CH=N), 8.49 (1H, q, J=0.9 Hz, 5-H), 6.91 (1H, s, 8-H), 6.60 (1H, s, 3-H), 4.74 (1H, t, J=5.4 Hz, *CH*(OMe)$_2$), 3.84 (2H, dd, J=5.4, 1.4 Hz, N–CH_2), 3.40 (6H, s, –OMe), 2.25 (3H, d, J=0.9 Hz, 6-Me). Anal. calcd for $C_{15}H_{18}N_2O_4$: C, 62.06; H, 6.24; N, 9.65. Found: C, 61.99; H, 6.28; N, 9.61.

4.4.3. 7-Hydroxy-4-(2′,2′-dimethoxyethylimino)methyl-1,6-dimethylquinolin-2-one (4c). Yield 73%; mp 300°C; IR (KBr) cm^{-1} 3410, 3000, 2950, 2850, 1670, 1620, 1540, 1420, 1250, 1130, 1020, 910, 830; ^{1}H NMR ($CDCl_3$) δ 8.53 (1H, t, J=1.3 Hz, CH=N), 8.26 (1H, s, 5-H), 6.88 (1H, s, 3-H or 8-H), 6.79 (1H, s, 3-H or 8-H), 4.77 (1H, t, J=5.2 Hz, *CH*(OMe)$_2$), 3.89 (2H, dd, J=5.2, 1.3 Hz, N–CH_2), 3.63 (6H, s, –OMe), 3.47 (3H, s, N–Me), 2.31 (3H, s, 6-Me). Anal. calcd for $C_{16}H_{20}N_2O_4$: C, 63.14; H, 6.62; N, 9.20. Found: C, 63.18; H, 6.59; N, 9.18.

4.5. General procedure for methyl-8-hydroxybenzo[*c*]-2,6-naphthyridin-5-ones (5)

Compound **4** (10.0 mmol) was dissolved in conc. H_2SO_4 (30 mL) and the solution was heated at 60°C for 2 h. The mixture was poured into cold water (300 mL) and the precipitate was collected, washed with water, and crystallized from MeOH to give **5**.

4.5.1. 8-Hydroxybenzo[*c*]2,6-naphthyridin-5-one (5a). Yield 54%; mp (dec.) 260°C; IR (KBr) cm^{-1} 3430, 3050, 2930, 2850, 1690, 1620, 1540, 1410, 1370, 1240, 1130, 1060, 830, 780; ^{1}H NMR (DMSO-d_6) δ 11.86 (1H, broad s, OH or NH), 10.20 (1H, broad s, OH or NH), 9.74 (1H, d, J=0.9 Hz, 1-H), 8.69 (1H, d, J=5.2 Hz, 3-H), 8.38 (1H, d, J=8.8 Hz,10-H), 8.04 (1H, dd, J=5.2, 0.9 Hz, 4-H), 6.82 (1H, d, J=2.3 Hz, 7-H), 6.77 (1H, dd, J=8.8, 2.3 Hz, 9-H). Anal. calcd for $C_{12}H_8N_2O_2$: C, 67.92; H, 3.80; N, 13.20. Found: C, 67.95; H, 3.82; N, 13.24.

4.5.2. 8-Hydroxy-9-methylbenzo[*c*]2,6-naphthyridin-5-one (5b). Yield 70%; mp dec 270°C; IR (KBr) cm^{-1} 3420, 3070, 2950, 2850, 1680, 1620, 1540, 1420, 1360, 1240, 1130, 1070, 820, 780; ^{1}H NMR (DMSO-d_6) δ 11.92 (1H, broad s, OH or NH), 10.30 (1H, broad s, OH or NH), 9.80 (1H, d, J=0.9 Hz, 1-H), 8.71 (1H, d, J=5.2 Hz, 3-H), 8.30 (1H, s, 10-H), 8.16 (1H, dd, J=5.2, 0.9 Hz, 4-H), 6.88 (1H, s, 7-H), 2.24 (3H, s, 9-Me). Anal. calcd for $C_{13}H_{10}N_2O_2$: C, 69.02; H, 4.46; N, 12.38. Found: C, 69.07; H, 4.47; N, 12.35.

4.5.3. 8-Hydroxy-6,9-dimethylbenzo[*c*]2,6-naphthyridin-5-one (5c). Yield 70%; mp >300°C; IR (KBr) cm^{-1} 3440, 3070, 2930, 2820, 1660, 1620, 1580, 1420, 1380, 1250, 1160, 1100, 1060, 820, 780; ^{1}H NMR (DMSO-d_6) δ 10.68 (1H, broad s, OH), 9.83 (1H, d, J=0.8 Hz, 1-H), 8.71 (1H, d, J=5.4 Hz, 3-H), 8.42 (1H, s, 10-H), 8.17 (1H, dd, J=5.4, 0.8 Hz, 4-H), 6.98 (1H, s, 7-H), 3.66 (3H, s, N–Me), 2.24 (3H, s, 9-Me). Anal. calcd for $C_{14}H_{12}N_2O_2$: C, 69.99; H, 5.03; N, 11.66. Found: C, 70.02; H, 5.00; N, 11.64.

4.6. General procedure for benzo[*c*]2,6-naphthyridin-5-one 8-*O*-ethers (6)

A mixture of **5** (7.0 mmol), 3-chloro-2-butanone or propargyl chloride (8.4 mmol) and anhydrous K_2CO_3 (5.0 g) in DMF (100 mL) was heated at 40°C until starting product disappeared (24 h, TLC). After cooling, the solid was filtered off and the filtrate was evaporated to dryness. The residue was crystallized from MeOH to give **6**.

4.6.1. 8-(1′-Methyl-2′-oxopropyloxy)benzo[*c*]2,6-naphthyridin-5-one (6a). Yield 55%; mp 246°C; IR (KBr) cm^{-1} 3020, 2920, 2850, 1720, 1670, 1610, 1530, 1420, 1360, 1270, 1230, 1200, 1090, 990, 880, 850, 820, 790; ^{1}H NMR (DMSO-d_6) δ 11.91 (1H, broad s, NH), 9.80 (1H, d, J=0.9 Hz, 1-H), 8.75 (1H, d, J=5.2 Hz, 3-H), 8.49 (1H, d, J=8.9 Hz, 10-H), 8.06 (1H, dd, J=5.2, 0.9 Hz, 4-H), 6.91 (1H, dd, J=8.9, 2.4 Hz, 9-H), 6.81 (1H, d, J=2.4 Hz, 7-H), 5.03 (1H, q, J=6.9 Hz, 2′-H), 2.24 (3H, s, 4′-H), 1.50 (3H, d, J=6.9 Hz, 1′-H). Anal. calcd for $C_{16}H_{14}N_2O_3$: C, 68.07; H, 5.00; N, 9.92. Found: C, 68.10; H, 4.98; N, 9.89.

4.6.2. 9-Methyl-8-(1′-methyl-2′-oxopropyloxy)-benzo-[*c*]2,6-naphthyridin-5-one (6b). Yield 43%; mp 260°C; IR (KBr) cm^{-1} 3100, 2940, 2890, 1730, 1670, 1610, 1540, 1420, 1360, 1280, 1240, 1200, 1150, 1090, 880, 840, 800; ^{1}H NMR (DMSO-d_6) δ 11.78 (1H, broad s, NH), 9.78 (1H, d, J=0.9 Hz, 1-H), 8.71 (1H, d, J=5.2 Hz, 3-H), 8.40 (1H, s, 10-H), 8.04 (1H, dd, J=5.2, 0.9 Hz, 4-H), 6.68 (1H, s, 7-H), 4.90 (1H, q, J=6.9 Hz, 2′-H), 2.32 (3H, s, 9-Me), 2.24 (3H, s, 4′-H), 1.51 (3H, d, J=6.9 Hz, 1′-H). Anal. calcd for $C_{17}H_{16}N_2O_3$: C, 68.91; H, 5.44; N, 9.45. Found: C, 68.93; H, 5.42; N, 9.47.

4.6.3. 6,9-Dimethyl-8-(1′-methyl-2′-oxopropyloxy)-benzo-[*c*]2,6-naphthyridin-5-one (6c). Yield 63%; mp >300°C; IR (KBr) cm^{-1} 2940, 2850, 1720, 1670, 1620, 1530, 1430, 1360, 1270, 1230, 1190, 1080, 990, 890, 850, 810; ^{1}H NMR (DMSO-d_6) δ 9.84 (1H, d, J=0.9 Hz, 1-H), 8.85 (1H, d, J=5.2 Hz, 3-H), 8.54 (1H, q, J=0.6 Hz, 10-H), 8.11 (1H, dd, J=5.2, 0.9 Hz, 4-H), 6.12 (1H, s, 7-H), 5.13 (1H, q, J=6.6 Hz, 2′-H), 3.71 (3H, s, N–Me), 2.38 (1H, d, J=0.6 Hz, 9-Me), 2.26 (3H, s, 4′H), 1.54 (3H, d, J=6.6 Hz, 1′-H). Anal. calcd for $C_{18}H_{18}N_2O_3$: C, 69.66; H, 5.85; N, 9.03. Found: C, 69.95; H, 5.87; N, 9.04.

4.6.4. 6,9-Dimethyl-8-propargyloxybenzo[*c*]2,6-naphthyridin-5-one (6d). Yield 68%; mp >300°C; IR (KBr) cm^{-1} 2930, 1650, 1620, 1560, 1420, 1360, 1230, 1150, 1100, 1060, 920, 880, 820; ^{1}H NMR (DMSO-d_6) δ 9.81 (1H, s, 1-H), 8.82 (1H, d, J=5.3 Hz, 3-H), 8.48 (1H, s, 10-H), 8.10 (1H, d, J=5.3 Hz, 4-H), 7.14 (1H, s, 7-H), 5.07 (2H, d, J=2.3 Hz, 1′-H), 3.74 (3H, s, N–Me), 3.69 (1H, t, J=2.3 Hz, 3′-H), 2.30 (3H, s, 9-Me). Anal. calcd for $C_{17}H_{14}N_2O_2$: C, 73.37; H, 5.07; N, 10.06. Found: C, 73.35; H, 5.06; N, 10.10.

4.7. General procedure for 7,8-dimethylbenzofuro[4,5-*c*]-2,6-naphthyridin-5(6*H*)-ones (7a–c)

Compounds **6a–c** (1.0 mmol) were dissolved in conc. H_2SO_4 (10 mL) and the solution was kept at room temperature until starting material disappeared (4 h, TLC). The mixture was poured into cold water (100 mL) and the precipitate was collected, washed with water and purified by column chromatography to give **7a–c**.

4.7.1. 7,8-Dimethylbenzofuro[4,5-*c*]-2,6-naphthyridin-5(6*H*)-one (7a). Yield 63%; dec 200°C; UV (EtOH 95%) λ_{max} 210, 258, 348 nm, λ_{min} 231, 303 nm; IR (KBr) cm^{-1} 3300, 3030, 2920, 1670, 1660, 1550, 1450, 1400, 1360, 1280, 1110, 780; ^1H NMR ($CDCl_3$) δ 9.70 (1H, d, J= 0.8 Hz, 1-H), 9.02 (1H, broad s, NH), 8.79 (1H, d, J= 5.2 Hz, 3-H), 8.26 (1H, dd, J=5.2, 0.8 Hz, 4-H), 8.16 (1H, d, J=8.9 Hz, 11-H), 7.39 (1H, d, J=8.9 Hz, 10-H), 2.55 (3H, q, J=0.7 Hz, 7-Me or 8-Me), 2.45 (3H, q, J=0.7 Hz, 7-Me or 8-Me); ^{13}C NMR (DMSO-d_6) δ 160.01 (C-5), 154.81 (C-9a), 151.19 (C-8), 147.28 (C-3), 146.99 (C-1), 141.60 (C-6a), 129.70 (C-4a or C-11b), 129.46 (C-4a or C-11b), 119.90 (C-4), 119.01 (C-11), 117.05 (C-6b), 111.21 (C-11a), 109.54 (C-7), 107.38 (C-10), 11.64 (8-Me), 9.93 (7-Me); MS (EI): *m/z* (relative intensity) 264 (M^+, 100), 249 (55), 235 (18), 207 (15). Anal. calcd for $C_{16}H_{12}N_2O_2$: C, 72.72; H, 4.58; N, 10.60. Found: C, 72.68; H, 4.59; N, 10.62.

4.7.2. 7,8,10-Trimethylbenzofuro[4,5-*c*]-2,6-naphthyridin-5(6*H*)-one (7b). Yield 76%; dec 205°C; UV (EtOH 95%) λ_{max} 209, 258, 354 nm, λ_{min} 232, 301 nm; IR (KBr) cm^{-1} 3300, 3060, 2920, 1670, 1660, 1550, 1460, 1410, 1360, 1180, 1010, 840, 710; ^1H NMR ($CDCl_3$) δ 9.70 (1H, d, J=0.8 Hz, 1-H), 9.02 (1H, broad s, NH), 8.78 (1H, d, J=5.2 Hz, 3-H), 8.26 (1H, dd, J=5.2, 0.8 Hz, 4-H), 7.95 (1H, s, 11-H), 2.60 (3H, s, 10-Me), 2.55 (3H, q, J=0.7 Hz, 7-Me or 8-Me), 2.45 (3H, q, J=0.7 Hz, 7-Me or 8-Me); ^{13}C NMR ($CDCl_3$) δ 161.23 (C-5), 155.02 (C-9a), 151.27 (C-8), 146.97 (C-3), 145.83 (C-1), 140.81 (C-6a), 129.86 (C-4a or C-11b), 129.41 (C-4a or C-11b), 120.38 (C-4), 119.48 (C-6b), 119.06 (C-10), 118.77 (C-11), 112.35 (C-11a), 110.56 (C-7), 35.10 (N–Me), 15.97 (10-Me), 11.54 (8-Me), 9.96 (7-Me); MS (EI): *m/z* (relative intensity) 278 (M^+, 100), 263 (30), 249 (18), 221 (18). Anal. calcd for $C_{17}H_{14}N_2O_2$: C, 73.37; H, 5.07; N, 10.06. Found: C, 73.33; H, 5.05; N, 10.09.

4.7.3. 6,7,8,10-Tetramethylbenzofuro[4,5-*c*]-2,6-naphthy-ridin-5(6*H*)-one (7c). Yield 33%; mp >300°C; UV (EtOH 95%) λ_{max} 217, 263, 356 nm, λ_{min} 234, 306 nm; IR (KBr) cm^{-1} 3070, 2920, 1650, 1600, 1580, 1560, 1360, 1320, 1190, 1060, 800; ^1H NMR ($CDCl_3$) δ 9.67 (1H, d, J=0.8 Hz, 1-H), 8.68 (1H, d, J=5.2 Hz, 3-H), 8.26 (1H, dd, J=5.2, 0.8 Hz, 4-H), 7.99 (1H, q, J=0.9 Hz, 11-H), 3.89 (3H, s, N–Me), 2.61 (3H, d, J=0.9 Hz, 10-Me), 2.48 (3H, q, J=0.8 Hz, 7-Me or 8-Me), 2.39 (3H, q, J=0.8 Hz, 7-Me or 8-Me); ^{13}C NMR ($CDCl_3$) δ 162.72 (C-5), 155.68 (C-9a), 152.69 (C-8), 146.57 (C-3), 145.91 (C-1), 133.16 (C-6a), 129.77 (C-4a o C-11b), 129.65 (C-4a o C-11b), 120.88 (C-4), 119.43 (C-6b), 118.52 (C-10), 118.21 (C-11), 113.35 (C-11a), 109.56 (C-7), 40.62 (N–Me), 15.51 (10-Me), 14.72 (7-Me), 12.84 (8-Me); MS (EI) *m/z* (relative intensity) 292 (M^+, 100), 277 (52), 263 (15), 235 (15), 220 (15), 205 (25). Anal. calcd for $C_{18}H_{16}N_2O_2$: C, 73.95; H, 5.52; N, 9.58. Found: C, 74.00; H, 5.49; N, 9.58.

4.8. 6,8,10-Trimethylbenzofuro[4,5-*c*]-2,6-naphthyridin-5(6*H*)-one (7d)

A mixture of **6d** (0.83 g, 3.0 mmol) and CsF (0.46 g, 3.0 mmol) in *N*,*N*-diethylaniline (15 mL) was heated at 210°C until starting product disappeared (6 h, ^1H NMR). After cooling, the mixture was diluted with AcOEt (50 mL), washed with HCl 1N (3×50 mL) and water (3×50 mL) and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography to give **7d** (0.34 g, 42%): mp >300°C; UV (EtOH 95%) λ_{max} 226, 258, 348 nm, λ_{min} 243, 311 nm; IR (KBr) cm^{-1} 2930, 1650, 1600, 1530, 1500, 1400, 1320, 1240, 1150, 1090, 740; ^1H NMR ($CDCl_3$) δ 9.71 (1H, s, 1-H), 8.76 (1H, d, J=5.2 Hz, 3-H), 8.29 (1H, d, J=5.2 Hz, 4-H), 8.07 (1H, s, 11-H), 6.94 (1H, q, J=1.1 Hz, 7-H), 4.13 (3H, s, N–Me), 2.63 (3H, s, 10-Me), 2.57 (3H, d, J=1.1 Hz, 8-Me); ^{13}C NMR ($CDCl_3$) δ 161.42 (C-5), 156.00 (C-9a), 155.24 (C-8), 147.16 (C-3), 146.32 (C-1), 131.56 (C-6a), 129.62 (C-4a), 129.26 (C-11b), 121.06 (C-4), 119.01 (C-11), 118.18 (C-10), 117.91 (C-6b), 112.42 (C-11a), 104.76 (C-7), 34.45 (N–Me), 15.59 (10-Me), 14.50 (8-Me); MS (EI) *m/z* (relative intensity) 278 (M^+, 100), 263 (15), 249 (18), 221 (15), 206 (15). Anal. calcd for $C_{17}H_{14}N_2O_2$: C, 73.37; H, 5.07; N, 10.06. Found: C, 73.41; H, 5.07; N, 10.03.

4.9. 4-(2′,2′-Dimethoxyethylimino)methyl-7-(1″-methyl-2″-oxopropyloxy)quinolin-2-one (8)

A mixture of **4a** (0.20 g, 0.72 mmol), 3-chloro-2-butanone (0.11 g, 0.11 mL, 1.1 mmol) and anhydrous K_2CO_3 (2.0 g) in DMF (20 mL) was heated at 40°C until the starting product disappeared (24 h, TLC). After cooling, the solid was filtered off and the filtrate was evaporated to dryness. The residue was crystallized from MeOH to give **8** (0.20 g, 80%): mp 143°C; ^1H NMR (acetone-d_6) δ 9.17 (1H, broad s, NH), 8.67 (1H, d, J=8.9 Hz, 5-H), 8.60 (1H, t, J=1.4 Hz, CH=N), 6.89 (1H, d, J=2.4 Hz, 8-H), 6.76 (1H, dd, J=8.9, 2.4 Hz, 6-H), 6.62 (1H, s, 3-H), 4.90 (1H, q, J=6.9 Hz, 1″-H), 4.74 (1H, t, J=5.4 Hz, *CH*(OMe)$_2$), 3.84 (2H, dd, J=5.4, 1.4 Hz, N–CH_2), 3.38 (6H, s, –OMe), 2.20 (3H, s, 3″-H), 1.53 (3H, d, J=6.8 Hz, 1″-Me). Anal. calcd for $C_{18}H_{22}N_2O_5$: C, 62.42; H, 6.40; N, 8.09. Found: C, 62.49; H, 6.38; N, 8.11.

4.10. 7,8-Dimethylbenzofuro[4,5-*c*]-2,6-naphthyridin-5(6*H*)-one (7a) from 8

Compound **8** (0.20 g, 0.58 mmol) was dissolved in conc. H_2SO_4 (4 mL) and the solution was kept at room temperature until starting material disappeared (24 h, TLC). The mixture was poured into cold water (40 mL) and the obtained precipitate was collected, washed with water and purified by column chromatography to give **7a** (0.02 g, 10%), with analytical data as reported above.

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