Heterocycles [*f*]-Fused onto Quinolones. Synthesis of Novel Dioxo-*N*-ethylpyrano[2,3-*f*]- and [3,2-*f*]quinoline-10-carboxylic Acids

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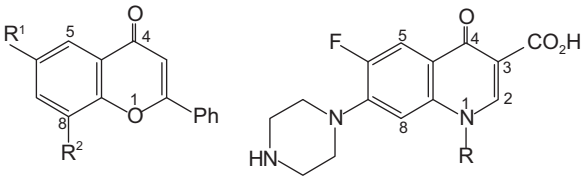
A model *N*-ethyl-1,10-dioxo-3-phenylpyrano[3,2-*f*]quinoline-9-carboxylic acid (**8**) and the isomeric (2-substituted) pyrano[2,3-*f*]quinoline-9-carboxylic acids (**6** and **7**) were prepared from the corresponding 6/7-aminochromen-4-ones *via* the Gould-Jacobs reaction. The new tricyclic heterocycles **6**–**8** exhibit moderate antibacterial activity (MIC = 16 – 64 μg mL^{-1}) against *E. coli* and *S. aureus*.

Key words: 7-Aminoflavone, 6-Aminoflavone, 7-Amino-2-methyl-4*H*-chromen-4-one, Regioselective Cyclization, Pyrano[2,3-*f*] and [3,2-*f*]quinolones

Introduction

Chromones are naturally occurring compounds with a 4-benzopyrone moiety [1, 2]. The compounds of this family are well-known as antioxidants [3, 4]. Some chromone derivatives, such as khellin [5] and 2,4-thiazolidenedione [6 – 8], have antispasmodic and antidiabetic activities, respectively. These biological properties made this family of compounds the target of innumerous studies focusing on syntheses and structural modifications [9 – 15]. Flavones, *e. g.* **1**–**3**, are 2-phenyl-substituted chromones [16, 17] which exhibit biocidal [18 – 20], antitumor [21], anti-inflammatory [22, 23], antiviral [24, 25], anti-HIV [26], and other activities.

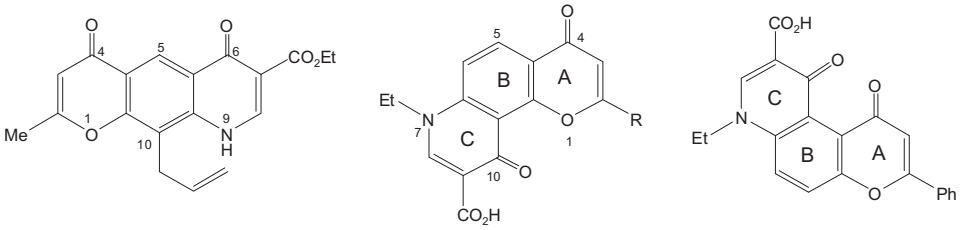
Synthetic 4-oxoquinoline-3-carboxylic acids, exemplified by norfloxacin (**4a**) [27, 28] and ciprofloxacin (**4b**) [29 – 32] (Fig. 1), constitute a major class of therapeutic agents which have a broad spectrum of antibacterial activity. For most current SAR studies, a hydrogen atom at position 2, a free carboxyl group at position 3, and a keto group at position 4 cannot be changed without significant loss of activity. Incorporation of a suitable substituent at $N-1$ position (*e. g.*, an ethyl or cyclopropyl group) is also essential for attainment of high potency [33 – 36]. Fused heterocyclic rings with a bridge between the 5- and 6-positions have not been extensively investigated in this system. Accordingly, we have envisaged to prepare new tricyclic heterocycles (**6**–**8**, Fig. 2), whereby a 4-pyranone ring is [*f*]-fused onto the 1-ethyl-4-oxoquinoline-3-carboxylic acid moiety. Such hybrid molecules combine the structural features of flavone (rings A, B) and 4-quinolone (rings B, C) entities and might display interesting biological properties. In this context it is worth noting that a linear



1 (R^1 = OH; R^2 = H)
2 (R^1 = H; R^2 = OH)
3 (R^1 = R^2 = OH)

4a (R = Et)
4b (R = *c*-C_3H_7)

Fig. 1.



5 **6** (R = Me) **7** (R = Ph) **8**

Fig. 2.

4*H*-pyrano[*g*]-fused quinoline **5** has recently been reported [37]. This single example is a 7-carboxylic *ester* that also lacks a suitable alkyl substituent at *N*(9)-locus and is thus expected to exhibit low anti-bacterial activity.

Results and Discussion

Syntheses

The synthetic strategy towards the target tricyclic compounds **6** and **7** commenced with the 7-aminochromen-4-one, expected to be annelating the 4-pyridone moiety as outlined in Scheme 1. Thus, treatment of **9** and **10** with diethyl ethoxymethylenemalonate gave the respective enamine derivatives **11** and **12**. The latter intermediates underwent thermal intramolecular cyclization, regioselectively at C-8, to deliver the corresponding pyrano[2,3-*f*]quinoline-9-carboxylic esters **13** and **14** under Gould-Jacobs reaction conditions [38]. Subsequent *N*(1)-ethylation of **13** and **14** afforded the respective derivatives **15** and **16**, and their acid-catalyzed hydrolysis furnished the respective targeted 9-carboxylic acids **6** and **7**. Likewise, 6-aminoflavone **17** was converted into the respective *N*-ethylpyrano[3,2-*f*]quinoline-9-carboxylic acid **8** *via* the consecutive intermediates **18**, **19** and **20** as depicted in Scheme 2. The newly synthesized compounds **6**–**20** were characterized by NMR and MS spectral data (see Experimental Section) which are consistent with the suggested structures. Thus, the mass spectra display the correct molecular ion peaks for which the measured high resolution (HRMS) data are in good agreement with the calculated values. DEPT and 2D (COSY, HMQC, HMBC) experiments showed correlations that helped in the ^{1}H and ^{13}C signal assignments to the different carbons and their attached and/or neighboring hydrogens.

Antibacterial activity

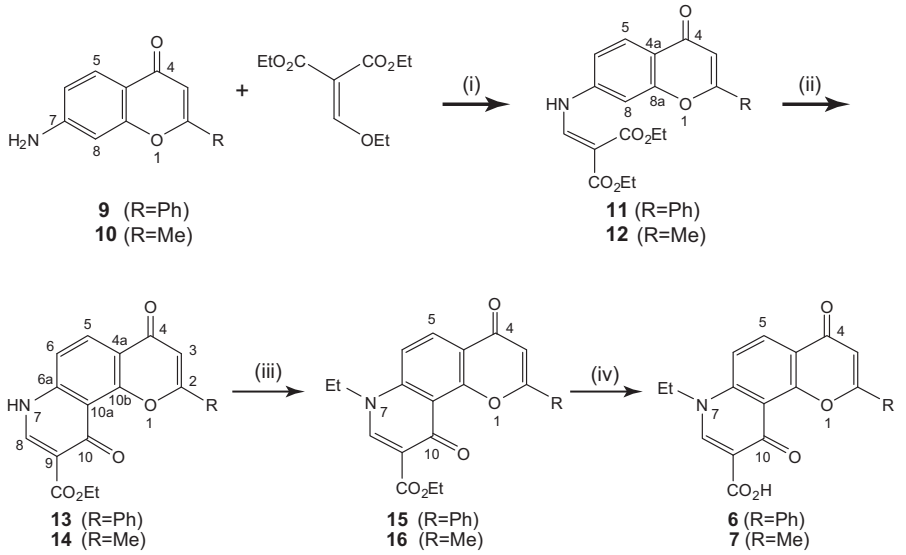
Compounds **6**–**8** were tested *in vitro* in aqueous DMSO solutions against Gram-negative *Escherichia coli* ATCC 8739 and Gram-positive *Staphylococcus aureus* ATCC 6538 bacterial species using ciprofloxacin as reference. The antibacterial activity was evaluated by the minimal inhibitory concentration (MIC) technique. Compounds **6**–**8** exhibit a moderate level of antibacterial activity (MIC = 16 – 64 μg mL^{-1}) against *E. coli* and *S. aureus*.

Experimental Section

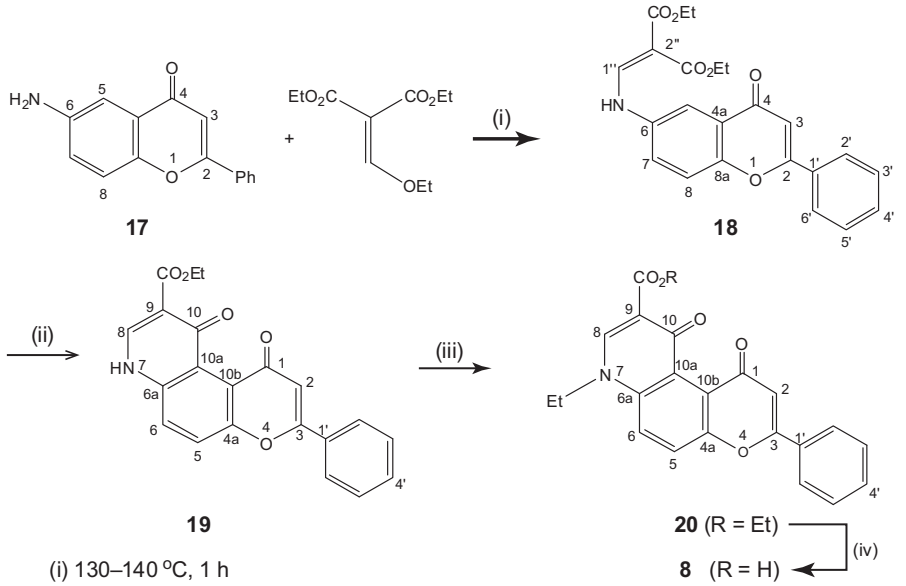
The following chemicals, used in this study, were purchased from Acros and used as received: Diethyl ethoxymethylenemalonate, diphenyl ether and iodoethane. 7-Aminoflavone, 6-aminoflavone and 7-amino-2-methyl-4*H*-chromen-4-one were purchased from Aldrich. Melting points were determined on a Gallenkamp electrothermal melting apparatus in open capillary tubes. ^{1}H and ^{13}C NMR spectra were recorded on a 500 MHz spectrometer (Bruker Avance-III). Chemical shifts are expressed in ppm (δ units), with TMS as internal standard; J values for ^{1}H-^{1}H coupling constants are given in Hertz. High-resolution mass spectra (HRMS) were acquired (in positive or negative ion mode) using electrospray ion trap (ESI) technique by collision-induced dissociation on a Bruker APEX-4 (7-Tesla) instrument. The samples were dissolved in acetonitrile, diluted in spray solution (methanol-water 1 : 1 v/v + 0.1 % formic acid) and infused using a syringe pump with a flow rate of 2 μL min^{-1}. External calibration was conducted using arginine cluster in a mass range m/z = 175 – 871. Elemental analyses were performed on a Euro Vector elemental analyzer, model EA 3000.

Antibacterial tests

The MICs were determined by the conventional agar dilution procedures according to the method of Mueller-Hinton.



Scheme 1.



Scheme 2.

Stock solutions (1000 μg mL^{-1}) of the test compounds were prepared with DMSO. Serial dilutions were then made to obtain test concentrations in the range 128 – 0.5 μg mL^{-1}. The agar plates were inoculated with approximately 105 *CFU* per spot. The agar plates were then incubated at 37 °C for 18 h. The MICs were taken as the lowest concentration of the test compounds that inhibits visible growth.

*Diethyl 2-[(4-oxochromenylamino)methylene]malonates **11**, **12** and **18**; general procedure*

A mixture of the particular aminochromen-4-one (4.2 mmol) and diethyl ethoxymethylenemalonate (5.0 mmol) was heated at 130 – 140 °C for 2 h, during which time the resulting ethanol was distilled off. Thereafter, the reaction mixture was cooled to 60 °C and poured onto 50 mL of *n*-hexane. The resulting solid precipitate was collected by suction filtration, dried and recrystallized from ethyl acetate to give the respective 2-[(4-oxochromenylamino)methylene]malonate.

*Diethyl 2-[(4-oxo-2-phenyl-4H-chromen-7-ylamino)-methylene]malonate (**11**)*

Yield: 94 %; m. p. 185 – 187 °C. – ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 1.27 – 1.47 (m, 6H, 2(C*H*$_3$CH$_2$O)), 4.17 (q, J = 7.1 Hz, 2H, MeC*H*$_2$O), 4.24 (q, J = 7.1 Hz, 2H, MeC*H*$_2$O), 6.98 (s, 1H, H-3), 7.48 (dd, J = 8.6, 1.5 Hz, 1H, H-6), 7.59 – 7.62 (m, 3H, H-3′ + H-4′ + H-5′), 7.83 (d, J = 1.5 Hz, 1H, H-8), 7.99 (d, J = 8.6 Hz, 1H, H-5), 8.10 (dd, J = 8.5, 2.0 Hz, 2H, H-2′ + H-6′), 8.48 (s, 1H, H-1″), 10.77 (br s, 1H, N-H, exchangeable with D$_2$O). – ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 14.6, 14.7 (2(*C*H$_3$CH$_2$O)), 60.4, 60.6 (2(Me*C*H$_2$O)), 96.9 (C-2″), 105.5 (C-3), 107.4 (C-8), 116.1 (C-6), 119.9 (C-4a), 126.7 (C-2′/C-6′),127.0 (C-5), 129.6 (C-3′/C-5′), 131.5 (C-1′), 132.3 (C-4′),144.9 (C-7), 149.7 (C-1″), 157.3 (C-8a), 163.2 (C-2), 165.3, 167.2 (2(*C*O$_2$Et)), 176.8 (C-4). – HRMS ((+)-ESI): m/z = 408.14416 (calcd. 408.14471 for C$_{23}$H$_{22}$NO$_6$, [M+H]$^+$).

*Diethyl 2-[(2-methyl-4-oxo-1H-chromen-7-ylamino)-methylene]malonate (**12**)*

Yield: 93 %; m. p. 250 – 252 °C. – ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 1.25 – 1.29 (m, 6H, 2 (C*H*$_3$CH$_2$O)), 2.38 (s, 3H, (C(2)-C*H*$_3$)), 4.16 (q, J = 7.1 Hz, 2H, MeC*H*$_2$O), 4.23 (q, J = 7.1 Hz, 2H, MeC*H*$_2$O), 6.19 (s, 1H, H-3), 7.44 (dd, J = 8.7, 1.9 Hz, 1H, H-6), 7.61 (d, J = 1.9 Hz, 1H, H-8), 7.95 (d, J = 8.7 Hz, 1H, H-5), 8.48 (d, J = 13.4 Hz, 1H, H-1′), 10.72 (d, J = 13.4 Hz, 1H, N-H, exchangeable with D$_2$O). – ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 14.5, 14.7 (2(*C*H$_3$CH$_2$O)), 20.4 (C(2)-*C*H$_3$)), 60.3, 60.5 (2(Me*C*H$_2$O)), 96.9 (C-2′), 105.5 (C-3), 110.4 (C-8), 115.5 (C-6), 119.9 (C-4a), 127.0 (C-5), 144.6 (C-7), 149.7 (C-1′), 157.5 (C-8a), 165.1 (C-2),167.1, 167.2 (2(*C*O$_2$Et)), 176.5 (C-4). – HRMS ((+)-ESI): m/z = 346.12948 (calcd. 346.12906 for C$_{18}$H$_{20}$NO$_6$, [M+H]$^+$).

*Diethyl 2-[(4-oxo-2-phenyl-1H-chromen-6-ylamino)-methylene]malonate (**18**)*

Yield: 99 %; m. p. 187 – 189 °C. – ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 1.24 – 1.30 (m, 6H, 2(C*H*$_3$CH$_2$O), 4.17 (q, J = 7.1 Hz, 2H, MeC*H*$_2$O), 4.24 (q, 2H, J = 7.1 Hz, MeC*H*$_2$O), 7.07 (s, 1H, H-3), 7.62 – 7.65 (m, 3H, H-5 + H-8 + H-4′), 7.78 – 7.92 (m, 3H, H-3′ + H-5′ + H-7), 8.13 (dd, J = 8.2, 2.0 Hz, 2H, H-2′ + H-6′), 8.44 (d, J = 13.5 Hz, 1H, H-1″), 10.77 (d, J = 13.5 Hz, 1H, N-H, exchangeable with D$_2$O). – ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 14.6, 14.7 (2(*C*H$_3$CH$_2$O)), 60.4, 60.6 (2(Me*C*H$_2$O)), 95.1 (C-2″), 107.0 (C-3), 112.0 (C-7), 112.7 (C-8), 124.5 (C-4a), 125.2 (C-5), 126.9 (C-2′/C-6′),129.6 (C-3′/C-5′), 131.6 (C-1′), 132.3 (C-4′), 137.8 (C-6), 151.2 (C-1″), 153.1 (C-8a), 162.9 (C-2), 165.5, 167.4 (2(*C*O$_2$Et)), 177.1 (C-4). – HRMS ((+)-ESI): m/z = 408.14416 (calcd. 408.14471 for C$_{23}$H$_{22}$NO$_6$, [M+H]$^+$).

*Ethyl pyranoquinoline-9-carboxylates **13**, **14** and **19**; general procedure*

The particular diethyl 2-[4-(oxochromenylamino)methylene]malonate (**11**, **12**, **18**) (2.45 mmol) was added to diphenyl ether (10 mL) and heated at 245 – 250 °C for 1 h. The product solution was allowed to cool to 60 °C, and then the warm solution was poured onto 50 mL of *n*-hexane. The precipitate was collected by suction filtration, washed with hot ethyl acetate, and dried to give the corresponding pyranoquinolone in fairly pure state.

*Ethyl 4,10-dioxo-2-phenyl-7,10-dihydro-4H-pyrano-[2,3-f]quinoline-9-carboxylate (**13**)*

Yield: 85 %; m. p. 292 – 293 °C. – ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 1.32 (t, J = 7.1 Hz, 3H, C*H*$_3$CH$_2$O), 4.27 (q, J = 7.1 Hz, 2H, MeC*H*$_2$O), 7.23 (s, 1H, H-3), 7.63 – 7.62 (m, 4H, H-3′ + H-4′ + H-5′, H-6), 8.24 (d, J = 8.8 Hz, 1H, H-5), 8.49 (m, 3H, H-2′ + H-6′, H-8) 12.61 (s, 1H, N-H, exchangeable with D$_2$O). – ^{13}C NMR (125 MHz, CF$_3$CO$_2$D): δ = 14.8 (*C*H$_3$CH$_2$O), 68.6 (Me*C*H$_2$O), 108.7 (C-3), 110.7 (C-9), 114.2 (C-10a), 121.4 (C-6), 121.7 (C-4a), 126.9 (C-5), 130.6 (C-2′/C-6′), 131.1 (C-1′), 132.4 (C-3′/C-5′), 132.5 (C-4′), 138.2 (C-6a), 147.6 (C-8), 150.2 (C-10b), 158.1 (C-2), 170.5 (*C*O$_2$Et), 174.4 (C-10), 177.5 (C-4). – HRMS ((–)-ESI): m/z = 360.08775 (calcd. 360.08720 for C$_{21}$H$_{14}$NO$_5$, [M–H]$^-$).

*Ethyl 2-methyl-4,10-dioxo-7,10-dihydro-4H-pyrano-[2,3-f]quinoline-9-carboxylate (**14**)*

Yield: 90 %; m. p. 308 – 309 °C. – ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 1.25 (t, J = 7.1 Hz, 3H, C*H*$_3$CH$_2$O), 2.41

(s, 3H, (C(2)-CH_3)), 4.20 (q, J = 7.1 Hz, 2H, MeCH_2O), 6.33 (s, 1H, H-3), 7.81 (d, J = 8.8 Hz, 1H, H-6), 8.27 (d, J = 8.8 Hz, 1H, H-5), 8.47 (s, 1H, H-8), 12.53 (s, 1H, N-H, exchangeable with D_2O). – ^{13}C NMR (125 MHz, CF_3CO_2D): δ = 15.0 (*C*H_3CH$_2$O), 22.3 (C(2)-*C*H_3), 68.4 (Me*C*H$_2$O), 110.4 (C-9), 113.7 (C-3), 114.0 (C-10a), 119.1 (C-4a), 121.0 (C-6), 136.8 (C-5), 147.3 (C-6a), 149.9 (C-8), 149.9 (C-10b), 158.4 (C-2), 170.4 (*C*O$_2$Et), 177.2 (C-10), 177.8 (C-4). – HRMS ((+)-ESI): m/z = 322.06855 (calcd. 322.06914 for $C_{16}H_{13}NO_5Na$, $[M+Na]^+$).

*Ethyl 1,10-dioxo-3-phenyl-7,10-dihydro-1H-pyrano-[3,2-f]quinoline-9-carboxylate (**19**)*

Yield: 94 %; m. p. 250 – 251 °C. – ^{1}H NMR (500 MHz, CF_3CO_2D): δ = 1.39 (t, J = 6.9 Hz, 3H, C*H*$_3$CH$_2$O), 4.26 (q, J = 7.1 Hz, 2H, MeC*H*$_2$N), 4.46 (q, J = 6.9 Hz, 2H, MeC*H*$_2$O), 8.19 (s, 1H, H-2), 8.19 – 8.35 (m, 3H, H-3′ + H-4′ + H-5′), 8.74 (dd, J = 2.0, 7.2 Hz, 2H,H-2′ + H-6′), 9.06 (d, J = 9.5 Hz, 1H, H-6), 9.14 (d, J = 9.5 Hz, 1H, H-5), 9.81 (s, 1H, H-8), 17.04 ([D$_6$]DMSO) (s, 1H, N-H, exchangeable with D_2O). – ^{13}C NMR (125 MHz, CF_3CO_2D): δ = 14.6 (*C*H$_3$CH$_2$O), 66.7 (Me*C*H$_2$O), 108.9 (C-2), 109.3 (C-9), 115.6 (C-6), 118.0 (C-5), 121.4 (C-10a), 129.6 (C-2′/C-6′), 129.9 (C-10b) 130.8 (C-1′), 132.0 (C-4′), 132.1 (C-3′/C-5′), 137.9 (C-6a), 142.8 (C-4a),148.3 (C-8), 161.0 (C-3), 164.9 (*C*O$_2$Et), 171.9 (C-10), 183.4 (C-1). – HRMS ((+)-ESI): m/z = 362.10230 (calcd. 362.10285 for $C_{21}H_{16}NO_5$, $[M+H]^+$).

*Ethyl 7-ethylpyrano[2,3-f]quinoline-9-carboxylates **15**, **16** and **20**; general procedure*

A stirred mixture of compound **5** (1.38 mmol), K_2CO_3 (6.92 mmol), iodoethane (6.92 mmol), and absolute ethanol (10 mL) was refluxed for 10 h. The reaction mixture was cooled to r. t. and diluted with 50 mL of water. The precipitated solid product was collected by suction filtration, washed with water, dried and recrystallized from the appropriate solvent.

*Ethyl 7-ethyl-4,10-dioxo-2-phenyl-7,10-dihydro-4H-pyrano[2,3-f]quinoline-9-carboxylate (**15**)*

Yield: 84 %; m. p. 233 – 234 °C. – ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 1.33 (t, J = 6.9 Hz, 3H, C*H*$_3$CH$_2$N), 1.41 (t, J = 7.0 Hz, 3H, C*H*$_3$CH$_2$O), 4.27 (q, J = 6.9 Hz, 2H, MeC*H*$_2$N), 4.45 (q, J = 7.0 Hz, 2H, MeC*H*$_2$O), 7.23 (s, 1H, H-3), 7.62 – 7.63 (m, 3H, H-3′ + H-4′ + H-5′), 7.83 (d, J = 9.0 Hz, 1H, H-6), 8.28 (d, J = 9.0 Hz, 1H, H-5), 8.49 (dd, J = 8.5, 2.0 Hz, 2H, H-2′ + H-6′), 8.67 (s, 1H, H-8). – ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 14.7 (*C*H$_3$CH$_2$N), 14.8 (*C*H$_3$CH$_2$O), 49.4 (Me*C*H$_2$N), 60.6 (Me*C*H$_2$O), 107.5 (C-3), 115.1 (C-6), 115.1 (C-9) 117.7 (C-10a), 119.5 (C-4a), 127.3 (C-2′/C-6′), 128.9 (C-5), 129.5 (C-3′/C-5′), 131.4 (C-1′), 132.4 (C-4′), 144.3 (C-6a), 148.2 (C-8), 155.7 (C-10b), 163.3 (C-2), 164.4 (*C*O$_2$Et), 172.5 (C-10), 176.4 (C-4). – HRMS ((+)-ESI): m/z = 390.13360 (calcd. 390.13415 for $C_{23}H_{20}NO_5$, $[M+H]^+$).

*Ethyl 7-ethyl-2-methyl-4,10-dioxo-7,10-dihydro-4H-pyrano[2,3-f]quinoline-9-carboxylate (**16**)*

Yield: 86 %; m. p. 186 – 187 °C. – ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 1.31 (t, J = 7.1 Hz, 3H, C*H*$_3$CH$_2$N), 1.38 (t, J = 7.1 Hz, 3H, C*H*$_3$CH$_2$O), 2.46 (s, 3H, (C(2)-C*H*$_3$)), 4.26 (q, J = 7.1 Hz, 2H, MeC*H*$_2$N), 4.44 (q, J = 7.1 Hz, 2H, MeC*H*$_2$O), 6.38 (s, 1H, H-3), 7.81 (d, J = 9.2 Hz, 1H, H-6), 8.27 (d, J = 9.2 Hz, 1H, H-5), 8.66 (s, 1H, H-8). – ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 14.7 (*C*H$_3$CH$_2$N), 14.8 (*C*H$_3$CH$_2$O), 20.6 (C(2)-*C*H$_3$) 49.3 (Me*C*H$_2$N), 60.6 (Me*C*H$_2$O), 111.2 (C-3), 114.8 (C-6), 114.8 (C-9), 117.7 (C-10a), 119.1 (C-4a), 128.4 (C-5), 144.3 (C-6a), 148.2 (C-8), 156.2 (C-10b), 164.8 (C-2), 167.5 (*C*O$_2$Et), 172.3 (C-10), 176.1 (C-4). – HRMS ((+)-ESI): m/z = 350.09989 (calcd. 350.10044 for $C_{18}H_{17}NO_5Na$, $[M+Na]^+$).

*Ethyl 7-ethyl-1,10-dioxo-3-phenyl-7,10-dihydro-1H-pyrano[3,2-f]quinoline-9-carboxylate (**20**)*

Yield: 89 %; m. p. 265 – 266 °C. – ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 1.33 (t, J = 7.1 Hz, 3H, C*H*$_3$CH$_2$N), 1.39 (t, J = 6.9 Hz, 3H, C*H*$_3$CH$_2$O), 4.26 (q, J = 7.1 Hz, 2H, MeC*H*$_2$N), 4.46 (q, J = 6.9 Hz, 2H, MeC*H*$_2$O), 7.09 (s, 1H, H-2), 7.59 – 7.64 (m, 3H, H-3′ + H-4′ + H-5′), 8.06 (d, J = 9.5 Hz, 1H, H-6), 8.12 (dd, J = 8.5, 2.0 Hz, 2H, H-2′ + H-6′), 8.14 (d, J = 9.5 Hz, 1H, H-5), 8.62 (s, 1H, H-8). – ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 14.8 (*C*H$_3$CH$_2$N), 15.1 (*C*H$_3$CH$_2$O), 48.6 (Me*C*H$_2$N), 60.3 (Me*C*H$_2$O), 107.5 (C-2), 112.5 (C-9), 122.4 (C-10a), 123.1 (C-6), 123.5 (C-5), 125.8 (C-10b) 126.6 (C-2′/C-6′), 129.6 (C-3′/C-5′), 131.4 (C-1′), 131.9 (C-4′) 137.9 (C-6a), 147.9 (C-8), 154.6 (C-4a), 160.2 (C-3), 164.8 (*C*O$_2$Et), 171.7 (C-10), 175.0 (C-1). – HRMS ((+)-ESI): m/z = 390.13360 (calcd. 390.13415 for $C_{23}H_{20}NO_5$, $[M+H]^+$).

*7-Ethylpyranoquinoline-9-carboxylic acids **6**–**8**; general procedure*

A suspension of the appropriate ethyl ester (0.51 mmol) in 20 mL of 6 N aq. HCl was refluxed (oil bath, 110 °C) for 48 h. Thereafter, the reaction mixture was cooled and poured onto ice water (30 mL); the precipitated product was collected by suction filtration, washed with water (3 × 4 mL), redissolved in 20 mL of 1 N aq. K_2CO_3 and filtered. The aqueous filtrate was neutralized with 6 N aq. HCl. The resulting solid was collected by suction filtration, dried and recrystallized from the appropriate solvent.

*7-Ethyl-4,10-dioxo-2-phenyl-7,10-dihydro-4H-pyrano-[2,3-f]quinoline-9-carboxylic acid (**6**)*

Yield: 94 %; m. p. 318 – 319 °C. – ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 1.46 (t, J = 7.0 Hz, 3H, CH_3CH$_2$N), 4.45 (q, J = 7.0 Hz, 2H, MeCH_2N), 7.27 (s, 1H, H-3), 7.62 – 7.75 (m, 3H, H-3′ + H-4′ + H-5′), 8.03 (d, J = 8.5 Hz, 1H, H-6), 8.39 – 8.51 (m, 3H, H-2′ + H-6′ + H-5), 9.13 (s, 1H, H-8), 15.45 (br s, 1H, CO$_2$H, exchangeable with D$_2$O). – ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 14.9 (*C*H$_3$CH$_2$N), 50.5 (MeCH$_2$N), 107.8 (C-3), 111.3 (C-9), 115.6 (C-6), 116.1 (C-10a), 120.3 (C-4a), 127.2 (C-2′/C-6′), 129.6 (C-3′/C-5′), 130.4 (C-5), 131.1 (C-1′), 132.6 (C-4′) 144.4 (C-6a), 149.9 (C-8), 155.5 (C-10b), 163.5 (C-2), 166.1 (*C*O$_2$H), 176.1 (C-10), 178.1 (C-4). – HRMS ((+)-ESI): m/z = 362.10230 (calcd. 362.10285 for C$_{21}$H$_{16}$NO$_5$, [M+H]$^+$).

*7-Ethyl-2-methyl-4,10-dioxo-7,10-dihydro-4H-pyrano-[2,3-f]quinoline-9-carboxylic acid (**7**)*

Yield: 82 %; m. p. 327 – 329 °C. – ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 1.31 (t, J = 7.1 Hz, 3H, CH_3CH$_2$N), 2.46 (s, 3H, (C(2)-CH_3)), 4.26 (q, J = 7.1 Hz, 2H, MeCH_2N, 6.42 (s, 1H, H-3), 7.71 (d, J = 9.3 Hz, 1H, H-6), 8.36 (d, J = 9.3 Hz, 1H, H-5), 9.09 (s, 1H, H-8), 15.41 (br s, 1H, CO$_2$H, exchangeable with D$_2$O). – ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 14.4 (*C*H$_3$CH$_2$N), 20.1 (C(2)-*C*H$_3$), 50.0 (MeCH$_2$N), 111.1 (C-3), 111.6 (C-9), 114.9 (C-6), 117.7 (C-10a), 119.1 (C-4a), 130.0 (C-5), 144.2 (C-6a), 149.9 (C-8), 156.2 (C-10b), 166.1 (C-2), 167.8 (*C*O$_2$H), 172.3 (C-10), 176.1 (C-4). – HRMS ((–)-ESI): m/z = 298.07210 (calcd. 298.07155 for C$_{16}$H$_{12}$NO$_5$, [M–H]$^-$).

*7-Ethyl-1,10-dioxo-3-phenyl-7,10-dihydro-1H-pyrano-[3,2-f]quinoline-9-carboxylic acid (**8**)*

Yield: 86 %; m. p. 277 – 278 °C. – ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 1.45 (t, J = 7.1 Hz, 3H, CH_3CH$_2$N), 4.68 (q, J = 7.1 Hz, 2H, MeCH_2N), 7.21 (s, 1H, H-2), 7.59 – 7.63 (m, 3H, H-3′ + H-4′ + H-5′), 8.15 (dd, J = 7.4, 1.6 Hz, 2H, H-2′ + H-6′), 8.27 (d, J = 9.5 Hz, 1H, H-6), 8.40 (d, J = 9.5 Hz, 1H, H-5), 9.05 (s, 1H, H-8), 15.23 (br s, 1H, CO$_2$H, exchangeable with D$_2$O). – ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 15.4 (*C*H$_3$CH$_2$N), 50.0 (MeCH$_2$N), 107.9 (C-2), 110.4 (C-9), 121.9 (C-10a), 122.8 (C-10b), 124.2 (C-6), 125.8 (C-5), 126.6 (C-2′/C-6′), 129.6 (C-3′/C-5′), 131.1 (C-1′), 132.1 (C-4′) 139.0 (C-6a), 148.0 (C-8), 155.5 (C-4a), 160.3 (C-3), 166.4 (*C*O$_2$H), 175.0 (C-10), 176.7 (C-1). – HRMS ((+)-ESI): m/z = 362.10230 (calcd. 362.10285 for C$_{21}$H$_{16}$NO$_5$, [M+H]$^+$).

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