Synthesis and Antibacterial Potency of 4-Methyl-2,7-dioxo-1,2,3,4,7,10-hexahydropyrido[2,3-*f*]quinoxaline-8-carboxylic acid, Selected [*a*]-Fused Heterocyles and Acyclic Precursors

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The reaction of 7-chloro-1-cyclopropyl-6-fluoro-8-nitro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (**7**) with each of sarcosine and (±)-pipecolinic acid afforded the corresponding *N*-(4-oxoquinolin-7-yl)-α-amino acids **8** and **9**. Reductive lactamization of the latter with sodium dithionite gave hexahydropyrido[2,3-*f*]quinoxaline (**10**) and octahydrodipyrido[1,2-*a* : 2,3-*f*]quinoxaline (**11**) derivatives, respectively. Compounds **8** – **11** and their homologs **1** – **6**, accessible from (*S*)-proline, (2*S*, 4*R*)-4-hydroxyproline and (*S*)-tetrahydroisoquinoline-3-carboxylic acid exhibit good to excellent antibacterial activities against *E. coli* and *S. aureus*.

Key words: Pipecolinic Acid, Sarcosine, 7-Chloro-8-nitro-4-oxoquinoline-3-carboxylic Acid, S_NAr Reactions, Reductive Lactamization, Antibacterial Activity

Introduction

New drugs are desperately searched for in order to counteract the alarming increase in evolution of antimicrobial resistance to existing antibiotics. There is a continuing need for the discovery and development of new agents against resistant strains with broad therapeutic index [1]. Synthetic fluoroquinolones [2, 3], *e. g.* ciprofloxacin [2], represent a recent successful achievement towards the design and development of potent antiinfectious drugs. On the other hand, substituted quinoxalinones have become interesting compounds for study of their bioproperties such as antibacterial [4] and antitumor [5] activity. Quite recently, we have described the synthesis of heterocycles [*a*]-fused onto pyrido[2,3-*f*]quinoxaline-3-carboxylic acids, exemplified by compounds **4** – **6** *via* reductive lactamization of their respective acyclic fluoroquinolone precursors **1** – **3** [6]. The heterocyclic derivatives **4** – **6** exhibit excellent potential as antitumor therapeutic agents [6]

In this study, we have investigated the antibacterial activity of compounds **1** – **6**, which were shown to display good to excellent potency against Gram negative and Gram positive bacterial strains. These findings have prompted us to prepare an additional set of related heterocycles **8** – **11** (Schemes 1 and 2) for further antibacterial testing.

Results and Discussion

Direct interaction between 7-chloro-1-cyclopropyl-6-fluoro-8-nitro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (**7**) with each of sarcosine and (±)-pipecolinic acid produced the respective *N*-(4-oxoquinolin-7-yl)-α-amino acids **8a**, **9a** which were converted into their methyl esters **8b**, **9b** upon reaction with diazomethane in ether (Scheme 1).

Reductive lactamization of **8a**, **9a** with sodium dithionite delivered the respective tri- and tetracyclic derivatives, namely hexahydro[2,3-*f*]quinoxaline **10** and octahydrodipyrido[1,2-*a*: 2,3-*f*]quinoxaline **11** (Scheme 2). This synthetic approach is similar to that described for compounds **1** – **6** [6] and is analogous to the methodology recently reported [7] for the preparation of heterocyclic [*c*]-fused 3,4-di-

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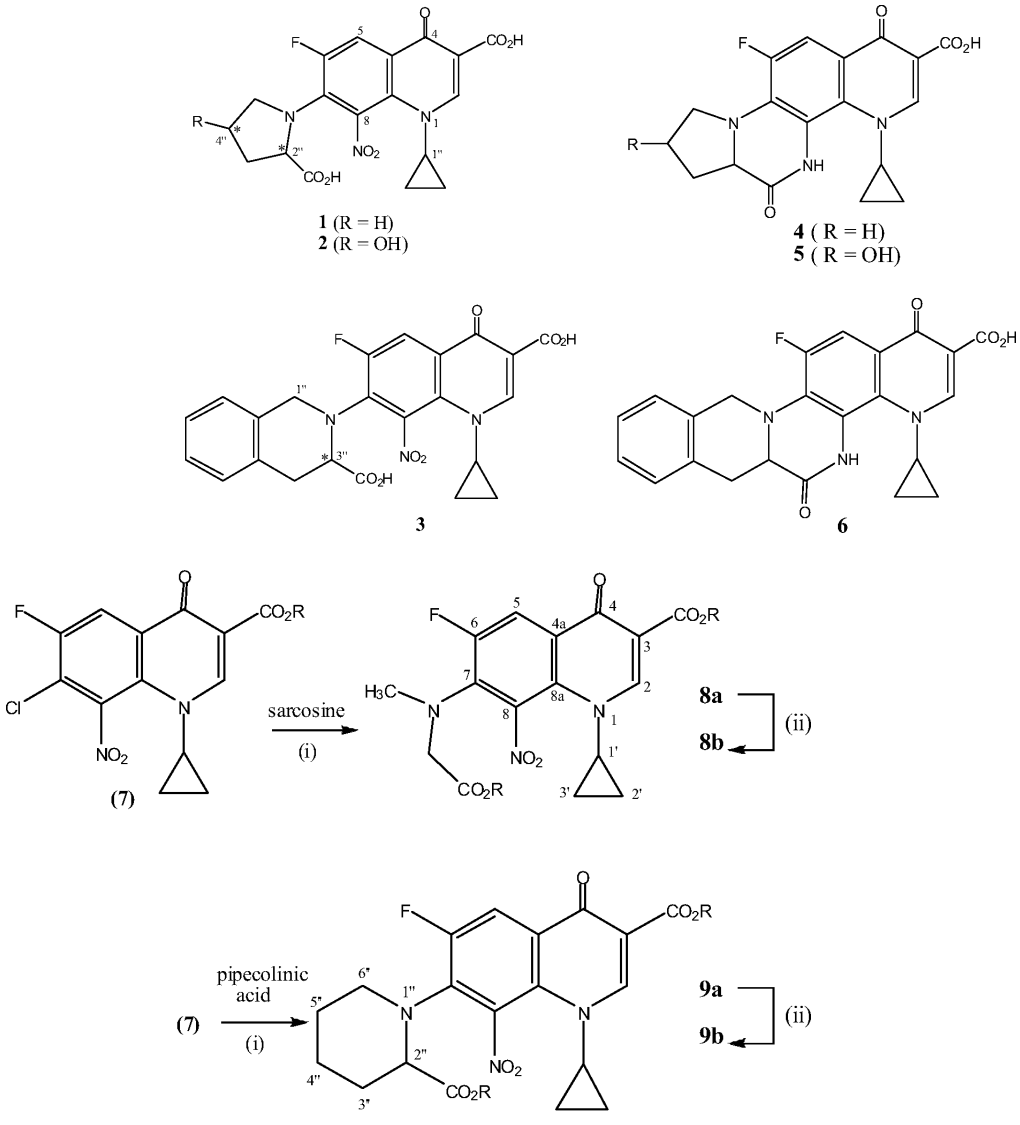


(i) $NaHCO_3$; 50 % aq. EtOH / Δ
(ii) CH_2N_2 in ether / 5–10 °C

compounds **8** and **9**
(**a**: R = H; **b**: R = Me)

Scheme 1.

hydroquinoxalin-2-ones starting from *N*-(2-nitrophenyl)cyclic imino acids.

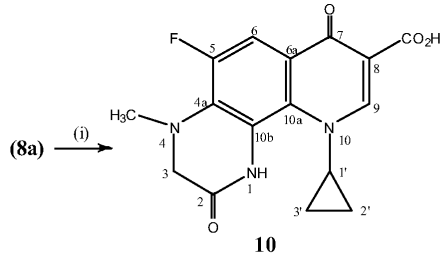
The spectral (IR, MS, NMR) and microanalytical data for the new compounds **8** – **11** are in accordance with the assigned structures, and are given in the Experimental Section. Thus, the mass spectra of **8** – **11** display the correct molecular ions for which the measured high-resolution (HRMS) data are in good agreement with the calculated values. The ^1H and ^{13}C signal assignments are based on DEPT and 2D (COSY, HMQC, HMBC) experiments wherein the associated spectra showed correlations that helped in assigning the various signals to the different carbon and their attached / neighboring hydrogen atoms.

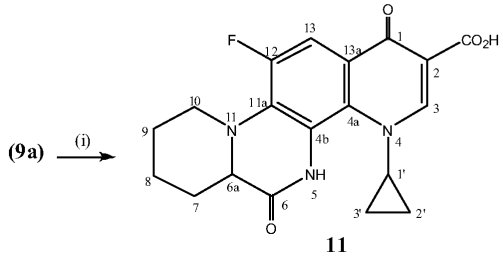
Antimicrobial Activity

In vitro antibacterial screening results of compounds **1** – **6** and **8** – **11** have shown that all tested compounds exhibit good to excellent antimicrobial po-

Compound No.	**1**	**2**	**3**	**4**	**5**	**6**	**8a**	**9a**	**10**	**11**	**Ref***
Staphylococcus aureus ATCC 6538p	11.5	9.93	6.5	39	11.64	2.8	12	12	10.5	12	1.23
Escherichia coli ATCC 8739	23	0.15	12.5	0.60	0.36	22.5	12	22	0.65	3.0	0.31

Table 1. *In vitro* antibacterial activity (MIC values, μg/mL) of model compounds **1 – 6** and **8 – 11** as compared with ciprofloxacin as the reference agent (Ref*).





(i) $Na_2S_2O_4$, aq. K_2CO_3 / 20 °C; (ii) $Na_2S_2O_4$, aq. K_2CO_3 / 0–3 °C
Scheme 2.

tency against both strains tested. Compound **6** is the most active derivative of this series, with MIC $\approx$ 2.5 μg/mL, against *Staphylococcus aureus* (representative of Gram-positive bacteria). On the other hand, compound **2** and its cyclized product **5** (and to a lesser extent **4** and **10**) display excellent activity against *Escherichia coli* (representative of Gram-negative bacteria). In general, it can be concluded that those derivatives have stronger activity against *E. coli*, indicating a mechanism of action similar to fluoroquinolones. Moreover, the cyclized products seem to have better activity against *E. coli* as compared to *S. aureus*. The *in vitro* antibacterial data of the model compounds are given in Table 1.

Experimental Section

The secondary α-amino acids sarcosine and (±)-pipecolinic acid, employed in this study, were of biochemical grades (Acros) and used as received. 2,4-Dichloro-5-fluoro-3-nitrobenzoic acid was purchased from Acros. Melting points (uncorrected) were determined on a Gallenkamp electrothermal melting temperature apparatus. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX-300 instrument with Me_4Si as internal reference. EIMS spectra were obtained using a Finnigan MAT TSQ-70 spectrometer at 70 eV, ion source temperature = 200 °C. High-resolution MS-ESI data were obtained with a Bruker Bio TOF III instrument. IR spectra were recorded as KBr discs on a Nicolet Impact-400 FT-IR spectrophotometer. Microanalyses were performed at the Microanalytical Laboratory – Medicinal Chemistry Division, Faculty of Pharmacy, University of Jordan, Amman.

Pharmacological tests

The minimal inhibitory concentrations (MICs) were determined by the conventional broth dilution method using the two serial dilution technique. The standardization of bacterial test suspension was carried out according to the McFarland standard method as described by the National Committee for Clinical Laboratories Standard (NCCLS) (1993). Stock solutions of the test compounds were prepared using DMSO. Serial dilutions were prepared to obtain test concentrations ranging from 156 μg/mL to 0.3 μg/mL. Each tube was then inoculated with 0.1 mL of the cultured bacteria (containing approximately 1 to 2×10^8 CFU / mL), mixed and incubated at 37 °C for 24 h. Growth inhibition with concentrations of 156 μg/mL or lower were carried out in duplicates. All test tubes showing positive/negative growth were confirmed by the agar plate method. The results were recorded according to presence and absence of growth. The MICs were calculated as the average concentration of the test agent in the broth tubes showing consecutive positive and negative growth.

*7-Chloro-1-cyclopropyl-6-fluoro-8-nitro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (**7**)*

This compound was prepared from 2,4-dichloro-5-fluoro-3-nitrobenzoic acid, ethyl 3-(*N*,*N*-dimethylamino)acrylate and cyclopropylamine by following literature procedures [8].

*7-[(Carboxymethyl) (methyl)amino]-1-cyclopropyl-6-fluoro-8-nitro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (**8a**)*

A stirred mixture of sarcosine (0.80 g, 9 mmol), 7-chloro-1-cyclopropyl-6-fluoro-8-nitro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **7** (1.00 g, 3.1 mmol) and sodium hydrogen carbonate (1.50 g, 18 mmol) in 50 % aqueous ethanol (140 mL) was heated at 75 – 80 °C under reflux conditions. The mixture slowly developed a light yellow color that changed into a bright yellow, then into a clear

orange solution. The progress of the reaction was monitored by TLC and was completed within 20 – 24 h. The orange solution was extracted with dichloromethane (50 mL) and the aqueous layer was separated, acidified with 3 N HCl to pH 6.5 and re-extracted with dichloromethane (50 mL). The aqueous layer was again separated, cooled and re-acidified with 3 N HCl to pH 3 – 4, whereby the title compound was precipitated as a yellowish solid which was collected by suction filtration, washed with cold water (2 × 10 mL), dried and recrystallized from ethanol. Yield of **8a**: 0.93 g (82 %), m. p. 214 – 216 °C (dec). – IR (KBr): ν = 3098, 2911, 1745 (br), 1609, 1455, 1319, 1260, 1217 cm^{-1}. – MS (FAB): *m/z* (%) = 380 (100) $[M+H]^+$ (calcd. 379 for $C_{16}H_{14}FN_3O_7$ $[M]^+$). – ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 1.00, 1.09 (2 m, 4H, 2′-H$_2$ + 3′-H$_2$), 2.89 (br s, 3H, N–C*H*$_3$), 3.68 (m, 1H, 1′-H), 3.91 (s, 2H, N–C*H*$_2$), 8.18 (d, $^3J_{H-F}$ = 11.6 Hz, 1H, 5-H), 8.74 (s, 1H, 2-H), 12.90 (br s, 1H, CH$_2$–CO$_2$*H*), 14.01 (br s, 1H, C3–CO$_2$*H*). – ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 11.0 (C-2′ + C-3′), 39.6 (C-1′), 42.7 (d, J_{C-F} = 3.5 Hz, N–*C*H$_3$), 57.1 (d, J_{C-F} = 4.7 Hz, N–*C*H$_2$), 108.9 (C-3), 114.5 (d, $^2J_{C-F}$ = 22.7 Hz, C-5), 124.4 (d, $^3J_{C-F}$ = 7.7 Hz, C-4a), 132.3 (d, $^4J_{C-F}$ = 1.9 Hz, C-8a), 139.9 (d, $^3J_{C-F}$ = 4.4 Hz, C-8), 140.4 (d, $^2J_{C-F}$ = 16.7 Hz, C-7), 152.9 (C-2), 157.3 (d, $^1J_{C-F}$ = 252.2 Hz, C-6), 165.1 (C3–*C*O$_2$H), 171.0 (CH$_2$–*C*O$_2$H), 175.8 (d, $^4J_{C-F}$ = 2.3 Hz, C-4). – $C_{16}H_{14}FN_3O_7$ (379.30): calcd. C 50.67, H 3.72, N 11.08; found C 50.70, H 3.88, N 11.39.

*Methyl 1-cyclopropyl-6-fluoro-7-[(methoxycarbonylmethyl) (methyl)amino]-8-nitro-4-oxo-1,4-dihydroquinoline-3-carboxylate (**8b**)*

To a fine powder of **8a** (0.38 g, 1.0 mmol), suspended in cold diethyl ether (20 mL), was added portionwise a cold fresh ethereal diazomethane solution until evolution of nitrogen ceased. The reaction mixture was kept at 5 – 10 °C for 20 min, and the solvent was then evaporated at r. t., whereby the title compound was obtained as a yellow solid. Yield of **8b**: 0.34 g (83 %), m. p. 145 – 146 °C (dec.). – IR (KBr): ν = 3086, 3002, 2953, 2851, 2808, 1745, 1702, 1651, 1617, 1549, 1455, 1408, 1328, 1240, 1208, 1044 cm^{-1}. – MS (TOF (+)-ES): *m/z* = 430 $[M+Na]^+$. – HRMS: *m/z* = 430.1021 (calcd. 430.1026 for $C_{18}H_{18}FN_3O_7Na$). – ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 1.03, 1.12 (2 m, 4H, 2′-H$_2$ / 3′-H$_2$), 2.93 (d, J_{H-F} = 1.6 Hz, 3H, N–C*H*$_3$), 3.60 (m, 1H, 1′-H), 3.68 (s, 3H, C3–CO$_2$C*H*$_3$), 3.87 (s, 2H, N–C*H*$_2$), 3.88 (s, 3H, CH$_2$–CO$_2$C*H*$_3$), 8.25 (d, $^3J_{H-F}$ = 11.4 Hz, 1H, 5-H), 8.60 (s, 1H, 2-H). – ^{13}C NMR (75 MHz, CDCl$_3$): δ = 10.9 (C-2′ + C-3′), 37.7 (C-1′), 42.8 (d, J_{C-F} = 3.7 Hz, N–*C*H$_3$), 52.0 (C3–CO$_2$*C*H$_3$), 52.4 (CH$_2$–CO$_2$*C*H$_3$), 57.2 (d, J_{C-F} = 4.6 Hz, N–*C*H$_2$), 111.1 (C-3), 116.1 (d, $^2J_{C-F}$ = 22.6 Hz, C-5), 128.4 (d, $^3J_{C-F}$ = 6.9 Hz, C-4a), 130.7 (d, $^4J_{C-F}$ = 2.2 Hz, C-8a), 138.4 (d, $^2J_{C-F}$ = 17.1 Hz, C-7), 144.1 (d, $^3J_{C-F}$ = 3.2 Hz, C-8), 151.7 (C-2), 157.4 (d, $^1J_{C-F}$ = 253 Hz, C-6), 165.1 (C(3)–*C*O$_2$Me), 169.8 (d, CH$_2$–*C*O$_2$Me), 171.3 (d, $^4J_{C-F}$ = 2.1 Hz, C-4). – $C_{18}H_{18}FN_3O_7$ (407.35): calcd. C 53.07, H 4.45, N 10.32; found C 53.17, H 4.44, N 10.24.

*(±)-7-(2-Carboxypiperidin-1-yl)-1-cyclopropyl-6-fluoro-8-nitro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid [(±)-**9a**]*

A stirred mixture of (±)-pipecolinic acid (1.20 g, 9.3 mmol), **7** (1.0 g, 3.1 mmol) and sodium hydrogen carbonate (1.50 g, 18 mmol) in 50 % aqueous ethanol (140 mL) was heated at 85 – 90 °C for 4 – 5 days under reflux conditions. Work up of the resulting reaction mixture was followed as described for **8a** above and produced the title compound as a light yellow solid which was recrystallized from ethanol. Yield of (±)-**9a**: 0.83 g (64 %), m. p. 229 – 230 °C (dec.). – IR (KBr): ν = 3251 (br), 2945, 2851, 1770, 1702 (br), 1617, 1532, 1438, 1328, 1268 cm^{-1}. – MS (FAB): *m/z* (%) = 420 (100) $[M+H]^+$ (calcd. 419 for $C_{19}H_{18}FN_3O_7[M]^+$). – MS (EI): *m/z* (%) = 399 (1) $[M–HF]^+$, 374 (3), 371 (2), 344 (4), 339 (5), 297 (12), 295 (17), 278 (9), 244 (11), 219 (100), 190 (14), 164 (8), 123 (5), 106 (5). – ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 0.91 (m, 1H), 1.10 (m, 1H) and 1.13 (m, 2H) (2′-H$_2$- / 3′-H$_2$), 1.57 (m, 2H, 5″-H$_2$), 1.58 (m, 2H, 4″-H$_A$ and 3″-H$_A$), 1.74 (m, 1H, 4″-H$_B$), 1.90 (m, 1H, 3″-H$_B$), 2.98 (m, 1H, 6″-H$_A$), 3.40 (m, 1H, 6″-H$_B$), 3.69 (m, 1H, 1′-H), 4.03 (m, 1H, 2″-H), 8.20 (d, $^3J_{H-F}$ = 11.7 Hz, 1H, 5-H), 8.77 (s, 1H, 2-H), 12.67 (br s, 1H, C2″–CO$_2$*H*), 13.94 (br s, 1H, C3–CO$_2$*H*). – ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 10.5, 11.5 (C-2′ + C-3′), 22.9 (C-4″), 25.7 (C-5″), 30.1 (C-3″), 39.5 (C-1′), 54.0 (C-6″), 63.3 (d, J_{C-F} = 6.2 Hz, C-2″), 109.0 (C-3), 114.4 (d, $^2J_{C-F}$ = 22.8 Hz, C-5), 125.3 (C-4a), 132.4 (C-8a), 140.6 (d, $^2J_{C-F}$ = 17.7 Hz, C-7), 141.1 (C-8), 153.0 (C-2), 157.7 (d, $^1J_{C-F}$ = 253 Hz, C-6), 165.1 (C3–*C*O$_2$H), 172.8 (C2″–*C*O$_2$H), 175.9 (d, $^4J_{C-F}$ = 2.3 Hz, C-4). – $C_{19}H_{18}FN_3O_7$ (419.36): calcd. C 54.42, H 4.33, N 10.02; found C 54.30, H 4.39, N 10.22.

*(±)-Methyl 1-cyclopropyl-6-fluoro-7-[2-(methoxycarbonyl) piperidin-1-yl]-8-nitro-4-oxo-1,4-dihydroquinoline-3-carboxylate [(±)-**9b**]*

This compound was prepared *via* the reaction of (±)-**9a** (0.42 g, 1.0 mmol) with diazomethane in ether following the procedure described above for **8b**. Yield of (±)-**9b**: 0.38 g (85 %), m. p. 181 – 182 °C (dec.). – IR (KBr): ν = 3100, 2939, 2843, 1737, 1702, 1635, 1604, 1544, 1468, 1326, 1289, 1178, 1092 cm^{-1}. – MS (TOF (+)-ES): *m/z* = 470 $[M+Na]^+$, 917 $[2M+ Na]^+$. – HRMS: *m/z* = 470.1334 (calcd. 470.1339 for $C_{21}H_{22}FN_3O_7Na$), 917.2776 (calcd. 917.2781 for $(C_{21}H_{22}FN_3O_7)_2Na$). – ^{1}H NMR (300 MHz,

[D_6]DMSO): δ = 1.03 (m, 3H) and 1.18 (m, 1H) (2′-H_2 + 3′-H_2), 1.54 (m, 1H, 4″-H_A), 1.65 (m, 2H, 5″-H_2), 1.81 (m, 1H, 4″-H_B), 1.95 (m, 2H, 3″-H), 2.98 (m, 1H, 6″-H_A), 3.38 (br m, 1H, 6″-H_B), 3.52 (s, 3H, C2″–CO_2CH_3), 3.62 (m, 1H, 1′-H), 3.88 (s, 3H, C3–CO_2CH_3), 4.13 (m, 1H, 2″-H), 8.20 (d, $^3J_{H-F}$ = 11.7 Hz, 1H, 5-H), 8.59 (s, 1H, 2-H). – ^{13}C NMR (75 MHz, [D_6]DMSO): δ = 10.2, 11.7 (C-2′ + C-3′), 23.4 (C-4″), 25.5 (C-5″), 30.3 (C-3″), 37.6 (C-1′), 51.9 (C2″–CO_2CH_3), 52.4 (C3–CO_2CH_3), 54.4 (C-6″), 63.0 (d, J_{C-F} = 5.4 Hz, C-2″), 111.1 (C-3), 115.9 (d, $^2J_{C-F}$ = 22.7 Hz, C-5), 128.6 (d, $^3J_{C-F}$ = 7.0 Hz, C-4a), 130.9 (C-8a), 138.6 (d, $^2J_{C-F}$ = 17.6 Hz, C-7), 141.4 (d, $^3J_{C-F}$ = 4.8 Hz, C-8), 151.7 (C-2), 157.5 (d, $^1J_{C-F}$ = 252 Hz, C-6), 165.2 (C3–CO_2Me), 171.3 (d, $^4J_{C-F}$ = 1.8 Hz, C-4), 172.0 (C2″–CO_2Me). – $C_{21}H_{22}FN_3O_7$ (447.41): calcd. C 56.37, H 4.96, N 9.39; found C 56.24, H 5.04, N 9.16.

*10-Cyclopropyl-5-fluoro-4-methyl-2,7-dioxo-1,2,3,4,7,10-hexahydropyrido[2,3-f]quinoxaline-8-carboxylic acid (**10**)*

To a stirred solution of **8a** (0.38 g, 1.0 mmol) and of potassium carbonate (0.96 g, 7.0 mmol) in 20 mL water, was added dropwise a solution of sodium dithionite (0.87 g, 5.0 mmol) in water (5 mL). The reaction mixture was further stirred at r.t. for 25 min. Thereafter, the pH of the solution was adjusted to about 4. The precipitated product was filtered, washed with water, air-dried and recrystallized from methanol / chloroform (2 : 1, v / v). Yield of **10**: 0.12 g (68 %), m.p. > 300 °C (darkens at 280 °C). – IR (KBr): ν = 3277, 3064, 1736, 1685, 1620, 1506, 1310, 1226 cm^{-1}. – MS (TOF (+)-ES): *m/z* = 354 $[M+Na]^+$. – HRMS: *m/z* = 354.0861 (calcd. 354.0866 for $C_{16}H_{14}FN_3O_4Na$). – ^{1}H NMR (300 MHz, [D_6]DMSO): δ = 0.92, 1.04 (2 m, 4H, 2′-H_2 + 3′-H_2), 3.20 (d, J_{H-F} = 5.1 Hz, 3H, N–CH_3), 3.84 (s, 2H, 3-H_2), 4.42 (m, 1H, 1′-H), 7.65 (d, $^3J_{H-F}$ = 13.0 Hz, 1H, 6-H), 8.69 (s, 1H, 9-H), 10.53 (br s, 1H, lactam N1–H), 14.96 (br s, 1H, CO_2H). – ^{13}C NMR (75 MHz, [D_6]DMSO): δ = 10.2 (C-2′ + C-3′), 39.1 (C-1′), 41.6 (d, J_{C-F} = 10.4 Hz, N4–CH_3), 54.8 (C-3), 106.7 (d, $^2J_{C-F}$ = 23.0 Hz, C-6), 107.5 (C-8), 119.3 (d, $^3J_{C-F}$ = 7.9 Hz, C-10b), 120.1 (d, $^3J_{C-F}$ = 6.8 Hz, C-6a), 129.7 (C-10a), 133.5 (d, $^2J_{C-F}$ = 12.8 Hz, C-4a), 151.3 (d, $^1J_{C-F}$ = 245 Hz, C-5), 151.7 (C-9), 164.9 (C-2), 166.1 (CO_2H), 176.6 (d, $^4J_{C-F}$ = 3.1 Hz, C-7). – $C_{16}H_{14}FN_3O_4$ (331.30): calcd. C 58.01, H 4.26, N 12.68; found C 58.14, H 4.40, N 12.52.

*(±)-4-Cyclopropyl-12-fluoro-1,6-dioxo-1,5,6,6a,7,8,9,10-octahydro-4H-dipyrido[1,2-a : 2′,3′-f]quinoxaline-2-carboxylic acid [(±)-**11**]*

This compound was prepared by reduction of (±)-**9a** (0.42 g, 1.0 mmol) with sodium dithionite following the procedure described above for the preparation of **10**; the reduction time was 25 min. following the addition of sodium dithionite. The product was recrystallized from methanol / chloroform (2 : 1, v / v). Yield of (±)-**11**: 0.27 g (73 %), m.p. 290 – 292 °C (dec., darkens at 280 °C). – IR (KBr): ν = 3234, 3089, 2944, 2851, 1745, 1677, 1612, 1540, 1502, 1438, 1311, 1237 cm^{-1}. – MS (TOF (+)-ES): *m/z* = 372 $(M+H)^+$. – HRMS: *m/z* = 372.1354 (calcd. 372.1360 for $C_{19}H_{19}FN_3O_4$). – ^{1}H NMR (300 MHz, [D_6]DMSO): δ = 0.89, 1.14 (2 m, 2H) and 0.98 (m, 2H, 2′-H_2 + 3′-H_2), 1.53 (m, 1H, 8-H_A), 1.65 (m, 1H, 8-H_B), 1.60 (m, 2H, 7-H_2), 1.78 (m, 1H, 9-H_A), 2.12 (m, 1H, 9-H_B), 3.12 (m, 1H, 10-H_A), 3.36 (m, 1H, 10-H_B), 3.81 (t, *J* = 4.7 Hz, 1H, 6a-H), 4.44 (m, 1H, 1′-H), 7.68 (d, $^3J_{H-F}$ = 11.9 Hz, 1H, 13-H), 8.73 (s, 1H, 3-H), 10.58 (s, 1H, lactam N5–H), 14.79 (br s, 1H, CO_2H). – ^{13}C NMR (75 MHz, [D_6]DMSO): δ = 9.4, 10.8 (C-2′ + C-3′), 21.1 (C-8), 23.2 (C-9), 25.0 (C-7), 39.1 (C-1′), 48.7 (d, J_{C-F} = 7.5 Hz, C-10), 57.0 (C-6a), 106.3 (d, $^2J_{C-F}$ = 23.0 Hz, C-13), 107.7 (C-2), 122.0 (d, $^3J_{C-F}$ = 8.0 Hz, C-13a), 123.2 (d, $^3J_{C-F}$ = 6.0 Hz, C-4b), 129.5 (C-4a), 133.4 (d, $^2J_{C-F}$ = 14.2 Hz, C-11a), 151.8 (C-3), 152.9 (d, $^1J_{C-F}$ = 247 Hz, C-12), 165.9 (C-6), 166.0 (CO_2H), 176.7 (d, $^4J_{C-F}$ = 2.6 Hz, C-1). – $C_{19}H_{18}FN_3O_4$ (371.36): calcd. C 61.45, H 4.89, N 11.32; found C 61.69, H 4.66, N 11.18.

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