Heterocycles [*h*]-Fused onto 4-Oxoquinoline-3-carboxylic Acid, V [1]. Synthesis and Antibacterial Activity of Some New 2,3-Disubstituted 7-Oxo-7,10-dihydropyrido[2,3-*f*]quinoxaline-8-carboxylic Acids and Esters

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Cyclocondensation reaction of ethyl 7,8-diamino-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylate (**2**) or the -3-carboxylic acid **3** with *sym*-1,2- diketones produced the corresponding ethyl 2,3-disubstituted pyrido[2,3-*f*]quinoxaline-8-carboxylates (**4a** – **h**) or the -8-carboxylic acids **5a** – **h**, respectively. The structures for these new heterocycles are supported by analytical and spectral (IR, MS, NMR) data. Compounds **5a** – **c**, **g**, **h** exhibit moderate activity against an assortment of bacterial species.

Key words: 7,8-Diamino-4-oxoquinoline-3-carboxylic Acid and Ester, *sym*-1,2-Diketones, Cyclocondensation, 7-Oxopyrido[2,3-*f*]quinoxalines, Antibacterial Activity

Introduction

The chemistry, biological properties and technical applications of quinoxalines have received much interest worldwide, and the subject has been revived [2 – 4]. Several synthetic and naturally occurring compounds containing the quinoxaline ring system were reported to exhibit a broad spectrum of biological activities including antitumor [5], anti-HIV [6], antimicrobial [7], antiprotozoal [8], antifungal [9], antibiotic [10, 11], and human cyclophilin A inhibitor [12] properties. On the other hand, synthetic second generation fluoroquinolones (*e. g*. ciprofloxacin) [13] have recently emerged as potent antiinfectious drugs [13, 14].

We became interested in the bioproperties of pyridoquinoxalines in which the 1-substituted-4-oxopyridine-3-carboxylic acid entity, characteristic of antibacterial quinolones, is [*f*]-fused to 2,3-disubstituted quinoxalines having an extended conjugated system. In particular, we wish to report on the synthesis of some new ethyl 7-oxo-7,10-dihydropyrido[2,3-*f*] quinoxaline-8-carboxylates (**4a** – **h**) and the respective acids (**5a** – **h**) *via* cyclocondensation of ethyl 7,8-diaminoquinoline-3-carboxylate (**2**) or its corresponding acid **3** with the appropriate *sym*-1,2-diketone as shown in Scheme 1. The preparation of the 7,8-diamino synthons **2** and **3**, utilizing the corresponding ethyl 7-azido-8-nitro-1,4-dihydroquinoline-3-carboxylate [15], is outlined in Scheme 2.

Results and Discussion

In the present study, reduction of ethyl 7-azido-1-cyclopropyl-6-fluoro-8-nitro-4-oxo-1,4-dihydroquinoline-3-carboxylate (**1**) [15] with stannous chloride in conc. HCl at r. t. yielded ethyl 7,8-diamino-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylate (**2**). However, when the reduction of **1** was conducted in ethanol under reflux, the corresponding 7,8-diamino-1,4-dihydroquinoline-3-carboxylic acid (**3**) was formed as the sole product (Scheme 2). This result is an improvement of the recently reported [16] reduction conditions of **1** that led to the formation of a separable mixture of **2** and **3**.

The synthesis of ethyl 2,3-disubstituted-10-cyclopropyl-5-fluoro-7-oxo-7,10-dihydropyrido[2,3-*f*] quinoxaline-8-carboxylates **4a** – **h** is achieved by utilizing ethyl 7,8-diaminoquinoline-3-carboxylate (**3**) as the common building block and constructing the pyrazine ring thereat (Scheme 1). For this purpose,

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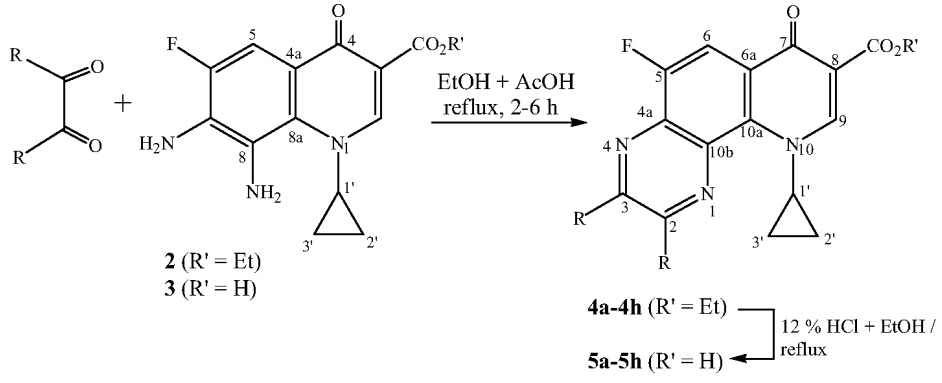

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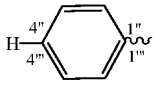
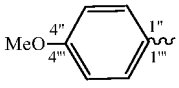
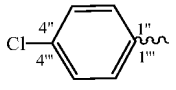
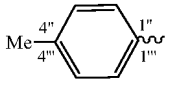
C(2) - R / C(3) - R	Me				

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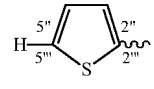
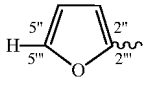
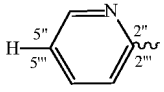
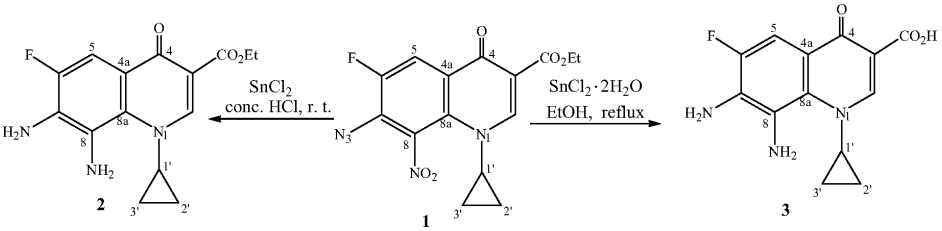
C(2) - R / C(3) - R			

Scheme 1.



Scheme 2.

the appropriate 1,2-dione is brought to interact with **3** wherein double sequential condensations (involving the amino- and keto-groups) are ensued with ultimate formation of the respective target products **4a**–**h**. Likewise, direct interaction of **2** with the particular 1,2-diones furnished the corresponding 2,3-(*sym*-disubstituted)-10-cyclopropyl-5-fluoro-7-oxo-7,10-dihydropyrido[2,3-*f*]quinoxaline-8-carboxylic acids **5a**–**h** (Scheme 1). The latter compounds are also accessible *via* acid-catalyzed hydrolysis of the respective ethyl esters **4a**–**h**.

The spectral (IR, MS, NMR) and microanalytical data for the new compounds **4a**–**h** and **5a**–**h** are compatible with the assigned structures and are given in the Experimental Section. Thus, the mass spectra of **4** and **5** display the correct molecular ion peaks as suggested by their molecular formula, and for which the measured high-resolution HRMS (ESI) data are in good agreement with the calculated values. Assignments of the ^{1}H and ^{13}C signals to the different respective protons and carbons are based on DEPT and 2D (COSY, HMQC, HMBC) experiments which showed correlations consistent with these assignments. Salient features of the skeletal carbons (C-3, C-5, C-6, C-4a, C-6a, C-10a, C-10b) of compounds **4a**–**h** and **5a**–**h** are their characteristic doublets arising from spin-spin coupling with the neighboring fluorine atom; of these the C-3 doublet, with $^{4}J_{C-F} \sim 2$ Hz, is centered in the range δ = 149–151.6 ppm [17]. On the other hand, C-2 resonates at lower field (δ = 152–155 ppm) [17] as a singlet. These features constitute distinct criteria that enabled the differentiation between C-2 and C-3. The NMR spectral data of some compounds, *e. g.* **4d** and **5d**, revealed clearly that the signals arising from the phenyl moiety at C-3 are distinguishable from those of the other phenyl group re-

Table 1. Agar diffusion tests of **5a – c**, **g**, **h** (40 μg/platelet, ∅ 9 mm).

Compound	*Staphylococcus aureus*	*Bacillus subtilis*	*Streptomyces viridochromogenes*	*Escherichia coli*
5a	17	0	19	12
5b	10	9.5	9.5	9.5
5c	10	0	11	0
5g	11	10	12	0
5h	14	0	18	0

siding at C-2. This is evidenced from the fact that 2‴-H / 6‴-H showed strong three-bond correlations with the C-3 doublet, while 2″-H / 6″-H are correlated with the C-2 singlet. Long-range correlations are also observed between 6-H and each of C-4a, C-10a and C-7, as well as between 9-H and each of C-10a, C-7, CO_2Et and C-1′, and between 1′-H and each of C-10a and C-9.

Antimicrobial Activity

Compounds **5a – d**, **f – h** were tested against an assortment of bacterial and fungal species using the agar diffusion method. Compounds **5a – c** and **5g**, **h** exhibited moderate potency against the tested bacterial strains as given in Table 1. However, compounds **5a – d**, **f – h** were inactive against *Candida albicans* and *Mucor miehei*; they were also inactive against three microalgae, namely *Chlorella vulgaris*, *C. sorokiniana* and *Scenedesmus subspicatus*.

Experimental Section

2,4-Dichloro-5-fluoro-3-nitrobenzoic acid, ethyl 3-(*N*,*N*-dimethylamino)acrylate, cyclopropylamine, 2,3-butanedione, benzil, 4,4′-dimethoxybenzil, 4,4′-dimethylbenzil, 4,4′-dichlorobenzil and α-furil were purchased from Acros. α-Thenil and α-pyridil were purchased from Aldrich. Melting points (uncorrected) were determined on a Gallenkamp electrothermal melting-temperature apparatus. ^{1}H, ^{13}C NMR, DEPT, and 2D (H-H COSY, HMQC, HMBC) spectra were measured on a Bruker DPX-300 instrument. Chemical shifts are expressed in ppm with reference to TMS as internal standard. Electron impact mass spectra (EIMS) were obtained using a Finnigan MAT TSQ-70 spectrometer at 70 eV and at an ion source temperature of 200 °C. High-resolution mass spectra (HRMS) were measured in positive ion mode by electrospray (ESI) on an APEX-Qe 94 instrument. Infrared spectra were recorded as KBr discs on a Nicolet Impact-400 FT-IR spectrophotometer. Microanalyses were preformed at the Microanalytical Laboratory of the Hashemite University, Zarqa-Jordan.

*Ethyl 7,8-diamino-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylate (**2**)*

Anhydrous stannous chloride (5.3 g, 28 mmol) was added portionwise to a stirred and ice-cooled (4 – 8 °C) solution of ethyl 7-azido-1-cyclopropyl-6-fluoro-8-nitro-4-oxo-1,4-dihydroquinoline-3-carboxylate (**1**) [15] (2.2 g, 6.3 mmol) in 36 % aqueous HCl (50 mL). The reaction mixture was further stirred at r. t. for 24 h, then diluted with ice-cooled water (50 mL), basified with 40 % cold aqueous NaOH solution to pH ∼ 8 and set aside for 10 – 20 min. The precipitated solid product was collected by suction filtration, purified by flash column chromatography using silica gel and eluting with chloroform, then chloroform + methanol (9 : 1, v/v), and finally recrystallized from ethanol. Yield: 1.5 g (78 %), m. p. 282 – 284 °C (dec.) (284 – 286 °C (dec.) [16]). – HRMS (ESI): *m/z* = 306.12475 (calcd. 306.12540 for $C_{15}H_{17}FN_3O_3^+$, $[M+H]^+$).

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

A solution of ethyl 7-azido-1-cyclopropyl-6-fluoro-8-nitro-4-oxo-1,4-dihydroquinoxaline-3-carboxylate (**1**) (2.2 g, 6.3 mmol) and $SnCl_2 \cdot 2H_2O$ (6.7 g, 30 mmol) in ethanol (50 mL) was refluxed for 40 – 45 h. The reaction mixture was cooled to r. t., then poured into water (50 mL), treated portionwise with 40 % cold aqueous NaOH to pH ∼ 9 – 10, and extracted with ethyl acetate (2 × 30 mL). The aqueous layer was made acidic with 3N HCl (to pH ∼ 3 – 4), then extracted with ethyl acetate (3 × 30 mL). The organic layer was dried (anhydrous sodium sulfate) and concentrated to a small volume under reduced pressure; the resulting solid product was collected and dried. Yield: 0.72 g (41 %), m. p. 291 – 293 °C (dec.) (295 – 296 °C (dec.) [16]). – HRMS (ESI): *m/z* = 278.09352 (calcd. 278.09410 for $C_{13}H_{13}FN_3O_3^+$, $[M+H]^+$).

*Ethyl 10-cyclopropyl-5-fluoro-2,3-dimethyl-7-oxo-7,10-dihydropyrido[2,3-f]quinoxaline-8-carboxylate (**4a**)*

A stirred mixture of **2** (0.61 g, 2 mmol) and 2,3-butanedione (0.17 g, 2 mmol) in absolute ethanol (50 mL) and glacial acetic acid (0.1 mL) was brought to gentle reflux for 2 – 3 h. The resulting clear reaction solution was

then cooled, and the precipitated white solid product was collected, washed with water, dried and recrystallized from ethanol. Yield: 0.44 g (62 %), m. p. 255 – 256 °C. – IR (KBr): ν = 3068, 3034, 2978, 2932, 1731, 1615, 1583, 1472, 1358, 1319, 1297, 1236, 1167, 1068 cm^{-1}. – ^1H NMR (300 MHz, $CDCl_3$): δ = 0.91 (m, 2H) and 1.21 (m, 2H, 2′-H_2 + 3′-H_2), 1.40 (t, 3H, J = 7.1 Hz, CH_3CH$_2$), 2.75 (s, 3H) and 2.80 (s, 3H, C2-CH_3 + C3-CH_3), 4.39 (q, 2H, J = 7.1 Hz, CH_2Me), 4.67 (m, 1H, 1′-H), 8.30 (d, 1H, $^3J_{C-F}$ = 10.4 Hz, 6-H), 8.76 (s, 1H, 9-H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.0 (C-2′ + C-3′), 14.5 (*C*H_3CH$_2$), 23.1 (C2-*C*H_3 and C3-*C*H_3), 42.4 (C-1′), 61.2 (*C*H_2Me), 109.4 (d, $^2J_{C-F}$ = 21.2 Hz, C-6), 112.3 (C-8), 128.9 (d, $^3J_{C-F}$ = 7.1 Hz, C-6a), 134.4 (d, $^4J_{C-F}$ = 1.8 Hz, C-10a), 134.6 (d, $^2J_{C-F}$ = 9.4 Hz, C-4a), 135.0 (br, C-10b), 150.1 (C-9), 151.6 (C-2), 154.2 (d, $^1J_{C-F}$ = 257 Hz, C-5), 154.8 (d, $^4J_{C-F}$ = 2 Hz, C-3), 165.4 (*C*O_2Et), 172.5 (d, $^4J_{C-F}$ = 2.3 Hz, C-7). – EIMS: *m/z* (%) = 355 (27) $[M]^+$, 327 (30), 310 (13), 283 (100), 255 (73), 251 (16), 228 (9), 201 (15), 186 (11), 133 (6). – HRMS (EI): *m/z* = 355.13205 (calcd. 355.13319). – $C_{19}H_{18}FN_3O_3$ (355.37): calcd. C 64.22, H 5.11, N 11.82; found C 64.02, H 5.12, N 11.68.

*Ethyl 10-cyclopropyl-5-fluoro-7-oxo-2,3-diphenyl-7,10-dihydropyrido[2,3-f]quinoxaline-8-carboxylate (**4b**)*

This compound was prepared from **2** (0.61 g, 2 mmol) and benzil (0.42 g, 2 mmol), following a similar procedure as described above for **4a**. Yield: 0.73 g (76 %), m. p. 261 – 262 °C. – IR (KBr): ν = 3078, 3061, 2984, 1694, 1634, 1593, 1536, 1466, 1354, 1240, 1195, 1173, 1125, 1022 cm^{-1}. – ^1H NMR (300 MHz, $CDCl_3$): δ = 0.98 (m, 2H) and 1.24 (m, 2H) (2′-H_2 + 3′-H_2), 1.41 (t, 3H, J = 7.1 Hz, CH_3CH$_2$), 4.39 (q, 2H, J = 7.1 Hz, CH_2CH$_3$), 4.75 (m, 1H, 1′-H), 7.35 (m, 6H, *Ar*-H: 3″-H, 4″-H, 5″-H + 3‴-H, 4‴-H, 5‴-H), 7.48 (dd, J = 7.5, 1.6 Hz, 2H) and 7.63 (dd, J = 7.4, 1.6 Hz, 2H, *Ar*-H: 2″-H + 6″-H and 2‴-H + 6‴-H), 8.36 (d, 1H, $^3J_{H-F}$ = 10.1 Hz, H-6), 8.77 (s, 1H, H-9). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 10.9 (C-2′ + C-3′), 14.5 (*C*H_3CH$_2$), 42.0 (C-1′), 61.2 (*C*H_2Me), 110.3 (d, ^2J = 20.8 Hz, C-6), 112.8 (C-8), 128.5, 128.6 (C-3″ + C-5″ and C-3‴ + C-5‴), 129.5, 130.2 (C-2″ + C-6″ and C-2‴ + C-6‴), 129.5 (d, $^3J_{C-F}$ = 7 Hz, C-6a), 129.6, 129.9 (C-4″ + C-4‴), 134.3 (d, $^2J_{C-F}$ = 13.8 Hz, C-4a), 134.7 (br s, C-10b), 134.9 (d, $^4J_{C-F}$ = 2.7 Hz, C-10a), 137.7, 138.3 (C-1″ + C-1‴), 150.1 (C-9), 150.7 (C-2), 153.6 (d, $^4J_{C-F}$ = 2 Hz, C-3), 154.4 (d, $^1J_{C-F}$ = 259 Hz, C-5), 165.3 (*C*O_2Et), 172.4 (d, $^4J_{C-F}$ = 2.3 Hz, C-7). – EIMS: *m/z* (%) = 479 (45) $[M]^+$, 451 (84), 434 (9), 407 (100), 379 (85), 350 (11), 325 (16), 277 (8), 251 (18), 223 (11), 188 (13), 165 (51), 149 (10). – HRMS (EI): *m/z* = 479.16154 (calcd. 479.16449). – $C_{29}H_{22}FN_3O_3$ (479.52): calcd. C 72.64, H 4.62, N 8.76; found C 72.44, H 4.54, N 8.63.

*Ethyl 10-cyclopropyl-5-fluoro-2,3-bis-(4-methoxyphenyl)-7-oxo-7,10-dihydropyrido[2,3-f]quinoxaline-8-carboxylate (**4c**)*

This compound was prepared from **2** (0.61 g, 2 mmol) and 4,4′-dimethoxybenzil (0.54 g, 2 mmol), following a similar procedure as noted above for **4a**. Yield: 0.70 g (65 %), m. p. 218 – 219 °C. – IR (KBr): ν = 3049, 2984, 2926, 2894, 2830, 1734, 1685, 1627, 1606, 1545, 1512, 1464, 1363, 1323, 1298, 1249, 1174, 1127, 1082, 1029 cm^{-1}. – ^1H NMR (300 MHz, [D_7]DMF): δ = 1.10 (m, 2H) and 1.28 (m, 2H, 2′-H_2 + 3′-H_2), 1.34 (t, J = 7.1 Hz, 3H, CH_3CH$_2$), 3.85 (s, 3H) and 3.87 (s, 3H, C4″–OCH_3 and C4‴–OCH_3), 4.31 (q, J = 7.1 Hz, 2H, CH_2Me), 4.84 (m, 1H, 1′-H), 6.99 (d, J = 8.8 Hz, 2H) and 7.02 (d, J = 8.8 Hz, 2H, 3″-H + 5″-H and 3‴-H + 5‴-H), 7.68 (d, J = 8.8 Hz, 2H) and 7.73 (d, J = 8.8 Hz, 2H, 2″-H + 6″-H and 2‴-H + 6‴-H), 8.18 (d, $^3J_{H-F}$ = 10.5 Hz, 1H, 6-H), 8.81 (s, 1H, 9-H). – ^{13}C NMR (75 MHz, [D_7]DMF): δ = 10.3 (C-2′ + C-3′), 14.0 (*C*H_3CH$_2$), 42.1 (C-1′), 55.2, 55.3 (C4″–OCH_3 and C4‴–OCH_3), 60.3 (*C*H_2Me), 108.6 (d, $^2J_{C-F}$ = 20.5 Hz, C-6), 112.6 (C-8), 114.0, 114.1 (C-3″ + C-5″ and C-3‴ + C-5‴), 128.5 (d, $^3J_{C-F}$ = 6.5 Hz, C-6a), 130.7, 131.0 (C-1″ + C-1‴), 131.5, 131.7 (C-2″ + C-6″ and C-2‴ + C-6‴), 133.4 (d, $^2J_{C-F}$ = 14 Hz, C-4a), 134.6 (C-10b), 135.5 (d, $^4J_{C-F}$ = 2.4 Hz, C-10a), 150.0 (C-2), 150.2 (C-9), 152.8 (d, $^4J_{C-F}$ = 2 Hz, C-3), 154.2 (d, $^1J_{C-F}$ = 257 Hz, C-5), 160.9, 161.3 (C-4″ + C-4‴), 164.6 (*C*O_2Et), 171.5 (d, $^4J_{C-F}$ = 2.4 Hz, C-7). – EIMS: *m/z* (%) = 539 (M^+, 37), 511 (62), 467 (51), 439 (26), 398 (5), 355 (6), 324 (6), 260 (7), 252 (22), 226 (24), 211 (100), 181 (13), 171 (12), 133 (78), 103 (28). – HRMS (ESI): *m/z* = 540.19294 (calcd. 540.19347 for $C_{31}H_{27}FN_3O_5^+$, $[M+H]^+$). – $C_{31}H_{26}FN_3O_5$ (539.55): calcd. C 69.01, H 4.86, N 7.79; found C 68.78, H 4.74, N 7.62.

*Ethyl 2,3-di(4-chlorophenyl)-10-cyclopropyl-5-fluoro-7-oxo-7,10-dihydropyrido[2,3-f]quinoxaline-8-carboxylate (**4d**)*

This compound was prepared from **2** (0.61 g, 2 mmol) and 4,4′-dichlorobenzil (0.56 g, 2 mmol), following a similar procedure as described above for **4a**. Yield: 0.88 g (80 %), m. p. 262 – 265 °C. – IR (KBr): ν = 3055, 2984, 2931, 1725, 1689, 1633, 1592, 1543, 1492, 1466, 1357, 1290, 1240, 1170, 1128, 1090, 1013 cm^{-1}. – ^1H NMR (300 MHz, $CDCl_3$): δ = 0.97 (m, 2H) and 1.22 (m, 2H, 2′-H_2 + 3′-H_2), 1.41 (t, 3H, J = 7.1 Hz, CH_3CH$_2$), 4.40 (q, 2H, J = 7.1 Hz, CH_2Me), 4.70 (m, 1H, 1′-H), 7.35 (d, 2H, J = 8.5 Hz) and 7.36 (d, 2H, J = 8.5 Hz, 3″-H + 5″-H and 3‴-H + 5‴-H), 7.43 (d, 2H, J = 8.5 Hz) (2″-H + 6″-H), 7.59 (d, 2H, J = 8.5 Hz, 2‴-H + 6‴-H), 8.39 (d, 1H, $^3J_{H-F}$= 10 Hz, 6-H), 8.78 (s, 1H, 9-H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.0 (C-2′ + C-3′), 14.5 (*C*H_3CH$_2$), 42.0 (C-1′), 61.3 (*C*H_2Me), 110.8 (d, $^2J_{C-F}$ = 20.8 Hz, C-6), 113.0 (C-8), 129.0, 129.2

(C-3″ + C-5″ and C-3‴ + C-5‴), 129.7 (d, $^3J_{C-F}$ = 6.8 Hz, C-6a), 130.7 (C-2″ + C-6″), 131.5 (C-2‴ + C-6‴), 134.4 (d, $^2J_{C-F}$ = 14.0 Hz, C-4a), 134.7 (C-10b), 134.8 (d, $^4J_{C-F}$ = 2.8 Hz, C-10a), 135.8, 136.1 (C-1″ + C-1‴), 136.5, 136.6 (C-4″ + C-4‴), 149.3 (C-2), 150.2 (C-9), 152.2 (d, $^4J_{C-F}$ = 2.0 Hz, C-3), 154.3 (d, $^1J_{C-F}$ = 252 Hz, C-5), 165.2 (*C*O$_2$Et), 172.4 (d, $^4J_{C-F}$ = 2.3 Hz, C-7). – HRMS (ESI): *m/z* = 548.09369 (calcd. 548.09400 for $C_{29}H_{21}Cl_2FN_3O_3^+$, $[M+H]^+$). – $C_{29}H_{20}Cl_2FN_3O_3$ (548.41): calcd. C 63.52, H 3.68, Cl 12.93, N 7.66; found C 63.38, H 3.62, Cl 12.64, N 7.50.

*Ethyl 10-cyclopropyl-5-fluoro-7-oxo-2,3-di(p-tolyl)-7,10-dihydropyrido[2,3-f]quinoxaline-8-carboxylate (**4e**)*

This compound was prepared from **2** (0.61 g, 2 mmol) and 4,4′-dimethylbenzil (0.48 g, 2 mmol), following a similar procedure as described above for **4a**. Yield: 0.75 g (74 %), m. p. 247 – 248 °C. – IR (KBr): ν = 3054, 3005, 2982, 2919, 2853, 1733, 1689, 1625, 1593, 1541, 1356, 1323, 1295, 1242, 1165, 1126, 1084, 1038 cm^{-1}. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.95 (m, 2H) and 1.24 (m, 2H, 2′-H$_2$ + 3′-H$_2$), 1.41 (t, 3H, *J* = 7.1 Hz, C*H*$_3$CH$_2$), 2.34 (s, 3H) and 2.36 (s, 3H, C4″-C*H*$_3$ and C4‴-C*H*$_3$), 4.40 (q, 2H, *J* = 7.1 Hz, C*H*$_2$Me), 4.75 (m, 1H, 1′-H), 7.13 (center of overlapped 2d, 4H, 3″-H + 5″-H and 3‴-H + 5‴-H), 7.38 (d, *J* = 8.1 Hz, 2H, 2″-H + 6″-H), 7.54 (d, *J* = 8.1 Hz, 2H, 2‴-H + 6‴-H), 8.34 (d, $^3J_{H-F}$ = 10.1 Hz, 1H, 6-H), 8.77 (s, 1H, 9-H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 10.9 (C-2′ + C-3′), 14.5 (*C*H$_3$CH$_2$), 21.4 (C4″-*C*H$_3$ and C4‴-*C*H$_3$), 42.0 (C-1′), 61.1 (*C*H$_2$Me), 110.0 (d, $^2J_{C-F}$ = 20.8 Hz, C-6), 112.6 (C-8), 129.2, 129.3 (C-3″ + C-5" and C-3‴ + C-5‴), 129.0 (d, $^3J_{C-F}$ = 6.2 Hz, C-6a), 129.4 (C-2″ + C-6″), 130.0 (C-2‴ + C-6‴), 134.1 (d, $^2J_{C-F}$ = 13.8 Hz, C-4a), 134.5 (C-10b), 134.8 (d, $^4J_{C-F}$ = 2.3 Hz, C-10a), 134.9, 135.6 (C-1″ + C-1‴), 139.7 (C-4″), 140.1 (C-4‴), 150.1 (C-9), 150.6 (C-2), 153.5 (d, $^4J_{C-F}$ = 1.6 Hz, C-3), 154.4 (d,$^1J_{C-F}$ = 258 Hz, C-5), 165.4 (*C*O$_2$Et), 172.5 (d, $^4J_{C-F}$ = 1.8 Hz, C-7). – $C_{31}H_{26}FN_3O_3$ (507.57): calcd. C 73.36, H 5.16, N 8.28; found C 73.08, H 5.02, N 8.12.

*Ethyl 10-cyclopropyl-5-fluoro-7-oxo-2,3-di(thien-2-yl)-7,10-dihydropyrido[2,3-f]quinoxaline-8-carboxylate (**4f**)*

This compound was prepared from **2** (0.61 g, 2 mmol) and 2,2′-thenil (0.44 g, 2 mmol), following a similar procedure as described above for **4a**. Yield: 0.68 g (70 %), m. p. 290 – 293 °C. – IR (KBr): ν = 3074, 2965, 2888, 1683, 1635, 1594, 1519, 1461, 1425, 1370, 1326, 1286, 1243, 1192, 1117, 1023 cm^{-1}. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.95 (m, 2H) and 1.38 (m, 2H, 2′-H$_2$ + 3′-H$_2$), 1.44 (t, *J* = 7.1 Hz, 3H, C*H*$_3$CH$_2$), 4.44 (q, *J* = 7.1 Hz, 2H, C*H*$_2$Me), 4.80 (m, 1H, 1′-H), 7.07 (two overlapped dd, 2H, 4″-H + 4‴-H), 7.43 (dd, *J* = 3.8, 0.8 Hz, 1H) and 7.54 (dd, *J* = 4.1, 0.8 Hz, 1H, 5″-H + 5‴-H), 7.59, 7.61 (center of two overlapped dd, 2H, 3″-H + 3‴-H), 8.38 (d, $^3J_{H-F}$ = 10 Hz, 1H, 6-H), 8.82 (s, 1H, 9-H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 10.8 (C-2′ + C-3′), 14.5 (*C*H$_3$CH$_2$), 41.9 (C-1′), 61.3 (*C*H$_2$Me), 110.6 (d, $^2J_{C-F}$ = 20.8 Hz, C-6), 113.0 (C-8), 127.9, 128.3 (C-4″ + C-4‴), 129.6 (d, $^3J_{C-F}$ = 6.8 Hz, C-6a), 129.8, 129.9 (C-5″ + C-5‴), 130.3, 130.9 (C-3″ + C-3‴), 133.5 (d, $^2J_{C-F}$ = 14.3 Hz, C-4a), 133.7 (C-10b), 134.4 (d, $^4J_{C-F}$ = 2.8 Hz, C-10a), 140.7, 141.3 (C-2″ + C-2‴), 143.0 (C-2), 146.4 (d, $^4J_{C-F}$ = 2 Hz, C-3), 150.1 (C-9), 154.1 (d, $^1J_{C-F}$ = 260 Hz, C-5), 165.4 (*C*O$_2$Et), 172.4 (d, $^4J_{C-F}$ = 2.4 Hz, C-7). – EIMS: *m/z* (%) = 491 (96) $[M]^+$, 463 (81), 446 (8), 419 (100), 418 (55), 391 (23), 350 (5), 308 (3), 280 (4), 235 (3), 178 (10), 131 (3), 91 (5). – HRMS (ESI): *m/z* = 492.09444 (calcd. 492.09519 for $C_{25}H_{19}FN_3O_3S_2^+$, $[M+H]^+$). – $C_{25}H_{18}FN_3O_3S_2$ (491.56): calcd. C 61.08, H 3.69, N 8.55, S 13.05; found C 60.82, H 3.58, N 8.39, S 12.86.

*Ethyl 10-cyclopropyl-5-fluoro-2,3-di(furan-2-yl)-7-oxo-7,10-dihydropyrido[2,3-f]quinoxaline-8-carboxylate (**4g**)*

This compound was prepared from **2** (0.61 g, 2 mmol) and α-furil (0.38 g, 2 mmol), following a similar procedure as described above for **4a**. Yield: 0.75 g (82 %), m. p. 258 – 260 °C. – IR (KBr): ν = 3126, 2978, 1686, 1641, 1586, 1535, 1463, 1358, 1294, 1237, 1194, 1173, 1125, 1088, 1027 cm^{-1}. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.93 (m, 2H) and 1.32 (m, 2H, 2′-H$_2$ + 3′-H$_2$), 1.41 (t, *J* = 7.1 Hz, 3H, C*H*$_3$CH$_2$), 4.41 (q, *J* =7.1 Hz, 2H, C*H*$_2$Me), 4.76 (m, 1H, 1′-H), 6.56 (dd, *J* = 3.5, 1.7 Hz, 1H) and 6.60 (dd, *J* = 3.5, 1.7 Hz, 1H, 4″-H + 4‴-H), 6.70 (dd, *J* = 0.6, 3.5 Hz, 1H) and 7.06 (dd, *J* = 0.6, 3.5 Hz, 1H, 3″-H + 3‴-H), 7.60 (dd, *J* = 0.6, 1.7 Hz, 1H) and 7.63 (dd, *J* = 0.6, 1.7 Hz, 1H, 5″-H + 5‴-H), 8.35 (d, $^3J_{H-F}$ = 10.1 Hz, 1H, 6-H), 8.78 (s, 1H, 9-H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 10.9 (C-2′ + C-3′), 14.5 (*C*H$_3$CH$_2$), 42.1 (C-1′), 61.3 (*C*H$_2$Me), 110.6 (d, $^2J_{C-F}$ = 20.9 Hz, C-6), 112.3, 112.5 (C-4″ + C-4‴), 112.9 (C-8), 114.5, 115.3 (C-3″ + C-3‴), 129.5 (d, $^3J_{C-F}$ = 6.7 Hz, C-6a), 133.5 (d, $^2J_{C-F}$ = 14.2 Hz, C-4a), 134.0 (C-10b), 134.6 (d, $^4J_{C-F}$ = 2.5 Hz, C-10a), 141.8, 141.9 (C-2″ + C-2‴), 145.0, 145.3 (C-5″ + C-5‴), 150.1 (C-9), 150.2, 150.5 (C-2 + C-3), 154.1 (d, $^1J_{C-F}$ = 260 Hz, C-5), 165.4 (*C*O$_2$Et), 172.4 (d, $^4J_{C-F}$ = 2.5 Hz, C-7). – EIMS: *m/z* (%) = 459 (41) $[M]^+$, 431 (75), 414 (9), 387 (100), 359 (73), 330 (18), 302 (15), 252 (12), 223 (10), 172 (8), 159 (11), 149 (23), 118 (13). – HRMS (EI): *m/z* = 459.12218 (calcd. 459.12301). – $C_{25}H_{18}FN_3O_5$ (459.44): calcd. C 65.36, H 3.95, N 9.15; found C 65.15, H 3.88, N 9.02.

*Ethyl 10-cyclopropyl-5-fluoro-7-oxo-2,3-di(pyridin-2-yl)-7,10-dihydropyrido[2,3-f]quinoxaline-8-carboxylate (**4h**)*

This compound was prepared from **2** (0.61 g, 2 mmol) and 2,2′-pyridil (0.42 g, 2 mmol), following a similar proce-

dure as described above for **4a**. Yield: 0.82 g (85 %), m. p. 244 – 275 °C. – IR (KBr): ν = 3088, 3058, 2997, 2902, 1687, 1632, 1589, 1541, 1473, 1394, 1356, 1330, 1299, 1250, 1234, 1172, 1136, 1035 cm^{-1}. – ^1H NMR (300 MHz, [D_7]DMF): δ = 1.14 (m, 2H) and 1.32 (m, 2H, 2′-H_2 + 3′-H_2), 1.34 (t, J = 7.1 Hz, 3H, CH_3CH$_2$), 4.32 (q, J = 7.1 Hz, 2H, CH_2Me), 4.84 (m, 1H, 1′-H), 7.42 (m, 2H, 5″-H + 5‴-H), 7.98 (ddd, J = 7.9, 7.7, 1.8, 1H) and 8.06 (ddd, J = 7.8, 7.7, 1.7 Hz, 1H, 4″-H + 4‴-H), 8.21 (d, J = 7.8 Hz, 1H) and 8.26 (d, J = 7.8 Hz, 1H) (3″-H + 3‴-H), 8.28 (d, $^3J_{H-F}$ = 10.4 Hz, 1H, 6-H), 8.34 (m, 2H, 6″-H + 6‴-H), 8.83 (s, 1H, 9-H). – ^{13}C NMR (75 MHz, [D_7]DMF): δ = 10.4 (C-2′ + C-3′), 14.0 (*C*H_3CH$_2$), 42.2 (C-1′), 60.3 (*C*H_2Me), 109.7 (d,$^2J_{C-F}$ = 20.4 Hz, C-6), 112.9 (C-8), 123.8, 124.0 (C-5″ + C-5‴), 124.1, 124.2 (C-3″ + C-3‴), 129.2 (d, $^3J_{C-F}$ = 6.5 Hz, C-6a), 133.7 (d, $^2J_{C-F}$ = 14.1 Hz, C-4a), 134.9 (C-10b), 135.6 (d, $^4J_{C-F}$ = 2.4 Hz, C-10a), 137.1, 137.2 (C-4″ + C-4‴), 148.5, 148.6 (C-6″ + C-6‴), 150.0 (C-2), 150.4 (C-9), 153.0 (d, $^4J_{C-F}$ = 2 Hz, C-3), 154.6 (d, $^1J_{C-F}$ = 258 Hz, C-5), 156.8, 156.9 (C-2″ + C-2‴), 164.4 (*C*O_2Et), 171.4 (d, $^4J_{C-F}$ = 2.3 Hz, C-7). – EIMS: *m/z* (%) = 481 (100) $[M]^+$, 453 (20), 462 (6), 436 (8), 408 (27), 381 (76), 353 (11), 331 (8), 217 (3), 203 (5), 131 (2), 105 (1). – HRMS (ESI): *m/z* = 482.16204 (calcd. 482.16284 for $C_{27}H_{21}FN_5O_3^+$, $[M+H]^+$). – $C_{27}H_{20}FN_5O_3$ (481.48): calcd. C 67.35, H 4.19, N 14.55; found C 67.11, H 4.06, N 14.38.

*10-Cyclopropyl-5-fluoro-2,3-dimethyl-7-oxo-7,10-dihydropyrido[2,3-f]quinoxaline-8-carboxylic acid (**5a**)*

Method (i): A stirred mixture of **3** (0.55 g, 2 mmol) and 2,3-butanedione (0.17 g, 2 mmol) in absolute ethanol (50 mL) and glacial acetic acid (0.1 mL) was brought to gentle reflux for 5 – 6 h. The resulting reaction solution was then cooled, treated with cold water (25 mL), and the precipitated white solid product was collected, washed with water and dried. Yield: 0.33 g (51 %), m. p. 269 – 270 °C. – IR (KBr): ν = 3412, 3058, 2924, 2855, 1728, 1628, 1606, 1541, 1512, 1433, 1377, 1353, 1317, 1179, 1118, 1026 cm^{-1}. – ^1H NMR (300 MHz, [D_6]DMSO): δ = 0.98 (m, 2H) and 1.21 (m, 2H, 2′-H_2 + 3′-H_2), 2.77 (br s, 6H, C2-CH_3 + C3-CH_3), 4.74 (m, 1H, 1′-H), 8.04 (d, 2H, $^3J_{H-F}$ = 10 Hz, 1H, 6-H), 8.87 (s, 1H, 9-H), 14.68 (br s, 1H, CO_2H). – ^{13}C NMR (75 MHz, [D_6]DMSO): δ = 11.0 (C-2′ + C-3′), 23.1 and 23.3 (2*C*H_3), 44.3 (C-1′), 107.2 (d,$^2J_{C-F}$ = 21 Hz, C-6), 109.7 (C-8), 125.7 (d, $^3J_{C-F}$ = 7.7 Hz, C-6a), 134.7 (d, $^2J_{C-F}$ = 13.4 Hz, C-4a), 135.1 (d, $^3J_{C-F}$ = 1.5 Hz, C-10b), 136.2(d, $^4J_{C-F}$ = 2.5 Hz, C-10a), 150.4 (C-9), 153.6 and 156.7 (C-2 + C-3), 154.7 (d, $^1J_{C-F}$ = 258 Hz, C-5); 165.7 (*C*O_2H), 176.5 (d, $^4J_{C-F}$ = 2.9 Hz, C-7). – EIMS: *m/z* (%) = 327 (17) $[M]^+$, 309 (5), 299 (19), 283 (100), 268 (27), 255 (40), 227 (6), 201 (15), 186 (7), 145 (6), 132 (9), 118 (3). – HRMS (EI): *m/z* = 327.10009 (calcd. 327.10189). – $C_{17}H_{14}FN_3O_3$ (327.31): calcd. C 62.38, H 4.31, N 12.84; found C 62.14, H 4.23, N 12.65.

Method (ii): A vigorously stirred suspension of ethyl 10-cyclopropyl-5-fluoro-2,3-dimethyl-7-oxo-7,10-dihydropyrido[2,3-*f*]quinoxaline-8-carboxylate (**4a**) (0.20 g, 0.56 mmol) in 12 % HCl (30 mL) and ethanol (10 mL) was heated at 80 – 85 °C under reflux. Progress of the ester hydrolysis was monitored by TLC and was completed within 30 – 40 h. Thereafter the reaction mixture was cooled, and the resulting precipitate was collected, washed with water and dried. Yield of **5a**: 0.17 g (93 %).

*10-Cyclopropyl-5-fluoro-7-oxo-2,3-diphenyl-7,10-dihydropyrido[2,3-f]quinoxaline-8-carboxylic acid (**5b**)*

Method (i): This compound was prepared from **3** (0.55 g, 2 mmol) and benzil (0.42 g, 2 mmol), following a similar procedure as described above in method (i) for **5a**. Yield: 0.58 g (65 %), m. p. 279 – 281 °C. – IR (KBr): ν = 3409, 3068, 3004, 2926, 1728, 1628, 1603, 1549, 1505, 1462, 1352, 1315, 1234, 1182, 1139, 1062, 1024 cm^{-1}. – ^1H NMR (300 MHz, [D_6]DMSO): δ = 1.01 (m, 2H) and 1.21 (m, 2H, 2′-H_2 + 3′-H_2), 4.75 (m, 1H, 1′-H), 7.42 (m, 6H, *Ar*-H: 3″-H, 4″-H, 5″-H + 3‴-H, 4‴-H, 5‴-H), 7.56 (br d, J = 7.1 Hz, 2H) and 7.64 (br d, J = 6.9 Hz, 2H, *Ar*-H: 2″-H + 6″-H and 2‴-H + 6‴-H), 8.18 (d, $^3J_{H-F}$ = 9.9 Hz, 1H, 6-H), 8.89 (s, 1H, 9-H), 14.75 (br s, 1H, CO_2H). – ^{13}C NMR (75 MHz, [D_6]DMSO): δ = 11.0 (C-2′ + C-3′), 43.8 (C-1′), 108.4 (d, $^2J_{C-F}$ = 20.6 Hz, C-6), 110.3 (C-8), 126.3 (d, $^3J_{C-F}$ = 7.3 Hz, C-6a), 128.9, 129.0 (C-3″ + C-5" and C-3‴ + C-5‴), 130.1, 130.4 (C-2″ + C-6″ and C-2‴ + C-6‴), 130.0, 130.5 (C-4″ + C-4‴), 134.4 (d, $^2J_{C-F}$ = 14.3 Hz, C-4a), 134.8 (d, $^4J_{C-F}$ = 2.5 Hz, C-10a), 136.7 (br s, C-10b), 137.9, 138.2 (C-1″ + C-1‴), 150.9 (C-9), 151.0 (C-2), 154.0 (d, $^4J_{C-F}$ = 1.6 Hz, C-3), 154.7 (d, $^1J_{C-F}$ = 258 Hz, C-7), 165.7 (*C*O_2H), 176.6 (d, $^4J_{C-F}$ = 2.4 Hz, C-7). – EIMS: *m/z* (%) = 451(23) $[M]^+$, 433 (4), 423 (36), 405 (100), 392 (18), 379 (75), 378 (31), 350 (7), 325 (8), 297 (6), 176 (7), 165 (35), 132 (9). – HRMS (EI): *m/z* = 451.13354 (calcd. 451.13319). – $C_{27}H_{18}FN_3O_3$ (451.45): calcd. C 71.83, H 4.02, N 9.31; found C 71.58, H 3.90, N 9.12.

Method (ii): The title compound was also prepared *via* hydrolysis of the respective ethyl ester **4b** (0.20 g, 0.42 mmol), following a similar procedure as described above in method (ii) for **5a**. Yield: 0.18 g (94 %).

*10-Cyclopropyl-5-fluoro-2,3-bis(4-methoxyphenyl)-7-oxo-7,10-dihydropyrido[2,3-f]quinoxaline-8-carboxylic acid (**5c**)*

Method (i): This compound was prepared from **3** (0.55 g, 2 mmol) and 4,4′-dimethoxybenzil (0.54 g, 2 mmol), follow-

ing a similar procedure as described above in method (i) for **5a**. Yield: 0.51 g (50 %), m. p. 283 – 285 °C. – IR (KBr): ν = 3434, 3081, 2978, 2933, 2836, 1727, 1625, 1602, 1514, 1467, 1360, 1304, 1255, 1174, 1135, 1027 cm^{-1}. – ^1H NMR (300 MHz, [D_7]DMF): δ = 1.20 (m, 2H) and 1.38 (m, 2H, 2′-H_2 + 3′-H_2), 3.86 (s, 3H) and 3.88 (s, 3H, C4″-OCH_3 and C4‴-OCH_3), 5.01 (m, 1H, 1′-H), 7.01 (d, J = 8.8 Hz, 2H) and 7.04 (d, J = 8.8 Hz, 2H, 3″-H + 5″-H and 3‴-H + 5‴-H), 7.71 (d, J = 8.8 Hz, 2H) and 7.77 (d, J = 8.8 Hz, 2H, 2″-H + 6″-H and 2‴-H + 6‴-H), 8.23 (d, $^3J_{H-F}$ = 10.1 Hz, 1H, 6-H), 9.04 (s, 1H, 9-H), 14.86 (br s, 1H, CO_2H). – ^{13}C NMR (75 MHz, [D_7]DMF): δ = 10.6 (C-2′ + C-3′), 43.7 (C-1′), 55.4, 55.5 (4″-OCH_3 and 4‴-OCH_3), 107.6 (d, $^2J_{C-F}$ = 20.9 Hz, C-6), 110.4 (C-8), 114.3, 114.4 (C-3″ + C-5″ and C-3‴ + C-5‴), 126.2 (d, $^3J_{C-F}$ = 7.5 Hz, C-6a), 130.6, 131.0 (C-1″ + C-1‴), 131.8, 132.0 (C-2″ + C-6″ and C-2‴ + C-6‴), 134.3 (d, $^2J_{C-F}$ = 14 Hz, C-4a), 134.7 (C-10b), 136.9 (d, $^4J_{C-F}$ = 2.1 Hz, C-10a), 150.4 (C-9), 150.5 (C-2), 153.4 (d, $^4J_{C-F}$ = 1.5 Hz, C-3), 155.2 (d, $^1J_{C-F}$ = 255 Hz, C-5), 161.3, 161.7 (C-4″ + C-4‴), 165.6 (CO_2H), 177.0 (d, $^4J_{C-F}$ = 2.9 Hz, C-7). – HRMS (ESI): *m/z* = 512.16162 (calcd. 512.16217 for $C_{29}H_{23}FN_3O_5^+$, $[M+H]^+$). – $C_{29}H_{22}FN_3O_5$ (511.50): calcd. C 68.10, H 4.34, N 8.22; found C 67.84, H 4.19, N 8.06.

Method (ii): Compound **5c** was also prepared *via* hydrolysis of the respective ethyl ester **4c** (0.43 g, 0.80 mmol), following a similar procedure as described above in method (ii) for **5a**. Yield: 0.37 g (91 %).

*2,3-Di(4-chlorophenyl)-10-cyclopropyl-5-fluoro-7-oxo-7,10-dihydropyrido[2,3-f]quinoxaline-8-carboxylic acid (**5d**)*

Method (i): This compound was prepared from **3** (0.55 g, 2 mmol) and 4,4′-dichlorobenzil (0.56 g, 2 mmol), following a similar procedure as described above in method (i) for **5a**. Yield: 0.61 g (60 %), m. p. 262 – 265 °C. – IR (KBr): ν = 3418, 3069, 3015, 2905, 1727, 1634, 1599, 1515, 1460, 1355, 1312, 1220, 1172, 1135, 1093, 1056, 1013 cm^{-1}. – ^1H NMR (300 MHz, [D_7]DMF): δ = 1.21 (m, 2H) and 1.37 (m, 2H, 2′-H_2 + 3′-H_2), 4.98 (m, 1H, 1′-H), 7.53 (d, J = 8.8 Hz, 2H) and 7.56 (d, J = 8.8 Hz, 2H, 3″-H + 5″ and 3‴-H + 5‴-H), 7.78 (d, J = 8.8 Hz, 2H, 2″-H + 6″-H), 7.81 (d, J = 8.8 Hz, 2H, 2‴-H + 6‴-H), 8.30 (d, $^3J_{H-F}$ = 10 Hz, 1H, 6-H), 9.06 (s, 1H, 9-H), 14.73 (br s, 1H, -CO_2H). – ^{13}C NMR (75 MHz, [D_7]DMF): δ = 10.5 (C-2′ + C-3′), 43.6 (C-1′), 108.3 (d, $^2J_{C-F}$ = 20.9 Hz, C-6), 110.4 (C-8), 126.5 (d, $^3J_{C-F}$ = 7.6 Hz, C-6a), 128.8, 128.9 (C-3″ + C-5″ and C-3‴ + C-5‴), 132.0 (C-2″ + C-6″), 132.1 (C-2‴ + C-6‴), 134.6 (d, $^2J_{C-F}$ = 14.3 Hz, C-4a), 135.0, 135.3 (C-1″ + C-1‴), 135.1 (d, $^3J_{C-F}$ = 1.3 Hz, C-10b), 136.7, 137.0 (C-4″ + C-4‴), 136.8 (d, $^4J_{C-F}$ = 2.5 Hz, C-10a), 150.0 (C-2), 150.6 (C-9), 152.9 (d, $^4J_{C-F}$ = 2 Hz, C-3), 154.8 (d, $^1J_{C-F}$ = 259 Hz, C-5), 165.4 (-CO_2H), 176.8 (d, $^4J_{C-F}$ = 2.8 Hz, C-7). – HRMS (ESI): *m/z* = 520.06265 (calcd. 520.06310 for $C_{27}H_{17}Cl_2FN_3O_3^+$, $[M+H]^+$), 542.04427 (calcd. 542.04504 for $C_{27}H_{16}Cl_2FN_3O_3Na^+$, $[M+Na]^+$). – $C_{27}H_{16}Cl_2FN_3O_3$ (520.35): calcd. C 62.32, H 3.10, Cl 13.63, N 8.08; found C 62.15, H 3.02, Cl 13.44, N 7.92.

Method (ii): Compound **5d** was also prepared *via* hydrolysis of the respective ethyl ester **4d** (0.38 g, 0.70 mmol), following a similar procedure as described above in method (ii) for **5a**. Yield: 0.34 g (94 %).

*10-Cyclopropyl-5-fluoro-7-oxo-2,3-di(p-tolyl)-7,10-dihydropyrido[2,3-f]quinoxaline-8-carboxylic acid (**5e**)*

Method (i): This compound was prepared from **3** (0.55 g, 2 mmol) and 4,4′-dimethylbenzil (0.48 g, 2 mmol), following a similar procedure as described above in method (i) for **5a**. Yield: 0.60 g (63 %), m. p. 315 – 316 °C (dec.). – IR (KBr): ν = 3438, 3058, 2922, 2856, 1726, 1631, 1608, 1558, 1506, 1462, 1352, 1317, 1240, 1183, 1015 cm^{-1}. – EIMS: *m/z* (%) = 479 (34) $[M]^+$, 461 (3), 451 (43), 435 (100), 420 (23), 407 (57), 379 (10), 353 (6), 263 (10), 247 (6), 195 (11), 179 (25), 132 (10), 119 (19). – HRMS (EI): *m/z* = 479.16119 (calcd. 479.16449). – $C_{29}H_{22}FN_3O_3$ (479.52): calcd. C 72.64, H 4.62, N 8.76; found C 72.38, H 4.48, N 8.58.

Method (ii): Compound **5e** was also prepared *via* hydrolysis of the respective ethyl ester **4e** (0.33 g, 0.65 mmol), following a similar procedure as described above in method (ii) for **5a**. Yield: 0.28 g (90 %).

*10-Cyclopropyl-5-fluoro-7-oxo-2,3-di(thien-2-yl)-7,10-dihydropyrido[2,3-f]quinoxaline-8-carboxylic acid (**5f**)*

Method (i): This compound was prepared from **3** (0.55 g, 2 mmol) and 2,2′-thenil (0.44 g, 2 mmol), following a similar procedure as described above in method (i) for **5a**. Yield: 0.60 g (65 %), m. p. 300 – 301 °C. – IR (KBr): ν = 3408, 3068, 2926, 2849, 1727, 1627, 1602, 1518, 1467, 1422, 1358, 1287, 1229, 1126, 1088 cm^{-1}. – ^1H NMR (300 MHz, [D_7]DMF): δ = 1.24 (m, 2H) and 1.43 (m, 2H, 2′-H_2 + 3′-H_2), 4.94 (m, 1H, 1′-H), 7.21 (center of two overlapped dd, 2H, 4″-H + 4‴-H), 7.60 (dd, J = 3.8, 1.0 Hz, 1H) and 7.68 (dd, J = 3.8, 1.0 Hz, 1H, 3″-H + 3‴-H), 7.94 (dd, J = 5.0, 1.0 Hz, 1H) and 7.98 (dd, J = 5.0, 1.0 Hz, 1H, 5″-H + 5‴-H), 8.24 (d, $^3J_{H-F}$ = 10.1 Hz, 1H, 6-H), 9.07 (s, 1H, 9-H), 14.86 (s, 1H, CO_2H). – ^{13}C NMR (75 MHz, [D_7]DMF): δ = 10.4 (C-2′ + C-3′), 43.5 (C-1′), 108.1 (d, $^2J_{C-F}$ = 21 Hz, C-6), 110.4 (C-8), 128.4, 128.5 (C-4″ + C-4‴), 130.1 (d, $^3J_{C-F}$ = 6.8 Hz, C-6a), 130.6, 131.2 (C-3″ + C-3‴), 131.3, 132.0 (C-5″ + C-5‴), 133.5 (C-10b), 134.2 (d, $^2J_{C-F}$ = 12.3 Hz, C-4a), 136.4 (d, $^4J_{C-F}$ = 2.1 Hz, C-10a), 140.6, 141.0 (C-2″ + C-2‴), 143.5 (C-2), 144.1 (d, $^4J_{C-F}$ = 2.6 Hz, C-3), 150.5 (C-9), 154.5 (d, $^1J_{C-F}$ =

258 Hz, C-5), 165.4 (CO_2H), 176.8 (d, $^4J_{C-F}$ = 2.4 Hz, C-7). – HRMS (ESI): *m/z* = 464.05330 (calcd. 464.05389 for $C_{23}H_{15}FN_3O_3S_2^+$, $[M+H]^+$). – $C_{23}H_{14}FN_3O_3S_2$ (463.51): calcd. C 59.60, H 3.04, N 9.07, S 13.84; found C 59.38, H 2.96, N 9.02, S 13.56.

Method (ii): Compound **5f** was also prepared *via* hydrolysis of the respective ethyl ester **4f** (0.36 g, 0.73 mmol), following a similar procedure as described above in method (ii) for **5a**. Yield: 0.31 g (92 %).

*10-Cyclopropyl-5-fluoro-2,3-di(furan-2-yl)-7-oxo-7,10-dihydropyrido[2,3-f]quinoxaline-8-carboxylic acid (**5g**)*

Method (i): This compound was prepared from **3** (0.55 g, 2 mmol) and α-furil (0.38 g, 2 mmol), following a similar procedure as described above in method (i) for **5a**. Yield: 0.51 g (60 %), m. p. 290 – 293 °C. – IR (KBr): ν = 3441, 3139, 2926, 2856, 1720, 1626, 1603, 1534, 1524, 1449, 1349, 1312, 1126, 1075, 1030 cm^{-1}. – ^{1}H NMR (300 MHz, [D$_7$]DMF): δ = 1.21 (m, 2H) and 1.40 (m, 2H, 2′-H$_2$ + 3′-H$_2$), 4.98 (m, 1H, 1′-H), 6.81 (dd, *J* = 1.8, 3.5 Hz, 1H) and 6.83 (dd, *J* = 1.8, 3.5 Hz, 1H, 4″-H + 4‴-H), 7.18 (dd, *J* = 0.7, 3.5 Hz, 1H) and 7.19 (dd, *J* = 0.7, 3.5 Hz, 1H, 3″-H + 3‴-H), 7.99 (dd, *J* = 0.7, 1.8 Hz, 1H) and 8.04 (dd, *J* = 0.7, 1.8 Hz, 1H, 5″-H + 5‴-H), 8.25 (d, $^3J_{H-F}$ = 10.1 Hz, 1H, 6-H), 9.06 (s, 1H, 9-H), 14.88 (s, 1H, CO_2H). – ^{13}C NMR (75 MHz, [D$_7$]DMF): δ = 10.5 (C-2′ + C-3′), 43.7 (C-1′), 108.0 (d, $^2J_{C-F}$ = 20.9 Hz, C-6), 110.4 (C-8), 112.8, 112.9 (C-4″ + C-4‴), 115.0, 115.7 (C-5″ + C-5‴), 126.3 (d, $^3J_{C-F}$ = 7.7 Hz, C-6a), 134.0 (d, $^2J_{C-F}$ = 14.0 Hz, C-4a), 136.5 (d, $^4J_{C-F}$ = 2.9 Hz, C-10a), 138.9 (C-10b), 141.8, 141.9 (C-2″ + C-2‴), 146.2, 146.6 (C-3″ + C-3‴), 150.4, 150.6 (C-2 + C-3), 150.5 (C-9), 154.6 (d, $^1J_{C-F}$ = 259 Hz, C-5), 165.4 (CO_2H), 176.7 (d, $^4J_{C-F}$ = 2.9 Hz, C-7). – EIMS: *m/z* (%) = 431 (32) $[M]^+$, 413 (3), 403 (34), 387 (100), 372 (14), 359 (52), 330 (12), 305 (10), 302 (9), 283 (22), 233 (15), 197 (9), 176 (8), 132 (9). – HRMS (EI): *m/z* = 431.09100 (calcd. 431.09171). – $C_{23}H_{14}FN_3O_5$(431.37): calcd. C 64.04, H 3.27, N 9.74; found C 63.86, H 3.14, N 9.58.

Method (ii): Compound **5g** was also prepared *via* hydrolysis of the respective ethyl ester **4g** (0.26 g, 0.57 mmol), following a similar procedure as described above in method (ii) for **5a**. Yield: 0.23 g (94 %).

*10-Cyclopropyl-5-fluoro-2,3-di(pyridin-2-yl)-7-oxo-7,10-dihydropyrido[2,3-f]quinoxaline-8-carboxylic acid (**5h**)*

Method (i): This compound was prepared from **3** (0.55 g, 2 mmol) and 2,2′-pyridil (0.42 g, 2 mmol), following a similar procedure as described above in method (i) for **5a**. Yield: 0.63 g (70 %), m. p. 296 – 298 °C (dec., darkens at 276 °C). – IR (KBr): ν = 3447, 3074, 3010, 2920, 2849, 1722, 1632, 1603, 1569, 1469, 1425, 1360, 1314, 1133, 1075, 1023 cm^{-1}. – ^{1}H NMR (300 MHz, [D$_7$]DMF): δ = 1.25 (m, 2H) and 1.42 (m, 2H, 2′-H$_2$ + 3′-H$_2$), 5.02 (m, 1H, 1′-H), 7.46 (m, 2H, 5″-H + H-5‴), 8.01 (ddd, *J* = 7.8, 7.7, 1.6 Hz, 1H) and 8.08 (ddd, *J* = 7.9, 7.7, 1.5 Hz, 1H, 4″-H + 4‴-H), 8.24 (d, *J* = 7.7 Hz, 1H) and 8.31 (d, *J* = 7.8 Hz, 1H, 3″-H + 3‴-H), 8.34 (d, *J* = 7.7 Hz, 1H) and 8.36 – 8.43 (br overlapping, 3H, 6″-H + 6‴-H and 6-H), 9.09 (s, 1H, 9-H), 14.81 (s, 1H, CO_2H). – ^{13}C NMR (75 MHz, [D$_7$]DMF): δ = 10.7 (C-2′ + C-3′), 43.9 (C-1′), 108.8 (d, $^2J_{C-F}$ = 20.9 Hz, C-6), 110.6 (C-8), 124.1, 124.3 (C-5″ + C-5‴), 124.4, 124.5 (C-3″ + C-3‴), 126.9 (d, $^3J_{C-F}$ = 7.8 Hz, C-6a), 134.6 (d, $^2J_{C-F}$ = 15.8 Hz, C-4a), 135.1 (C-10b), 136.9 (d, $^4J_{C-F}$ = 2.6 Hz, C-10a), 137.4, 137.5 (C-4″ + C-4‴), 148.8, 148.9 (C-6″ + C-6‴), 150.6 (C-2), 150.8 (C-9), 153.7 (d, $^4J_{C-F}$ = 1.9 Hz, C-3), 155.0 (d, $^1J_{C-F}$ = 259 Hz, C-5), 156.7, 156.8 (C-2″ + C-2‴), 165.5 (CO_2H), 176.9 (d, $^4J_{C-F}$ = 2.8 Hz, C-7). – EIMS: *m/z* (%) = 453 (100) $[M]^+$, 410 (9), 409 (38), 381 (37), 353 (9), 331 (26), 305 (3), 203 (10), 177 (4). – HRMS (ESI): *m/z* = 454.13097 (calcd. 454.13154 for $C_{25}H_{17}FN_5O_3^+$, $[M+H]^+$). – $C_{25}H_{16}FN_5O_3$ (453.42): calcd. C 66.22, H 3.56, N 15.45; found C 66.04, H 3.52, N 15.26.

Method (ii): A vigorously stirred suspension of **4h** (0.30 g, 0.62 mmol) in 12 % HCl (45 mL) and ethanol (15 mL) was heated at 80 – 85 °C under reflux. Progress of the ester hydrolysis was monitored by TLC and was completed within 2 – 3 h. Thereafter the reaction mixture was cooled, then poured onto ice-water and basified with a saturated aqueous solution of sodium hydrogen carbonate. The resulting precipitate was collected, washed with water and dried. Yield: 0.25 g (89 %).

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[17] The difuryl derivatives (**4g**, **5g**) are exceptions whereby C-3 resonates in the range δ = 144.0 – 146.4 ppm, and C-2 in the range δ = 143.0 – 143.5 ppm.