Synthesis of Some Ethyl 3-(Aryldiazenyl)-7-oxo-dihydropyrido[2,3-*f*]quinoxaline-8-carboxylates

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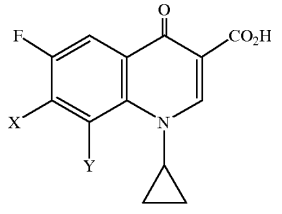
Ethyl 7,8-diamino-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylate (**6**) and its free acid **7** are prepared by chemical reduction of the respective 7-azido-8-nitroquinoline **5**. Consecutive nucleophilic addition and cyclocondensation reactions of **6** with α-acetyl-*N*-arylhydrazonoyl chlorides **8a – c** in ethanol and triethylamine are site-selective and yield the corresponding 3-(aryldiazinyl)-2-methylpyrido[2,3-*f*]quinoxalines **10a – c**. Analytical and spectral (IR, MS, NMR) data of **6**, **7**, and **10a – c** are in conformity with the assigned structures.

Key words: 7,8-Diamino-4-oxoquinoline-3-carboxylate, α-Acetyl-*N*-arylhydrazonoyl Chlorides, Ethyl 7-Oxopyrido[2,3-*f*]quinoxaline-8-carboxylates

Introduction

The quinoxaline system in its 2-quinoxalinylcarbonyl form is found appended to the cyclic peptide core of quinomycins related to naturally occurring quinoxaline-peptide antibiotics that also exhibit antitumor activity [1, 2]. Numerous quinoxaline derivatives have attracted attention owing to their biological importance and have been synthesized by many research groups [3 – 5]. Examples include species with antifungal [6], anticancer [7] and antituberculosis [8] activities as well as adenosine-binding [9] and benzodiazepine receptor binding [10] properties. On the other hand, synthetic second generation "floroquinolones" [11 – 13], exemplified by ciprofloxacin **1** [13], represent a major class of antibacterial agents with great therapeutic potential, while some related derivatives, such as **2** [14], exhibit antitumor activity [14, 15].

In the present study, we wish to report on the synthesis and properties of 4-oxopyridine-3-carboxylic acid condensed with a substituted quinoxaline entity (compounds **10a – c**) as depicted in Scheme 3. This tricyclic system, namely, ethyl 10-cyclopropyl-5-fluoro-2-methyl-7-oxo-3-(aryldiazenyl)-7,10-dihydropyrido[2,3-*f*]quinoxaline-8-carboxylate encompasses



1 (X = 1-piperazinyl; Y = H)
2 (X = *p*-(OH)C_6H_4; Y = F)

the structural features of both, fluoroquinolone (rings **A**, **B**) and substituted quinoxaline (rings **B**, **C**) chemotypes. Such hybrid heterocyclic systems might exhibit interesting bioproperties. In this context, it is worth mentioning that two 7-oxo-7,10-dihydropyrido[2,3-*f*]quinoxaline-8-carboxylic acid derivatives (**3a**, **3b**), lacking an *N*-10 substituent, were once prepared [16] by annulation of the pyridine moiety onto the appropriate 5-aminoquinoxaline *via* the Gould-Jacobs reaction (Scheme 1).

Results and Discussion

Ethyl 7-chloro-1-cyclopropyl-6-fluoro-8-nitro-6-oxo-1,4-dihydroquinoline-3-carboxylate (**4**) [17, 18]

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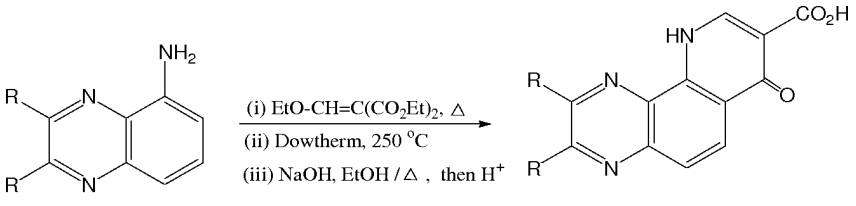
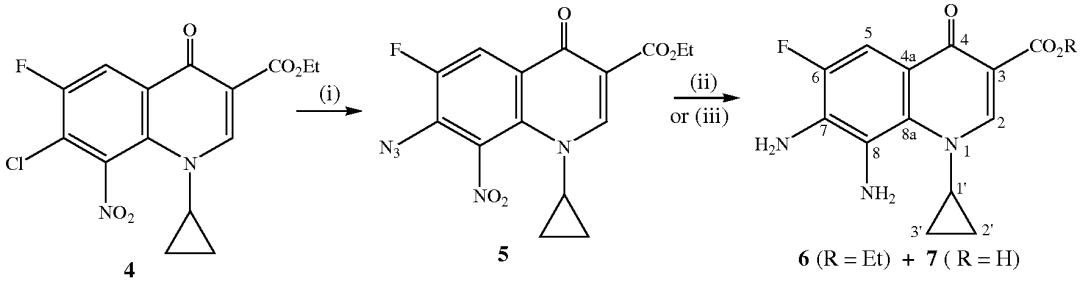


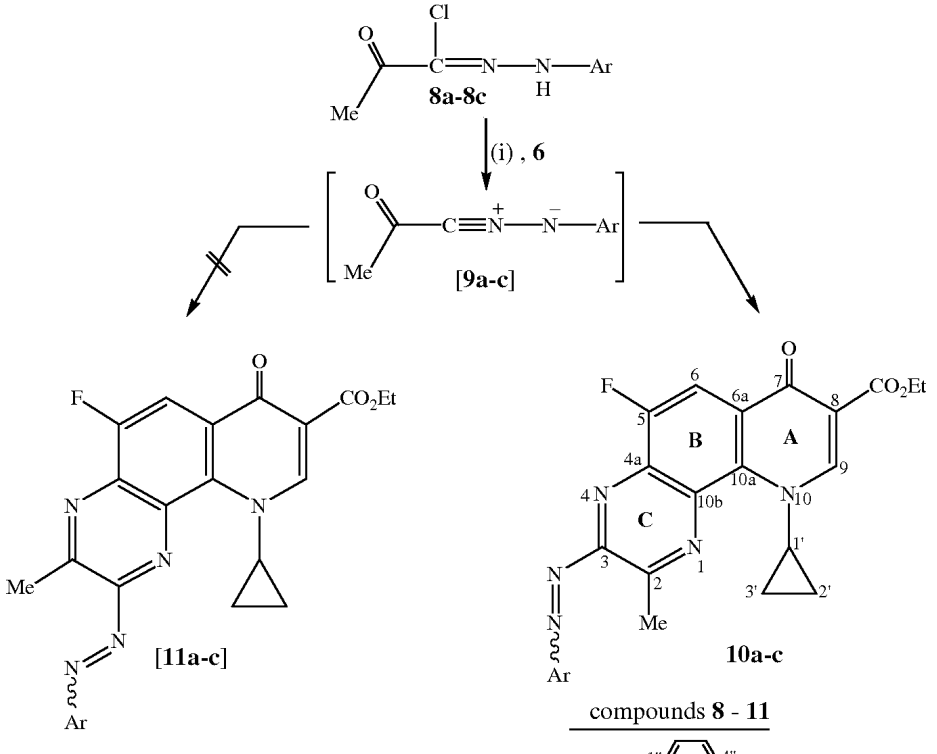
3(**a**: R = H; **b**: R = Ph)

Scheme 1.



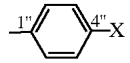
(i) NaN_3, Me_2SO, rt (ii) $SnCl_2$, EtOH, rt, 30-40 min / then reflux (iii) Sn + 3N HCl + EtOH / reflux

Scheme 2.



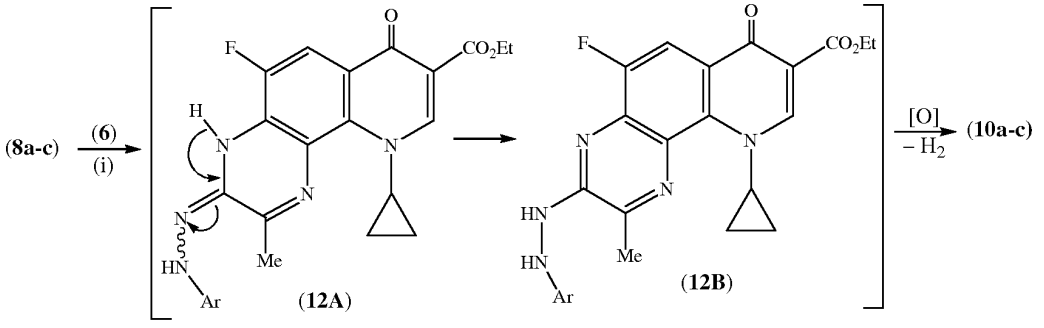
(i) EtOH, NEt_3 / Δ

compounds **8** - **11**

Ar = 

entry	**a**	**b**	**c**
X	H	Me	Cl

Scheme 3.



(i) as in Scheme 2

Scheme 4.

was readily converted into the corresponding 7-azido-8-nitroquinoline ester **5** following a reported procedure [19] (Scheme 2). Chemical reduction of **5** with stannous chloride in boiling ethanol furnished the corresponding 7,8-diaminoquinoline ester **6** together with the 7,8-diaminoquinoline-3-carboxylic acid **7** which was isolated in a separate step as detailed in the Experimental Section. Comparable results were obtained upon reduction of **5** with tin and 3N aqueous hydrochloric acid under reflux conditions, wherein **7** is produced in higher proportion than **6** (Scheme 2). The formation of **7** is the result of partial hydrolysis of the ester **6** as catalyzed by the prevailing acidic reduction conditions under reflux.

Direct interaction of the 7,8-diaminoquinoline ester **6** with each of the α-acetyl-*N*-arylhydrazonoyl chlorides **8a – c** in ethanol and triethylamine under reflux yielded the respective 3-arylazo-2-methylpyrido[2,3-*f*]quinoxalines **10a – c** regioselectively as the main isolable end products (Scheme 3). The synthon **6** with its 7,8-diamino groups acts as a bis-nucleophile, whilst the α-acetylnitrile imine 1,3-dipolar species **9a – c** (generated *in situ* from the respective precursors **8a – c**) act as bis-electrophiles. This reaction was modeled after the recently described interaction between *o*-diaminobenzene and α-acetylnitrile imine 1,3-dipolar species [20]. Such one-pot cyclocondensation processes are reminiscent of the known cyclization reactions of α-acetylnitrile imines towards various nucleophilic compounds for which some recent reviews were published [21, 22].

It is noteworthy that none of the 3-arylazo-2-methyl structural isomers **11a – c** (Scheme 3) were isolated in the process. The cyclization reaction thus appears to be site-selective, at least under the conditions employed, and to proceed *via* condensation of the more nucleophilic 8-amino group in **6** with the electrophilic keto group in **9a – c**. This step is followed by intramolecular 1,3-nucleophilic addition involving the 7-amino group and the electrophilic carbon atom of the nitrile imine. Ultimately, these consecutive steps would lead to the initial formation of the respective 3-(*N*-arylhydrazono)-1,2,7,10-tetrahydropyrido[2,3-*f*]quinoxalines **12A** which probably are in equilibrium with their 3-(*N*-arylhydrazono) tautomeric forms **12B** (Scheme 4). However, no attempt was made to isolate the intermediate free bases **12A** which are expected to be unstable upon contact with air oxygen and easily undergo oxidation (*via* **12B**) into the respective 3-arylazo derivatives **10a – c**.

The IR, MS and NMR spectral data of **6**, **7**, and **10a – c**, given in the Experimental Section, are in accordance with the suggested structures. Thus, their MS spectra display the correct molecular ion peaks for which the measured HRMS data are in good agreement with the values calculated for the molecular formulae. 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. Thus, strong 1,3-correlation is observed between the methyl protons of 2-Me at C-2 and C-3 which features as a doublet due to coupling with the fluorine atom; conversely, a much weaker 1,2-correlation is observed with the singlet signal of C-2. Such correlations are compatible with the structures **10a – c**. Long-range correlations are also observed between 9-H and each of *C*O$_2$Et, C-7, C-10a and C-1′, as well as between 6-H and each of C-7, C-4a and C-10a, and between 1′-H and each of C-9 and C-10a. In compounds **6** and **7**, corresponding long-range correlations are also observed between 2-H, 5-H and their neighbor carbons.

Experimental Section

2,4-Dichloro-5-fluoro-3-nitrobenzoic acid, ethyl 3-(*N*,*N*-dimethylamino)acrylate, cyclopropylamine and 3-chloropentane-2,4-dione were purchased from Acros. Melting points were determined on a Gallenkamp electrothermal melting-temperature apparatus. ^{1}H and ^{13}C NMR spectra were measured 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 and an ion source temperature of 200 °C. IR spectra were recorded as KBr discs on a Nicolet Impact-400 FT-IR spectrophotometer. Microanalyses were performed at the Microanalytical Laboratory of the Hashemite University, Zarqa, Jordan, and the results agreed with the calculated values within experimental error (±0.4 %).

*1-(N-Arylhydrazono)-1-chloropropanones (**8a – c**)*

These hydrazonoyl chlorides **8a** [23, 24], **8b** [23] and **8c** [23, 24] were previously characterized and were prepared in this study *via* the Japp-Klingemann reaction [25] which involves direct coupling of the appropriate arenediazonium chloride with 3-chloropentane-2,4-dione in aqueous pyridine, following standard procedures [23].

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

This synthon was prepared from 2,4-dichloro-5-fluoro-3-nitrobenzoic acid, ethyl 3-(*N*,*N*-dimethylamino)acrylate and cyclopropylamine by adopting the stepwise synthetic procedures reported [17] for the methyl ester analog; m.p. 175 – 176 °C (dec.) (ref. [18] 174 – 176 °C).

*Ethyl 7-azido-1-cyclopropyl-6-fluoro-8-nitro-4-oxo-1,4-dihydroquinoline-3-carboxylate (**5**)*

This intermediate was prepared *via* interaction of sodium azide and the corresponding 7-chloro-8-nitro-1,4-dihydroquinoline **4**, in dimethylsulfoxide at ambient temperature, according to a recently reported procedure [19].

*Ethyl 7,8-diamino-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylate (**6**) and the corresponding 3-carboxylic acid (**7**)*

Method (i): To a stirred solution of **5** (1.28 g, 3.6 mmol) in absolute ethanol (100 mL) was added portionwise stannous chloride dihydrate (6.6 g, 29.2 mmol). The reaction mixture was stirred at r. t. for additional 30 – 40 min and then heated under reflux for 6 h.

The resulting mixture was then poured onto crushed ice (80 g), basified with a saturated aqueous solution of sodium hydrogen carbonate and extracted with ethyl acetate (2 × 40 mL). The combined organic extracts were dried ($MgSO_4$), the solvent was evaporated *in vacuo* and the residual solid product recrystallized from chloroform / pet. ether (b. p. 40 – 60 °C) to deliver 0.37 g (37 %) of the diamino ester **6**, m. p. 284 – 286 °C (dec.). – IR (KBr): ν = 3462 (br), 3389, 3295, 3081, 2977, 1718, 1672, 1612, 1561, 1461, 1343, 1279, 1232, 1178, 1129, 1035 cm^{-1}. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.88 [(m, 2H) and 1.08 (m, 2H), 2′-H_2 + 3′-H_2)], 1.21 (t, J = 7.1 Hz, 3H, CH_3CH$_2$), 4.14 (q, J = 7.1 Hz, 2H, CH_2Me), 4.30 (m, 1H, 1′-H), 5.05 (s, 2H, C8-NH_2), 5.43 (s, 2H, C7-NH_2), 7.19 (d,$^3J_{H-F}$ =11.2 Hz, 1H, 5-H), 8.39 (s, 1H, 2-H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 10.6 (C-2′ + C-3′), 14.8 (*C*H$_3$CH$_2$), 38.5 (C-1′), 60.0 (*C*H$_2$Me), 100.6 (d, $^2J_{C-F}$ = 21 Hz, C-5), 107.9 (C-3), 120.3 (d, $^3J_{C-F}$ = 7.2 Hz, C-4a), 125.7 (d, $^3J_{C-F}$ = 5.9 Hz, C-8), 127.3 (C-8a), 129.3 (d, $^2J_{C-F}$ = 15.8 Hz, C-7), 149.8 (d, $^1J_{C-F}$ = 235 Hz, C-6), 151.2 (C-2), 165.1 (*C*O$_2$Et), 172.6 (d, $^4J_{C-F}$ = 2.7 Hz, C-4). – $C_{15}H_{16}FN_3O_3$ (305.30): calcd. C 59.01, H 5.28, N 13.76; found C 58.79, H 5.33, N 13.45.

The aqueous layer was acidified with 3N HCl and extracted with ethyl acetate (2 × 40 mL). The combined organic extracts were evaporated *in vacuo*, and the residual solid product was recrystallized from chloroform / methanol (1 : 1, v / v) and identified as the corresponding 3-carboxylic acid **7**. Yield: 0.36 g (36 %), m. p. 295 – 296 °C. – IR (KBr): ν = 3421 (br), 3238, 3061, 2920, 2831, 1712, 1688, 1606, 1545, 1488, 1457, 1321, 1267, 1206, 1168, 1035 cm^{-1}. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.99 [(m, 2H) and 1.15 (m, 2H), 2′-H_2 + 3′-H_2)], 4.46 (m, 1H, 1′-H), 5.23 (s, 2H, C8-NH_2), 5.83 (s, 2H, C7-NH_2), 7.32 (d,$^3J_{H-F}$ =10.9 Hz, 1H, 5-H), 8.59 (s, 1H, 2-H), 15.47 (s, 1H, CO_2H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 10.7 (C-2′ + C-3′), 39.8 (C-1′), 100.0 (d, $^2J_{C-F}$ = 21.2 Hz, C-5), 105.5 (C-3), 116.7 (d, $^3J_{C-F}$ = 8.6 Hz, C-4a), 125.8 (d, $^3J_{C-F}$ = 6.4 Hz, C-8), 128.1 (C-8a), 131.2 (d, $^2J_{C-F}$ = 15.6 Hz, C-7), 150.0 (d, $^1J_{C-F}$ = 238 Hz, C-6), 150.5 (C-2), 166.8 (*C*O$_2$H), 177.2 (d, $^4J_{C-F}$ = 3.5 Hz, C-4). – $C_{13}H_{12}FN_3O_3$ (277.25): calcd. C 56.32, H 4.36, N 15.16; found C 56.48, H 4.42, N 15.02.

Method (ii): Tin granules (5.9 g, 0.05 gram atom) were introduced into a stirred solution of **5** (1.28 g, 3.6 mmol) in 3N HCl. Thereafter, the resulting mixture was heated under reflux and became turbid. Ethanol was added to the turbid reaction mixture until a clear solution was obtained whilst heating under reflux was continued for 4 h. The resulting mixture was then poured onto crushed ice (80 g) and worked up as described in method (i) above for the diamino ester **6**. Yield: 0.29 g (29 %).

The aqueous layer was acidified with 3N HCl and worked up as described in method (i) above for the isolation of the 7,8-diamino acid **7**. Yield: 0.41 g (41 %).

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

A stirred mixture of 1-chloro-1-(*N*-phenylhydrazono)-propanone (**8a**) (0.43 g, 2.2 mmol) and ethyl 7,8-diamino-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylate (**6**, 0.56 g, 2 mmol) in ethanol (40 mL) and chloroform (2 mL) was treated at r. t. with triethylamine (2 mL). The resulting reaction mixture was then brought slowly to gentle reflux for 3 – 4 h. Thereafter, the reaction mixture was cooled (~ 0 °C), and the precipitated product was collected and purified on preparative silica gel TLC plates, eluting with chloroform plus methanol (98 : 2, v / v). Yield: 0.32 g (36 %), m. p. 271 – 272 °C (dec.). – IR (KBr): ν = 3433 (br), 3081, 2972, 2920, 2865, 1730, 1690, 1629, 1543, 1467, 1323, 1290, 1231, 1138, 1033 cm^{-1}. – EIMS: *m/z* (%) = 445 (28) $[M]^+$, 417 (8), 416 (12), 373 (39), 372 (26), 356 (17), 345 (19), 328 (10), 284 (60), 283 (40), 253 (31), 214 (12), 184 (15), 149 (24), 105 (30), 93 (100), 77 (81). – HRMS: calcd. 445.1550; found 445.1501. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.97 [(m, 2H) and 1.28 (m, 2H), 2′-H_2 + 3′-H_2)], 1.42 (t, *J* = 7.1 Hz, 3H, CH_3CH$_2$), 2.98 (s, 3H, C2-CH_3), 4.42 (q, *J* = 7.1 Hz, 2H, CH_2Me), 4.74 (m, 1H, 1′-H), 7.59 (m, 3H, 3″-H + 5″-H and 4″-H), 8.09 (dd, *J* = 8.0, 2.2 Hz, 2H, 2″-H + 6″-H), 8.42 (d, $^3J_{H-F}$ = 10 Hz, 1H, 6-H), 8.82 (s, 1H, 9-H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.1 (C-2′ + C-3′), 14.5 (*C*H_3CH$_2$), 21.8 (C2-*C*H_3), 42.5 (C-1′), 61.3 (*C*H_2Me), 110.6 (d, $^2J_{C-F}$ = 20.5 Hz, C-6), 112.7 (C-8), 124.2 (C-2″ + C-6″), 129.4 (C-3″ + C-5″), 130.0 (d, $^3J_{C-F}$ = 6.8 Hz, C-6a), 133.6 (C-4″), 134.4 (d, $^4J_{C-F}$ = 2 Hz, C-10a), 134.5 (d, $^2J_{C-F}$ = 13.7 Hz, C-4a), 136.5 (C-10b), 149.4 (C-2), 150.4 (C-9), 153.1 (C-1″), 155.0 (d, $^1J_{C-F}$ = 260 Hz, C-5), 155.5 (d, $^4J_{C-F}$ = 1.5 Hz, C-3), 165.3 (*C*O_2Et), 172.4 (d, $^4J_{C-F}$ = 1.6 Hz, C-7). – C_{24} H_{20} F N_5 O_3: calcd. C 64.71, H 4.53, N 5.72; found C 64.52, H 4.51, N 15.58.

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

This compound was prepared from **8b** (0.46 g, 2.2 mmol) and **6** (0.56 g, 2 mmol), following a similar procedure as noted above for the preparation of **10a**. Yield: 0.35 g (38 %), m. p. 260 – 261 °C (dec.). – IR (KBr): ν = 3447 (br), 3325, 3094, 2990, 2971, 2933, 2887, 1719, 1623, 1598, 1464, 1318, 1292, 1162, 1137, 1031 cm^{-1}. – EIMS: *m/z* (%) = 459 (7) $[M]^+$, 431 (3), 430 (3), 403 (6), 387 (13), 356 (24), 328 (14), 311 (6), 284 (64), 283 (39), 256 (25), 253 (19), 209 (15), 188 (9), 132 (6), 119 (32), 107 (77), 106 (100), 91 (86). – HRMS: calcd. 459.1706; found 459.1675. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.97 [(m, 2H) and 1.28 (m, 2H), 2′-H_2 + 3′-H_2)], 1.42 (t, *J* = 7.1 Hz, 3H, CH_3CH$_2$), 2.47 (s, 3H, C4″-CH_3), 2.98 (s, 3H, C2-CH_3), 4.42 (q, *J* = 7.1 Hz, 2H, CH_2Me), 4.74 (m, 1H, 1′-H), 7.37 (d, *J* = 8.2, 2H, 3″-H + 5″-H), 8.01 (d, *J* = 8.2 Hz, 2H, 2″-H + 6″-H), 8.42 (d, $^3J_{H-F}$ = 10 Hz, 1H, 6-H), 8.82 (s, 1H, 9-H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.0 (C-2′ + C-3′), 14.5 (*C*H_3CH$_2$), 21.8 (C4″-*C*H_3), 21.9 (C2-*C*H_3), 42.4 (C-1′), 61.3 (*C*H_2Me), 110.5 (d, $^2J_{C-F}$ = 20.5 Hz, C-6), 112.7 (C-8), 124.3 (C-2″ + C-6″), 129.9 (d, $^3J_{C-F}$ = 6.8 Hz, C-6a), 130.1 (C-3″ + C-5″), 134.4 (d, $^4J_{C-F}$ = 2.9 Hz, C-10a), 134.5 (d, $^2J_{C-F}$ = 14.1 Hz, C-4a), 136.4 (C-10b), 144.9 (C-4″), 149.5 (C-2), 150.3 (C-9), 151.5 (C-1″), 155.0 (d, $^1J_{C-F}$ = 260 Hz, C-5), 155.6 (d, $^4J_{C-F}$ = 2 Hz, C-3), 165.4 (*C*O_2Et), 172.4 (d, $^4J_{C-F}$ = 2.4 Hz, C-7). – C_{25} H_{22} F N_5 O_3: calcd. C 65.35, H 4.83, N 15.24; found C 65.12, H 4.74, N 15.06.

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

This compound was prepared from **8c** (0.51 g, 2.2 mmol) and **6** (0.56 g, 2 mmol), following a similar procedure as noted above for the preparation of **10a**. Yield: 0.41 g (43 %), m. p. 267 – 268 °C. – IR (KBr): ν = 3428 (br), 3074, 3002, 2967, 2849, 1719, 1622, 1524, 1465, 1290, 1161, 1135, 1085 cm^{-1}. – EI MS: *m/z* (%) = 479 (12) $[M]^+$, 450 (6), 407 (35), 378 (7), 356 (22), 328 (14), 311 (7), 284 (100), 256 (32), 253 (22), 213 (14), 186 (11), 139 (25), 127 (75), 111 (79). – HRMS: calcd. 479.1160; found 479.1102. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.98 [(m, 2H) and 1.28 (m, 2H), 2′-H_2 + 3′-H_2)], 1.42 (t, *J* = 7.2 Hz, 3H, CH_3CH$_2$), 2.99 (s, 3H, C2-CH_3), 4.41 (q, *J* = 7.2 Hz, 2H, CH_2Me), 4.73 (m, 1H, 1′-H), 7.55 (d, *J* = 8.7 Hz, 2H, 3″-H + 5″-H), 8.05 (d, *J* = 8.7 Hz, 2H, 2″-H + 6″-H), 8.42 (d, $^3J_{H-F}$ = 10 Hz, 1H, 6-H), 8.82 (s, 1H, 9-H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.1 (C-2′ + C-3′), 14.5 (*C*H_3CH$_2$), 21.9 (C2-*C*H_3), 42.5 (C-1′), 61.3 (*C*H_2Me), 110.7 (d, $^2J_{C-F}$ = 20.8 Hz, C-6), 112.7 (C-8), 125.4 (C-2″ + C-6″), 129.8 (C-3″ + C-5″), 130.1 (d, $^3J_{C-F}$ = 6.8 Hz, C-6a), 134.4 (d, $^4J_{C-F}$ = 2.9 Hz, C-10a), 134.5 (d, $^2J_{C-F}$ = 14.1 Hz, C-4a), 136.7 (C-10b), 140.0 (C-4″), 149.6 (C-2), 150.4 (C-9), 151.4 (C-1″), 155.0 (d, $^1J_{C-F}$ = 260 Hz, C-5), 155.1 (d, $^4J_{C-F}$ = 2 Hz, C-3), 165.3 (*C*O_2Et), 172.4 (d, $^4J_{C-F}$ = 2.3 Hz, C-7). – C_{24} H_{19} Cl F N_5 O_3 (479.89): calcd. C 60.07, H 3.99, N 14.59; found C 59.88, H 3.86, N 14.45.

Acknowledgement

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