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HETEROCYCLES [*h*]FUSED ON 4-OXOQUINOLINE-3-CARBOXYLIC ACID, II.[1] A FACILE SYNTHESIS OF SOME 2,7-DIOXO[1,4]-THIAZIN[2,3-*h*]QUINOLINE-8-CARBOXYLIC ACIDS

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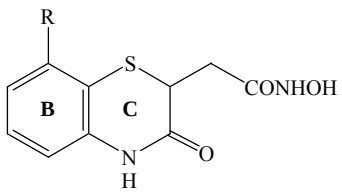
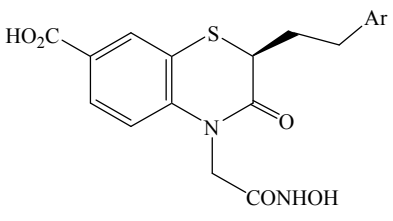
Abstract– Model tetrahydro[1,4]thiazino[2,3-*h*]quinoline-8-carboxylic acids (**7a-c**) are synthesized *via* reductive lactamisation, using sodium dithionite, of the respective 7-[(carboxyalkyl)thio]-8-nitro-1,4-dihydroquinolines (**5a-c**). The latter compounds are made accessible *via* the reaction of 7-chloro-1-cyclopropyl-6-flouro-8-nitro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (**4**) with each of α-mercaptoacetic, α-mercaptopropionic and α-mercaptosuccinic acids in aqueous ethanol and triethylamine. The suggested structures of **5a-c** and **7a-c** are supported by microanalytical and spectral (IR, MS, NMR) data.

INTRODUCTION

Chemical and pharmacological properties of 1,4-benzothiazines have been widely studied.[2] In particular, some 1,4-benzothiazines exhibit convincing antifungal activity,[3] but rather moderate antimicrobial potency.[4] Certain derivatives, e.g. **1a, 1b** (Figure 1), are reported as excellent inhibitors of Nickel peptide deformylase (Ni-PDF) and showed improved antibacterial potency,[5] while others exhibited anti-inflammatory potency, e.g. **2**,[6] *in vivo* antitumor efficacy,[7] or against neuro-degenerative diseases such as Parkinson's disease and Alzheimer disease.[8] On the other hand, synthetic second generation "fluoroquinolones", exemplified by ciprofloxacin (**3** / Figure 1),[9] have become one of the most promising groups of antibacterial drugs. Time and again, these bio-properties stimulated interest in the search for new substituted fluoroquinolones, 1,4-benzothiazin-3-ones and their congeners.



1a (R = H)
1b (R = Br)



2 (Ar = *p*-(MeO) C_6H_4)

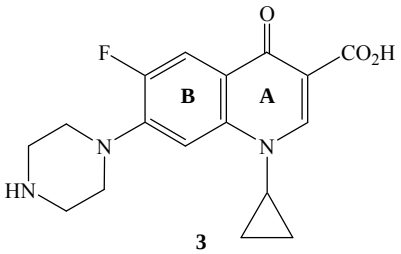


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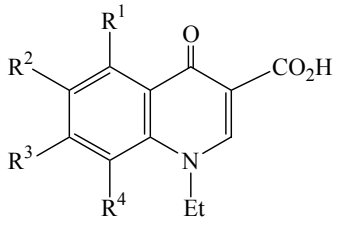
Figure 1

The present work aims at the synthesis and characterization of some new [1,4]thiazino[2,3-*h*]quinoline-8-carboxylic acid derivatives (**7a-c**) as outlined in Scheme 1. This latter hybrid tricyclic system encompasses the structural features of both ″fluoroquinolone″ (rings **A, B**) and dihydro-1,4-benzothiazine-4-one (rings **B, C**) chemotypes, and derivatives thereof (**7a-c**) might be anticipated to exhibit interesting bio-properties, such as antimicrobial activity. A number of non-fluorinated 1,4-thiazinoquinoline-carboxylic acids (**8** / Figure 2) were prepared[10] by a different route utilizing appropriately substituted amino-1,4-benzothiazin-3-ones and annulating the pyridone entity thereupon *via* interaction with diethyl ethoxymethylenemalonate under the Gould-Jacobs reaction conditions. Also, another related series (**9** / Figure 2) was likewise prepared[11] using suitably substituted tetrahydro-1,4-benzothiazines. Some derivatives of **8** and **9** were reported to exhibit appreciable antibacterial activity.[10,11]



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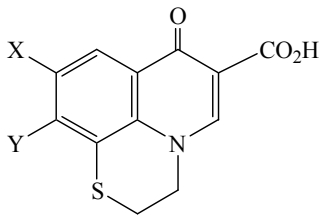
(R^1R^2, R^2R^1, R^2R^3, R^3R^2, R^3R^4, R^4R^3 = -SCH_2CONH-)



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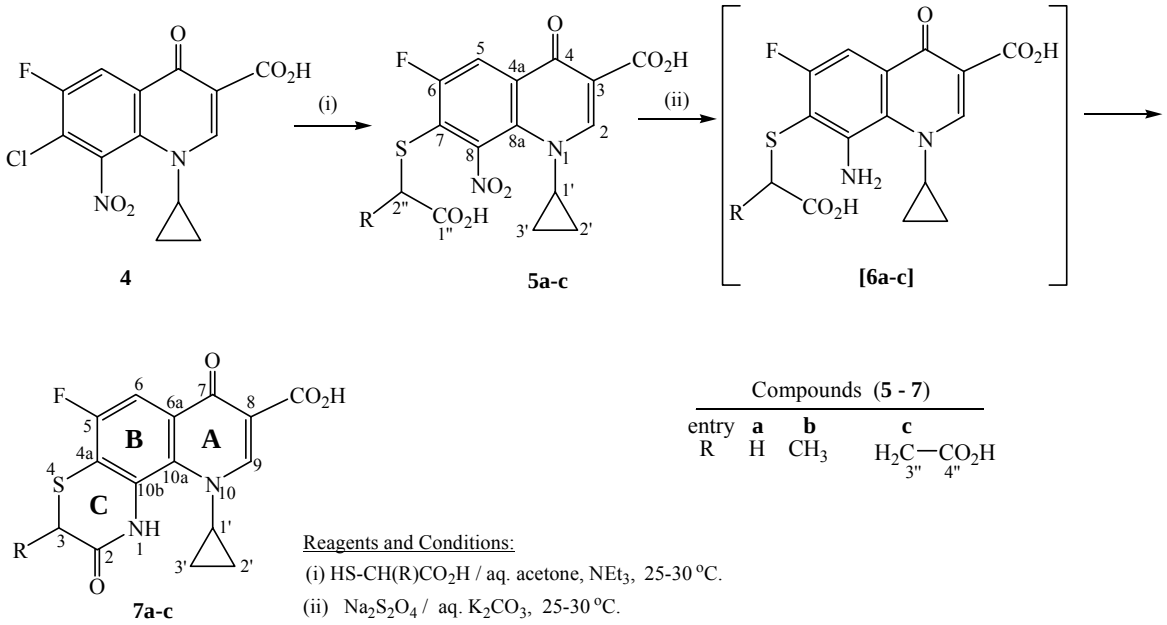
(X = H, Cl, F; Y = (substituted) piperazin-1-yl, pyrrolidin-1-yl)

Figure 2

RESULTS AND DISCUSSION

The synthesis of compounds (**7a-c**) is achieved by utilizing 7-chloro-1-cyclopropyl-6-fluoro-8-nitro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (**4**) as the common synthon, and constructing the thiazinone nucleus thereupon through two-step conversions as illustrated in Scheme 1 and detailed in the experimental part. The first step entails the preparation of the acyclic precursors (**5a-c**) (Scheme 1) by direct interaction of the appropriate α–mercaptoalkanoic acid with the synthon (**4**) in aqueous acetone containing triethylamine. Reduction of **5a-c** with sodium dithionite in aqueous potassium carbonate medium converts the nitro group into an amino group, and is followed by spontaneous lactamization of the resultant 8-amino intermediates (**6a-c**) to afford good yields of the corresponding target products (**7a-c**) in fairly pure form.



Scheme 1

The required synthon (**4**) is prepared by acid-catalyzed hydrolysis of the corresponding ethyl ester (using AcOH + H_2SO_4, as reported for the methyl ester analog).[12] The ethyl ester is formed *via* reaction of 2,4-dichloro-5-fluoro-3-nitrobenzoyl chloride with the respective ethyl 3-*(N,N*-dimethylamino)acrylate following the procedure reported for the methyl ester analog,[12] and shows identical properties to that prepared by another route.[13] The assigned structures for the new compounds (**5a-c**) and (**7a-c**) are supported by their spectral (IR, MS, NMR) and microanalytical data, given in the experimental part. Thus, the mass spectra of **5a-c** and of **7a-c** display the correct molecular ions for which the measured high resolution (HRMS) data are in good agreement with the calculated values. The ^{1}H- 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 carbons and their attached / neighboring hydrogens. For compounds (**7a-c**), long-range correlations are observed between H-9 and each of C-10a, C-7, CO_2H, between H-6 and C-10a, C-7, C-4a, C-5 as well as between H-1' and each of C-10a and C-9. Corresponding long-range correlations between H-2, H-5, H-1' and their neighbor carbons are observed for compounds (**5a-c**). Those skeletal carbons of the fluorinated benzenoid ring (**B**) in **5a-c** and **7a-c** are recognizable through their characteristic signal-doublets arising from coupling with the fluorine atom, while through space ^{13}C…^{19}F coupling is noticeable for the *alpha* C-2″ in **5a-c.** It turned out that H-5 in **5a-c** which resonates at *ca*. 8.3 ppm (d, $^{3}J_{H\text{-}F} \approx 9$ Hz), shows sizable upfield shift in the corresponding annulated products (**7a-c**) (to ~7.7 ppm / H-6). Yet, the cyclopropyl methine proton (H-1'), which resonates at *ca*. 3.7 ppm in **5a-c**, experiences downfield shift (to ~ 4.4 ppm) in the respective annulated products (**7a-c**), probably due to the deshielding effect caused by the proximal lone-pair at the thiazinoid nitrogen (N1 / ring **C**).

EXPERIMENTAL

2,4-Dichloro-5-fluoro-3-nitrobenzoic acid, ethyl 3-(*N*,*N*-dimethylamino)acrylate and cyclopropylamine were purchased from Acros. (±)-2-Mercaptopropionic acid, (±)-2-mercaptosuccinic acid and mercaptoacetic acid were purchased from Aldrich. Melting points were determined on a Gallenkamp electrothermal melting point apparatus. ^{1}H and ^{13}C NMR spectra were measured on a Bruker DPX-300 instrument with Me_4Si as internal reference. MS spectra were obtained with a Varian IonSpec QFT-7 instrument (using ZSpray ESI source, and a scroll pump) or a Finnigan MAT TSQ-70 spectrometer (at 70 eV). IR 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.

7-[(Carboxymethyl)thio]-1-cyclopropyl-6-fluoro-8-nitro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (5a)

Mercaptoacetic acid (0.46 g, 5 mmol) was added to a stirred solution of 7-chloro-1-cyclopropyl-6-fluoro-8-nitro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **(4)** (1.37 g, 4.2 mmol) in water + acetone (45 mL, 1 : 2 v / v) and triethylamine (6 mL) at 25-30 ^{o}C, and was kept in the dark for 6-8 h. Thereafter, the reaction mixture was washed with chloroform (2 x 10 mL), the aqueous layer was acidified with 3*N* HCl and the precipitated product was collected, dried and recrystallized from chloroform – petroleum ether (bp 40-60 ^{o}C) to give yellow crystals. Yield = 1.24 g (77 %), mp 220-221 ^{o}C (decomp). *Anal.* Calcd for $C_{15}H_{11}N_2O_7FS$: C, 47.12; H, 2.90; N, 7.33; S, 8.39. Found: C, 47.04; H, 2.75; N, 7.31; S, 8.40; IR (KBr): ν 3453, 3125, 3016, 2958, 1720, 1698, 1615, 1544, 1460, 1428, 1326, 1263 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.98**,** 1.06 (2m, 4H, H_2-2'/ H_2-3'), 3.71 (m, 1H, H-1'), 3.93 (s, 2H, H_2-2″), 8.29 (d, $^{3}J_{H\text{-}F}$ = 9.4 Hz, 1H, H-5), 8.79 (s, 1H, H-2), 13.76 (br s_2H, 2CO_2H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 11.0 (C-2'/ C-3'); 36.5 (d, $J_{C\text{-}F}$ = 9.1 Hz, C-2″), 39.8 (C-1'), 109.4 (C-3), 114.3 (d, $^{2}J_{C\text{-}F}$ = 25.6 Hz, C-5), 127.0 (d, $^{2}J_{C\text{-}F}$ = 24.3 Hz, C-7), 128.7 (d, $^{3}J_{C\text{-}F}$ = 7.8 Hz, C-4a), 131.6 (d, $^{4}J_{C\text{-}F}$ = 2.1 Hz, C-8a), 144.1 (d, $^{3}J_{C\text{-}F}$ = 2.0 Hz, C-8), 153.4 (C-2), 158.4 (d, $^{1}J_{C\text{-}F}$ = 248 Hz, C-6), 164.9 [C(3)-*C*O_2H], 169.7 [C(2″)-*C*O_2H], 175.6 (d, $^{4}J_{C\text{-}F}$ = 2.2 Hz, C-4); HRMS (EI): Calcd for $C_{15}H_{10}N_2O_7S$ (*M*-HF): 362.02083. Found: 362.02519.

(±)-7-[(1-Carboxyethyl)thio]-1-cyclopropyl-6-fluoro-8-nitro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid [(±)-5b]

This compound was prepared from **(±)**-2-mercaptopropionic acid (0.53g , 5 mmol) and **4** (1.37 g, 4.2 mmol) by following the same procedure and experimental conditions described above for the preparation of **5a**. The title compound was precipitated as pale yellow solid which was recrystallized from chloroform – petroleum ether (bp 40-60 ^{o}C). Yield = 1.48 g (89 %), mp 178-180 ^{o}C (decomp). *Anal.* Calcd for

$C_{16}H_{13}N_2O_7FS$: C, 48.49; H, 3.31; N, 7.07; S, 8.09. Found: C, 48.5; H, 3.30; N, 7.11; S, 8.18; IR (KBr): ν 3427, 3067, 2984, 2932, 1724 (br.), 1595, 1555, 1435, 1447, 1375, 1337, 1255 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 1.00, 1.10 (2m, 4H, H_2-2' / H_2-3'), 1.20 (d, J = 7 Hz, 3H, CH_3), 3.70 (m, 1H, H-1'), 4.11 (q, J = 7 Hz, 1H, H-2″), 8.28 (d, $^3J_{H\text{-}F}$ = 8.9 Hz, 1H, H-5), 8.76 (s, 1H, H-2), 12.84 (br s, 2H, $2CO_2H$); ^{13}C NMR (75 MHz, DMSO-d_6): δ 11.0 / 11.2 (C-2'/ C-3'), 18.9 (CH_3), 39.6 (C-1'), 48.0 (d, $J_{C\text{-}F}$ = 6.5 Hz, C-2″), 109.3 (C-3), 113.9 (d, $^2J_{C\text{-}F}$ = 25.8 Hz, C-5), 127.2 (d, $^2J_{C\text{-}F}$ = 25.0 Hz, C-7), 129.5 (d, $^3J_{C\text{-}F}$ = 7.2 Hz, C-4a), 131.3 (d, $^4J_{C\text{-}F}$ = 1.3 Hz, C-8a), 145.1 (d, $^3J_{C\text{-}F}$ = 1.1 Hz, C-8), 153.2 (C-2), 158.6 (d, $^1J_{C\text{-}F}$ = 248 Hz, C-6), 165.0 [C(3)-CO_2H], 172.4 [C(2″)-CO_2H], 175.6 (d, $^4J_{C\text{-}F}$ = 1.0 Hz, C-4). MS (EI), *m/z* (%): 396 (M^+, 3), 376 (15), 352 (33), 332 (49), 305 (100), 276 (53), 259 (44), 233 (38), 218 (27), 191 (62), 172 (24), 133(18); HRMS (EI): Calcd for $C_{16}H_{13}N_2O_7FS$ (M^+): 396.04271. Found: 396.04681. MS (ESI), *m/z* (%): 419 (M + Na^+, 100), 397 (M + H^+, 38), 365 (5), 309 (27), 301 (5), 239 (19), 229 (23); HRMS (ESI): Calcd for $C_{16}H_{14}N_2O_7F^{+1}$ (M + H^+): 397.0500. Found: 397.0501; Calcd for $C_{16}H_{13}N_2O_7FSNa^{+1}$ (M + Na^+): 419.0320. Found: 419.0312; Calcd for $C_{16}H_{12}N_2O_7FSNa_2^{+1}$ (M + Na_2^+): 441.0139. Found: 441.0140.

(±)-2-[(3-Carboxy-1-cyclopropyl-6-fluoro-8-nitro-4-oxo-1,4-dihydroquinolin-7-yl)thio]succinic acid [(±)-5c]

This compound was prepared from **(±)**-2-mercaptosuccinic acid (0.75 g, 5 mmol) and **4** (1.37 g, 4.2 mmol) by following the same procedure and experimental conditions described above for the preparation of **5a**. The title compound was obtained as pale yellow precipitate which was washed with chloroform (2 x 10 mL), methanol (8 mL) and dried. Yield = 1.55 g (84 %), mp 198-199 °C. *Anal.* Calcd for $C_{17}H_{13}N_2O_9FS$: C, 46.37; H, 2.98; N, 6.36; S, 7.28. Found: C, 46.29; H, 2.94; N, 6.33; S, 7.30; IR (KBr): ν 3440, 3260, 3074, 2952, 1720 (br.), 1705, 1603, 1567, 1534, 1419, 1383, 1329 1254, 1200 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 0.94 /1.07 (2 m, 4H, H_2-2' / H_2-3'), 2.72 (m, 2H, H_2-3″), 3.70 (m, 1H, H-1'), 4.22 (dd, J = 8.1Hz, 8.2 Hz, 1H, H-2″), 8.36 (d, $^3J_{H\text{-}F}$ = 8.8 Hz, 1H, H-5), 8.79 (s, 1H, H-2), 13.12, 13.69 (2br s, 3H, $3CO_2H$); ^{13}C NMR (75 MHz, DMSO-d_6): δ 10.9/ 11.4 (C-2' / C-3'), 36.3 (C-3″), 39.6 (C-1'), 46.0 (d, $J_{C\text{-}F}$ = 5.8 Hz, C-2″), 109.4 (C-3), 114.4 (d, $^2J_{C\text{-}F}$ = 25.6 Hz, C-5), 124.6 (d, $^2J_{C\text{-}F}$ = 24.9 Hz, C-7), 129.9 (d, $^3J_{C\text{-}F}$ = 7.8 Hz, C-4a), 131.3 (d, $^4J_{C\text{-}F}$ = 2.4 Hz, C-8a), 145.3 (d, $^3J_{C\text{-}F}$ = 1.2 Hz, C-8), 153.5 (s, C-2), 158.7 (d, $^1J_{C\text{-}F}$ = 248 Hz, C-6), 164.9 [C(3)-CO_2H], 171.1 (C(3″)-CO_2H), 171.6 [C(2″)-CO_2H], 175.5 (d, $^4J_{C\text{-}F}$ = 2.1 Hz, C-4); MS (ESI), *m/z* (%): 441 (M + H^+, 100), 413 (2), 365 (3), 309 (8), 239 (6), 147 (4); HRMS (ESI): Calcd for $C_{17}H_{14}N_2O_9FS^{+1}$ (M + H^+): 441.0399. Found: 441.0393; Calcd for $C_{17}H_{13}N_2O_9FSNa^{+1}$ (M + Na^+): 463.0218. Found: 463.0223.

10-Cyclopropyl-5-fluoro-2,7-dioxo-2,3,7,10-tetrahydro-1*H*-[1,4]thiazino[2,3-*h*]quinoline-8-carboxylic acid (7a)

A solution of sodium dithionite (0.87 g, 5 mmol) in 5 mL of water was added dropwise to a stirred solution of **5a** (0.38 g, 1 mmol) in water (20 mL) containing potassium carbonate (0.96 g. 7 mmol) at 25-30 °C. The reaction mixture was stirred at 25-30 °C for additional 6-8 h and extracted with chloroform (2 x 10 mL). The aqueous layer was then acidified with 6*N* HCl, whereby the desired product was obtained as pale brown precipitate which was collected, washed with chloroform (2 x 5 mL) and dried. Yield = 0.27 g (81 %), mp 312-314 °C. *Anal*. Calcd for $C_{15}H_{11}N_2O_4FS$: C, 53.89; H, 3.32; N, 8.38; S, 9.59. Found: C, 53.77; H, 3.32; N, 8.59; S, 9.41; IR (KBr): ν 3427, 3215, 3061, 3010, 2913, 1750, 1672, 1615, 1537, 1499, 1410, 1362, 1319, 1231, 1037 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 0.97, 1.03 (2m, 4H, H_2-2' / H_2-3'), 3.68 (s, 2H, H_2-3), 4.40 (m, 1H, H-1'), 7.72 (d, $^3J_{H\text{-}F}$ = 8.8 Hz, H-6), 8.78 (s, 1H, H-9), 10.87(s, 1H, *N*(1)-H), 14.52 (br s, 1H, CO_2H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 10.1 (C-2' / C-3'), 29.2(C-3), 39.6 (C-1'), 104.8 (d, $^2J_{C\text{-}F}$ = 23 Hz, C-6), 108.2 (C-8), 123.3 (d, $^2J_{C\text{-}F}$ = 23.9 Hz, C-4a), 126.1 (d, $^3J_{C\text{-}F}$ = 8.1 Hz, C-6a), 129.9 (d, $^3J_{C\text{-}F}$ = 4.8 Hz, C-10b), 130.3 (d, $^4J_{C\text{-}F}$ = 1.5 Hz, C-10a), 152.2 (C-9), 156.2 (d, $^1J_{C\text{-}F}$ = 243 Hz, C-5), 164.5 (C-2), 165.7 (CO_2H), 176.8 (d, $^4J_{C\text{-}F}$ = 3 Hz, C-7); MS (EI), *m/z* (%): 334(M^+, 25), 290(100); HRMS (EI): Calcd for $C_{15}H_{11}N_2O_4FS$ (M^+): 334.04233. Found: 334.04178.

(±)-10-Cyclopropyl-5-fluoro-3-methyl-2,7-dioxo-2,3,7,10-tetrahydro-1*H*-[1,4]thiazino[2,3-h]-quinoline-8-carboxylic acid [(±)-7b]

This compound was prepared *via* reductive cyclocondensation of (±)-**5b** (0.4 g, 1 mmol) by using sodium dithionite (0.87 g, 5 mmol) and following the same procedure and experimental conditions described above for the preparation of **7a**. The title derivative was isolated as pale yellow precipitate which was recrystallized from chloroform. Yield = 0.30 g (86 %), mp 270-272 °C. *Anal.* Calcd for $C_{16}H_{13}N_2O_4FS$: C, 55.17; H, 3.76; N, 8.04; S, 9.21. Found: C, 55.12; H, 3.76; N, 8.00; S, 9.21; IR (KBr): ν 3472, 3192, 3074, 2945, 1728, 1676, 1604, 1534, 1506, 1362, 1317, 1263, 1238, 1181 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 0.95 / 1.08 (2 m, 4H, H_2-2' / H_2-3'), 1.44 (d, *J* =7 Hz, 3H, CH_3), 3.95 (q, *J* = 7.0 Hz, 1H, H-3), 4.42 (m, 1H, H-1'), 7.76 (d, $^3J_{C\text{-}F}$ = 8.8 Hz, 1H, H-6), 8.79 (s, 1H, H-9), 10.93 [s, 1H, *N*(H)-1], 14.05 (br s, 1H, CO_2H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 9.4 / 10.5 (C-2' / C-3'), 14.3 (CH_3), 36.3 (C-3), 39.7 (C-1'), 105.0 (d, $^3J_{C\text{-}F}$ = 23.0 Hz, C-6), 108.3 (C-8), 121.6 (d, $^2J_{C\text{-}F}$ = 23.7 Hz), 126.3 (d, $^3J_{C\text{-}F}$ = 8.1 Hz, C-6a) 129.2 (d, $^3J_{C\text{-}F}$ = 4.7 Hz, C-10b), 130.2 (d, $^4J_{C\text{-}F}$ = 1.8 Hz,C-10a), 152.1 (C-9), 156.3 (d, $^1J_{C\text{-}F}$ = 243 Hz,C-5), 165.7 (CO_2H), 166.3 (C-2), 176.8 (d,$^4J_{C\text{-}F}$ = 3Hz,C-7); MS (EI), *m/z* (%): 348 (M^+, 24), 330 (8), 319 (10), 304 (100), 275 (19), 262 (31), 247 (22), 218 (40), 193 (23), 189 (26), 149 (44), 122 (9); HRMS (EI): Calcd for $C_{16}H_{13}N_2O_4FS$ (M^+): 348.05798. Found: 348.05615. MS (ESI), *m/z* (%): 349 (M + H^+, 100), 371 (92), 335 (8), 309 (54), 301 (9), 239 (38); 229 (28); HRMS (ESI), Calcd for $C_{16}H_{14}N_2O_4FS^{+1}$ (M + H^+): 349.0653. Found: 349.0653; Calcd for $C_{16}H_{13}N_2O_4FSNa^{+1}$ (M + Na^+): 371.0472. Found: 371.0472.

(±)-3-(Carboxymethyl)-10-cyclopropyl-5-fluoro-2,7-dioxo-2,3,7,10-tetrahydro-1*H*-[1,4]thiazino-[2,3-*h*]quinoline-8-carboxylic acid [(±)-7c]

This compound was prepared *via* reductive cyclocondensation of **(±)-5c** (0.44 g, 1 mmol) by using sodium dithionite (0.87 g, 5 mmol) and following the same procedure and experimental conditions described above for the preparation of **7a**. The title derivative was formed as yellow precipitate that was recrystallized from chloroform / methanol. Yield = 0.33 g (84 %), mp 194-195 ^{o}C. *Anal.* Calcd for $C_{17}H_{13}N_2O_6FS$: C, 52.04; H, 3.34; N, 7.14; S, 8.17. Found: C, 52.18; H, 3.32; N, 7.21; S, 8.20; IR (KBr): ν 3440, 3234, 3074, 2955, 1691 (br.), 1609, 1547, 1505, 1451, 1424, 1384, 1325, 1269, 1237, 1186 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.97, 1.18 (2m, 4H, H_2-2'/H_2-3'), 2.72 (dd, J = 7 Hz, 16.8 Hz, 1H, H_A-3"), 2.97 (dd, J = 7 Hz, 16.8 Hz, 1H, H_B-3"), 4.02 (t, J = 7.1 Hz, 1H, H-3), 4.41 (m, 1H, H-1'), 7.71 (d, $^3J_{H\text{-}F}$ = 8.8 Hz, 1H, H-6), 8.78 (s, 1H, H-9), 11.03 (s, 1H, H-1), 12.70 (br s, 1H, C(3")-CO2*H*), 14.49 (br s, 1H, C(8)-CO_2H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 9.1, 10.9 (C-2' / C-3'), 32.8 (C-3"), 37.9 (C-3), 39.7 (C-1'), 105.1 (d, $^2J_{C\text{-}F}$ = 23.0 Hz, C-6), 108.3 (C-8), 122.3 (d, $^2J_{C\text{-}F}$ = 23.6 Hz, C-4a), 126.3 (d, $^3J_{C\text{-}F}$ = 7.9 Hz, C-6a), 129.1 (d, $^3J_{C\text{-}F}$ = 4.6 Hz, C-10b), 130.5 (d, $^4J_{C\text{-}F}$ = 1.4 Hz, C-10a), 152.0 (C-9), 156.2 (d, $^1J_{C\text{-}F}$ = 243 Hz, C-5), 164.8 (C-2), 165.6 [C(8)-CO_2H], 171.4 [C(3")-CO_2H], 176.8 (d, $^4J_{C\text{-}F}$ = 3 Hz, C-7); MS (EI), *m/z* (%): 392 (M^+, 5), 374 (7), 348 (36), 330 (83), 315 (14), 286 (100), 271 (47), 247 (24), 220 (22), 164 (14), 134 (8), 122 (3); HRMS (EI), Calcd for $C_{17}H_{13}N_2O_6FS$ (M^+) 392.04780. Found: 392.04578; MS (ESI) *m/z* (%): 393 (M + H^+, 82), 365 (29), 345 (12), 337 (18), 309 (100), 301 (16), 296 (19), 255 (12), 239 (55); HRMS (ESI): Calcd for $C_{17}H_{14}FN_2O_6S^{+1}$ (M + H^+): 393.0551. Found: 393.0549; Calcd for $C_{17}H_{13}N_2O_6FSNa^{+1}$ (M + Na^+): 415.0371. Found: 415.0373.

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