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Heterocycles [*h*]Fused onto 4-Oxoquinoline-3-Carboxylic Acid, Part IV. Convenient Synthesis of Substituted Hexahydro [1,4]Thiazepino[2,3-*h*]quinoline-9-carboxylic Acid and Its Tetrahydroquino[7,8-*b*]benzothiazepine Homolog †

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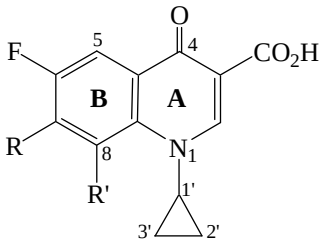
Abstract: Substituted [1,4]thiazepino[2,3-*h*]quinolinecarboxylic acid **3** is prepared by PPA-catalyzed thermal lactamization of the respective 8-amino-7-[(2-carboxyethyl)thio]-1,4-dihydroquinoline-3-carboxylic acid **9**. The latter synthon is obtained by reduction of the 8-nitro-1,4-dihydroquinoline precursor **8** which, in turn, is made accessible *via* interaction of 3-mercaptopropionic acid with 7-chloro-1-cyclopropyl-6-fluoro-8-nitro-1,4-dihydroquinoline-3-carboxylic acid **7** in the presence of triethylamine. A benzo-homolog of **3**, namely tetrahydroquino[7,8-*b*]benzothiazepine-3-carboxylic acid **6**, is analogously prepared *via* the raction of 2-mercaptobenzoic acid with **7**, followed by reduction of the resulting 7-[(2-carboxyphenyl)thio]-8-nitro product **10** into the corresponding 8-amino derivative **11,** and subsequent lactamization. The structures assigned to **3**, **6** and **8-11** are based on microanalytical and spectral (IR, MS, NMR) data.

Keywords: 7-Chloro -8-nitro-4-oxoquinoline-3-carboxylic acid, 3-mercaptopropanoic acid, 2-mercaptobenzoic acid, S_N-Ar reaction, lactamization

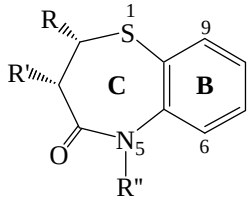
Introduction

Synthetic fluoroquinolones (e.g. ciprofloxacin (**1a)** [2]) represent a successful achievement towards the design and development of potent antiinfectious drugs [2,3], while some related derivatives, such as **1b** [4], exhibit antitumor activity[4-6]. On the other hand, 2,3-dihyro-1,5-benzothiazpin-4(5*H*)-one (**2a**) and several derivatives thereof, e.g diltiazem [7] (**2b**, Figure 1), are of considerable interest both synthetically [8] and pharmacologically [9-13]. Depending on the nature of substituents at C-2, C-3 and N-5 of the parent skeleton (ring **C**, Figure 1), such derivatives exhibit coronary vasodilator [9], calcium antagonist [10], antidepressant [11], anticonvulsant [12] or antimicrobial [13] activities.

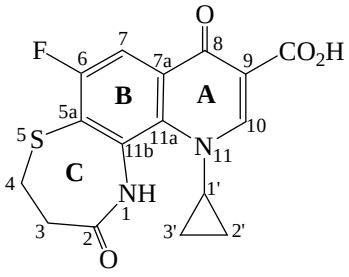
Figure 1. Structures of 4-oxoquinolines **1a**, **1b**, dihydro-1,5-benzothiazepin-4(5*H*)-ones **2a**, **2b** and 2,8-dioxo-hexahydro[1,4]thiazepino[2,3-*h*]quinoline **3**.



1a (R = 1-piperazinyl; R' = H)
1b (R = *p*-(OH)C_6H_4; R' = F)



2a (R = R' = R" = H)
2b (R = *p*-(MeO)C_6H_4; R' = OAc; R" = $CH_2CH_2NMe_2$)



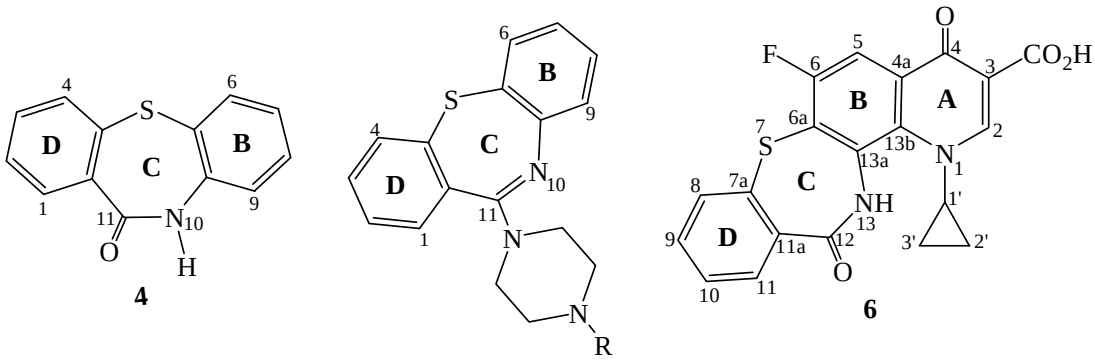
3

Several dibenzo[*b,f*][1,4]thiazepin-11(10*H*)-ones (e.g. **4**, Figure 2) were also prepared [14-17], some of which were reported to exhibit activity against the HIV virus [15] or useful agents for the prevention and treatment of AIDS [16], while others act as leukotriene antagonists [17]. Compounds of type **4** have been readily transformed into 11-piperazinyldibenzo[*b,f*][1,4]thiazepines, exemplified by 11-{4-[2-(2-Hydroxyethoxy)-ethyl]piperazinyl}dibenzo[*b,f*][1,4]thiazepine, commonly known as quetiapine [18] (**5**, Figure 2).

The latter compound and its congeners are useful agents for treating anxiety [19] and substance-related disorders [20], act as calcium channel antagonists [21], neuroleptic and antipsychotic agents [22], and display antidopaminergic activity [23].

Herein, we wish to report on the synthesis of new heterocyclic ring systems incorporating a 4-oxopyridine entity condensed either to 1,5-benzothiazepinone (compound **3**, Figure 1), or to dibenzo [*b,f*][1,4]thiazepinone (compound **6**, Figure 2) as depicted in Schemes 1 and 2, respectively. The tricyclic system **3** encompasses the structural features both of fluoroquinolone (rings **A**, **B**) and 1,5-benzothiazepinone (rings **B**, **C**), while the tetracyclic assembly **6** incorporates fluoroquinolone (rings **A**, **B**) and dibenzo[1,4]thiazepinone (rings **B**, **C**, **D**) chemotypes. Such new hybrid heterocyclics might display interesting bioproperties.

Figure 2. Structures of dibenzo[*b*,*f*][1,4]thiazepine-11(10*H*)-ones **4**, quetiapine **5** and tetrahydroquino[7,8-*b*][1,4]benzothiazepine **6**.

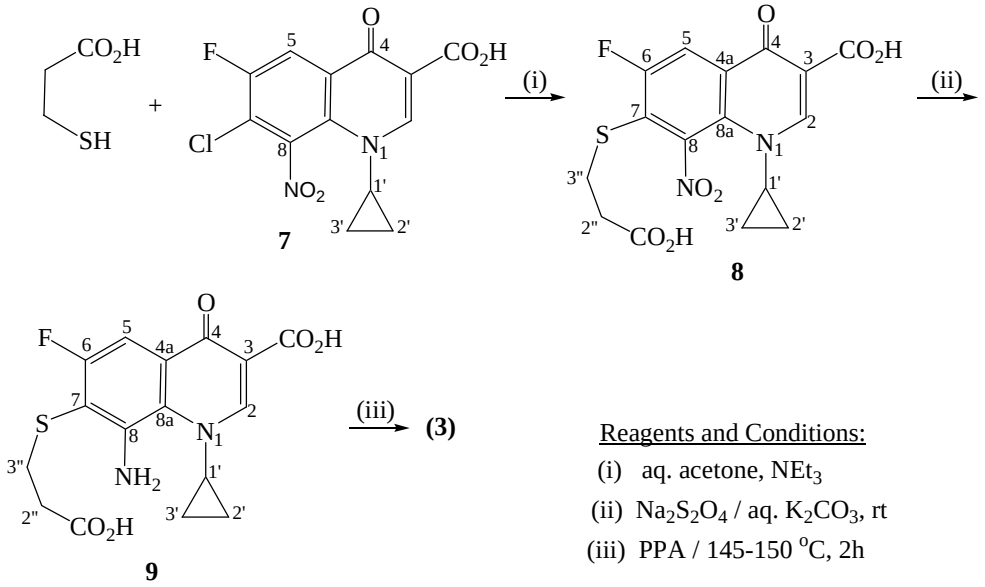


4 **5** (R = $CH_2CH_2OCH_2CH_2OH$) **6**

Results and Discussion

Direct interaction between 7-chloro-1-cyclopropyl-6-fluoro-8-nitro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (**7**) [24, 25] and 3-mercaptopropionic acid, in aqueous acetone containing triethylamine, produced the corresponding 7-[(2-carboxyethyl)thio]-8-nitro-1,4-dihydroquinoline derivative (**8**) (Scheme 1).

Scheme 1. Synthesis of hexahydro[1,4]thiazepino[2,3-*h*]quinoline-9-carboxylic acid **3**.

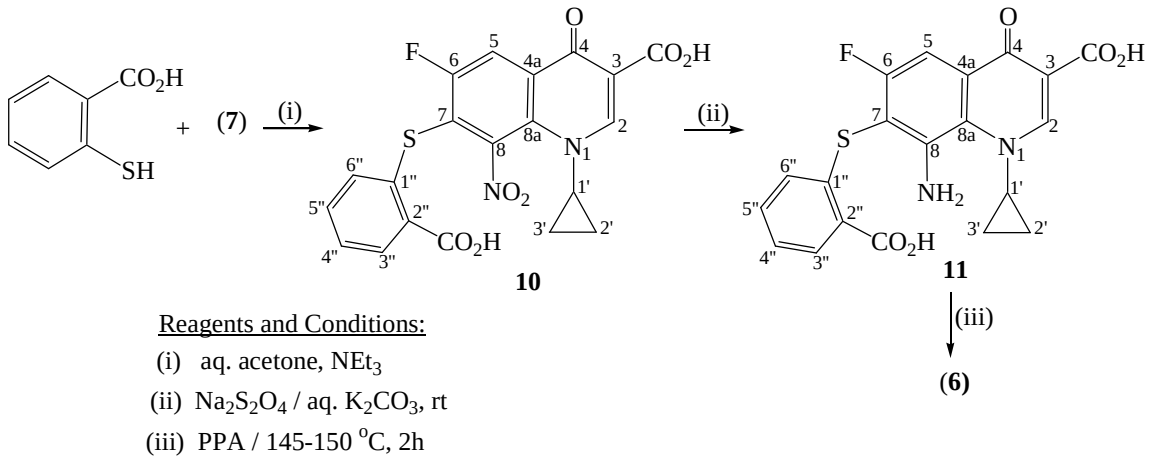


7 **8** **9**

Herein, 3-mercaptopropionic acid acts as 'sulfur' nucleophile that displaces the C(7)- chlorine atom in the substrate (**7**). This reaction follows a nucleophilc aromatic substitution 'S_N-Ar' (addition – elimination) path, and is facilitated by the presence of the electron withdrawing C(6)-fluoro, C(4)-keto, and C(8)-nitro groups. Reduction of the latter 8-nitro compound **8** with sodium dithionite in aqueous potassium carbonate gives the respective 8-amino derivative **9**. In a separate step, compound **9** underwent lactamization upon heating with polyphosphoric acid (PPA) to afford a tricyclic system,

namely 2,8-dioxohexahydro[1,4]thiazepino[2,3-*h*]quinoline-3-carboxylic acid (**3**). Likewise, the reaction of 2-mercaptobenzoic acid with **7** provided the corresponding 7-[(2-carboxyphenyl)thio]-8-nitro-1,4-dihydroquinoline derivative **10** which was then reduced to the respective 7-amino-1,4-dihydroquinoline-3-carboxylic acid **11** (Scheme 2). Subsequent lactamization of **11**, using PPA, afforded the target tetracyclic product, namely 4,12-dioxotetrahydroquino[7,8-*b*]benzothiazepine-3-carboxylic acid (**6**). The elemental analyses and spectral (IR, MS, NMR) data of **3, 6** and **8-11**, given in the Experimental part, are in conformity 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.

Scheme 2. Synthesis of tetrahydroquino[7,8-*b*]benzothiazepine-3-carboxylic acid **6**.



For compound **3**, distinct "three-bond" (^{1}H, ^{13}C)–correlations are observed between H-10 and each of CO_2H, C-8, C-11a and C-1', as well as between H-7 and each of C-8, C-11a and C-5a, and between H-1' and each of C-10 and C-11a. Corresponding long-range correlations are also observed for compounds **6** and **8-11** between H-2, H-5, H-1' and their neighbor carbons. The skeletal carbons of benzo-fused entity (ring **B**) in **3, 6** and **8-11** are recognizable by their doublet signals originating from scalar (through bond) coupling with the neighboring fluorine atom. Also, the C-3" methylene carbon in **8** appears as a doublet due to through-space (dipolar) coupling with the nearby fluorine atom.

Experimental

General

Ethyl 3-(*N*,*N*-dimethylamino)acrylate, 2,4-dichloro-5-fluoro-3-nitrobenzoic acid and cyclopropyl-amine were purchased from Acros. 3-Mercaptopropionic acid and 2-mercaptobenzoic acid were purchased from Aldrich. Melting points were determined on a Gallenkamp capillary melting point apparatus and are uncorrected. ^{1}H- (300 MHz), ^{13}C-NMR (75 MHz) and DEPT spectra, and 2D (H-H

COSY, HMQC, HMBC) experiments were measured on a Bruker DPX-300 instrument with Me_4Si as internal reference and DMSO-d_6 as solvent. High resolution mass spectra (HRMS) were measured in positive ion mode by Electrospray (ESI) on Bruker APEX-Qe 94 instrument. The samples were dissolved in acetonitrile, diluted in spray solution (methanol/water 1:1 v/v + 0.1% formic acid) and infused using a syringe pump with a flow rate of 2 µL/min. External calibration was conducted using the arginine cluster in a mass range *m/z* 175-871. Electron-impact mass spectra (EIMS) were obtained using a Varian MAT-212 spectrometer at 70 eV and at ion source temperature of 200 ^oC. IR spectra were recorded as KBr discs on a Nicolet Impact-400 FT-IR spectrophotometer. Elemental analyses were preformed at the Microanalytical Laboratory of the Hashemite University, Zarqa, Jordan.

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

This compound [mp 256-257^oC (decomp); Lit. [25] 261^oC (decomp)] was prepared according to literature methods [24] by acid-catalyzed hydrolysis of the corresponding ethyl ester, in turn prepared from 2,4-dichloro-5-fluoro-3-nitrobenzoic acid, ethyl 3-(*N*,*N*-dimethylamino)acrylate and cyclopropyl-amine by following the stepwise synthetic procedures as reported for the corresponding methyl ester analog [mp 175-176 ^oC (decomp); Lit. [24] 174-176 ^oC (decomp)] [25,26].

7-[(2-Carboxyethyl)thio]-1-cyclopropyl-6-fluoro-8-nitro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (**8**)

3-Mercaptopropionic acid (0.18 g, 1.7 mmol) was added to a stirred solution of **7** (0.5 g, 1.5 mmol) in aqueous acetone (45 mL, 1:2 v / v) and Et_3N (6 mL) at room temperature (rt) and kept in the dark for 7 h. Thereafter, the reaction mixture was washed with $CHCl_3$ (2 x 10 mL), the aqueous layer was separated and acidified with 3N HCl. The resulting yellow precipitate was collected and recrystallized from $CHCl_3$. Yield 0.54 g (91%); mp 205-207^oC; IR (cm^{-1}) 3500, 3430, 3080, 2914, 2742, 1720, 1679, 1564, 1532, 1481, 1430, 1347, 1329, 1259; ^{1}H-NMR δ 1.00/1.10 (2 m, 4H, 2H-2'/2H-3'), 2.45 (t, J = 6.7 Hz, 2H, H-2''), 3.20 (t, J = 6.7 Hz, 2H, H-3''), 3.70 (m, 1H, H-1'), 8.29 (d, $^3J_{H\text{-}F}$ = 9 Hz, 1H, H-5), 8.78 (s, 1H, H-2), 13.05 (br s, 2H, $2CO_2H$); ^{13}C-NMR δ 11.1 (C-2'/C-3'), 30.5 (d, $J_{C\text{-}F}$ = 7.3 Hz, C-3''), 34.9 (C-2''), 39.6 (C-1'), 109.2 (C-3), 114.4 (d, $^2J_{C\text{-}F}$ = 25.6 Hz, C-5), 126.9 (d, $^2J_{C\text{-}F}$ = 24.7 Hz, C-7), 129.0 (d, $^3J_{C\text{-}F}$ = 7.9 Hz, C-4a), 131.3 (d, $^4J_{C\text{-}F}$ = 2.6 Hz, C-8a), 144.9 (d, $^3J_{C\text{-}F}$ = 1.5 Hz, C-8), 153.3 (C-2), 158.5 (d, $^1J_{C\text{-}F}$ = 248 Hz, C-6), 164.9 [C(3)CO_2H], 172.7 [C(2'')CO_2H], 175.6 (d, $^4J_{C\text{-}F}$ = 2.3 Hz, C-4). EIMS *m/z* (%): 396 (M^+, 6), 378 (9), 352 (64), 334 (56), 307 (29), 269 (43), 263 (68), 233 (52), 200 (47), 191 (71), 172 (35), 108 (15), 55 (100); HRMS (EI): Calcd. for $C_{16}H_{13}FN_2O_7S$ 396.04271; found 396.03918; Anal. calcd. for $C_{16}H_{13}FN_2O_7S$ (396.35): C, 48.49; H, 3.31; N, 7.07; S, 8.09. Found: C, 48.26; H, 3.24; N, 7.16; S, 7.93.

8-Amino-7-[(2-carboxyethyl)thio]-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (**9**)

A solution of sodium dithionite (0.87 g, 5 mmol) in water (5 mL) was added dropwise at rt to a stirred solution of **8** (0.4 g, 1.0 mmol) in water (20 mL) containing K_2CO_3 (0.96 g, 7 mmol). The

reaction mixture was stirred at rt for an additional 8 h and then extracted with $CHCl_3$ (2 x 10 mL). The aqueous layer was then acidified with 6N HCl, whereby the title compound was obtained as a pale yellow precipitate which was collected and recrystallized from $CHCl_3$/MeOH. Yield 0.3 g (81%); mp 216-218^{o}C; IR (cm^{-1}) 3498, 3343, 3080, 3919, 1730, 3919, 1730, 1595, 1582, 1530, 1492, 1447, 1337, 1254, 1170; ^{1}H-NMR δ 1.04, 1.16 (2 m, 4H, 2H-2' / 2H-3'), 2.44 (t, J = 7 Hz, 2H, 2H-2"), 2.93 (t, J = 7 Hz, 2H, 2H-3"), 4.53 (m, 1H, H-1'), 6.51 (br s, 2H, NH_2), 7.20 (d, $^3J_{H\text{-}F}$ = 8.4 Hz, 1H, H-5), 8.72 (s, 1H, H-2), 14.70 (br s, 2H, 2CO_2H); ^{13}C-NMR δ 10.6 (C-2'/C-3'), 29.4 (C-3"), 34.6 (C-2"), 39.9 (C-1'), 97.0 (d, $^2J_{C\text{-}F}$ = 27.1 Hz, C-5), 107.2 (C-3), 109.9 (d, $^2J_{C\text{-}F}$ = 23.4 Hz, C-7), 126.9 (d, $^4J_{C\text{-}F}$ = 1 Hz, C-8a), 129.2 (d, $^3J_{C\text{-}F}$ = 9.8 Hz, C-4a), 145.2 (d, $^3J_{C\text{-}F}$ = 3.3 Hz, C-8), 151.5 (C-2), 161.4 (d, $^1J_{C\text{-}F}$ = 240 Hz, C-6), 166.0 [C(3)CO_2H), 173.1 [C(2″)-CO_2H], 177.2 (d, $^4J_{C\text{-}F}$ = 2 Hz, C-4); HRMS(ESI): calcd for $C_{16}H_{16}FN_2O_5S^+$ $[M+H]^+$ **:** 367.07640, found**:** 367.07568; Anal. calcd. for $C_{16}H_{15}FN_2O_5S$ (366.36): C, 52.45; H, 4.13; N, 7.65; S, 8.75. Found: C, 52.31; H, 4.08; N, 7.55; S, 8.48.

11-Cyclopropyl-6-fluoro-2,8-dioxo-1,2,3,4,8,11-hexahydro[1,4]thiazepino[2,3-h]quinoline-9-carboxylic acid (**3**)

Compound **9** (0.2 g, 0.55 mmol) was suspended in polyphosphoric acid (PPA, 7 g) and heated at 145-150 °C for 2h. The reaction mixture was then poured into water (30 mL) and stirred for 20 min. The resulting white precipitate was collected and recrystalised from $CHCl_3$/MeOH. Yield 0.13g (68%); mp 307-309 ^{o}C; IR (cm^{-1}) 3427, 3286, 3080, 2932, 1717, 1595, 1530, 1498, 1460, 1408, 1389, 1312, 1254, 1228, 1183; ^{1}H-NMR δ 1.03 (m, 4H, 2H-2' / H-3'), 2.74 (t, J = 7 Hz, 2H, 2H-4), 3.53 (t, J = 7 Hz, 2H, 2H-3), 4.29 (m, 1H, H-1'), 7.94 (d, $^3J_{H\text{-}F}$ = 8.1 Hz, 1H, H-7), 8.79 (s, 1H, H-10), 10.02 (br s, 1H, N(1)H), 13.42 (br s, 1H, CO_2H); ^{13}C-NMR δ 9.5 (C-2'/C-3'), 33.2 (C-4), 34.6 (C-3), 41.0 (C-1'), 108.2 (C-9), 108.6 (d, $^3J_{C\text{-}F}$ = 26.1 Hz, C-7), 126.6 (d, $^2J_{C\text{-}F}$ = 20.7 Hz, C-5a), 128.6 (d, $^3J_{C\text{-}F}$ = 8.6 Hz, C-7a), 133.7 (d, $^3J_{C\text{-}F}$ = 2.2 Hz, C-11a), 135.9 (d, $^3J_{C\text{-}F}$ = 1.6 Hz, C-11b), 152.5 (C-10), 159.6 (d, $^1J_{C\text{-}F}$ = 244 Hz, C-6), 165.5 (C(9)-CO2H), 172.0 (C-2), 176.8 (d, $^4J_{C\text{-}F}$ = 3 Hz, C-8); EIMS *m/z* (%): 348(M^+, 27), 320(5), 276(15), 247(15), 233(12), 220(20), 193(8), 118(6), 152(4), 135(14), 108(9), 55(100); HRMS (ESI): calcd for $C_{16}H_{14}FN_2O_4S^+$ $[M+H]^+$: 349.06583. Anal. calcd. for $C_{16}H_{13}FN_2O_4S$ (348.35): C, 55.17; H, 3.76; N, 8.04; S, 9.20. Found: C, 55.86; H, 3.74; N, 7.91; S, 9.27.

7-[(2-Carboxyphenyl)thio]-1-cyclopropyl -6-fluoro-8-nitro-4-oxo-1,4-dihydroquinolin-3-carboxylic acid (**10**)

Prepared from 2-mercaptobenzoic acid (0.26 g, 1.7 mmol) and **7** (0.5 g, 1.5 mmol) using the procedure and experimental conditions described above in the preparation of **8**. The title compound was obtained as a white precipitate which was collected and recrystallized from chloroform/petroleum ether. Yield 0.62 g (93 %); mp 279-281^{o}C. IR (cm^{-1}) 3395, 3067, 2971, 2932, 2669, 2605, 1692, 1605, 1542, 1351, 1459, 1419, 1339, 1328, 1288, 1115; ^{1}H-NMR δ 1.02, 1.18 (2 m, 4H, 2H-2' / 2H-3'), 3.74 (m, 1H, H-1'), 6.80 (dd, J = 7.9, 1.0 Hz, 1H, H-6"), 7.30 (ddd, J = 7.3, 7.5, 1 Hz, 1H, H-4"), 7.38 (ddd, J = 7.9, 7.3, 1.6 Hz, 1H, H-5"), 7.97 (dd, J = 7.5, 1.6 Hz,1H, H-3"), 8.33 (d, $^3J_{H\text{-}F}$ = 8 Hz, 1H, H-5), 8.82 (s, 1H, H-2), 13.75 (br s, 2H, 2CO_2H); ^{13}C-NMR δ 11.2 (C-2'/C-3'), 39.6 (C-1'), 109.4 (C-3), 115.0 (d, $^2J_{C\text{-}F}$ = 25.6 Hz, C-5), 124.3 (d, $^2J_{C\text{-}F}$ = 25.7 Hz, C-7), 126.9 (C-4"), 127.4 (C-6"), 128.5 (C-

2"), 130.9 (d, $^{3}J_{C\text{-}F}$ = 7.8 Hz, C-4a), 131.6 (d, $^{3}J_{C\text{-}F}$ = 2.6 Hz, H-8a), 131.7 (C-3"), 133.7 (C-5"), 137.6 (C-1"), 146.3 (C-8), 153.3 (C-2), 155.1 (d, $^{1}J_{C\text{-}F}$ = 262 Hz, C-6), 165.0 [C(3)-*C*O_2H], 168.1 [C(2″)-*C*O_2H], 175.6 (d, $^{4}J_{C\text{-}F}$ = 2.2 Hz, C-4); HRMS (ESI): calcd. for $C_{20}H_{14}FN_2O_7S^+$[M+H]$^+$: 445.05058 , found: 445.04989; Anal. calcd. for $C_{20}H_{13}FN_2O_7S$ (444.39): C, 54.05; H, 2.95; N, 6.30; S, 7.22. Found: C, 54.23; H, 3.04; N, 6.18; S, 7.01.

8-Amino-7-[(2-carboxyphenyl)thio]-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (**11**)

A solution of sodium dithionite (0.52 g, 3.0 mmol) in water (5 mL) was added dropwise to a stirred solution of **10** (0.4 g, 0.9 mmol) in water (10 mL) containing dissolved K_2CO_3 (0.56 g. 4.0 mmol) at rt. Thereafter, the reaction mixture was stirred at rt for 5 h and then washed with $CHCl_3$ (2 x 8 mL). The aqueous layer was neutralized with 6N HCl, the precipitated product was collected, dried, and recrystallized from $CHCl_3$. Yield = 0.29 g (77%); mp 312-313 ^{o}C; IR (cm^{-1}) 3491, 3379, 3086, 2771, 2610, 1704, 1678, 1582, 1524, 1453, 1350, 1235, 1138; ^{1}H-NMR δ 1.09 (m, 4H, 2H-2'/2H-3'), 4.51 (m, 1H, H-1'), 6.49 (br s, 2H, NH_2), 6.66 (d, *J* = 7.9 Hz, 1H, H-6"), 7.22 (dd, *J* = 6.8, 7.2 Hz, 1H, H-4"), 7.29 (d, $^{3}J_{H\text{-}F}$ = 8.3 Hz, 1H, H-5), 7.34 (dd, *J* = 7.9, 7.2 Hz, 1H, H-5"), 7.97 (d, *J* = 6.8 Hz, 1H, H-3"), 8.76 (s, 1H, H-2), 13.40 [br s, 1H, C(2")-CO_2H], 14.80 [br s, 1H, C(3)-CO_2H]; ^{13}C-NMR δ 10.6 (C-2'/C-3'), 39.8 (C-1'), 97.2 (d, $^{2}J_{C\text{-}F}$ = 27.1 Hz, C-5), 107.5 (C-3), 107.6 (d, $^{2}J_{C\text{-}F}$ = 23.2 Hz, C-7), 125.2 (C-6"), 125.6 (C-4"), 127.3 (C-8a), 128.7 (C-2"), 130.3 (d, $^{3}J_{C\text{-}F}$ = 10.3 Hz, C-4a), 132.0 (C-3"), 133.2 (C-5"), 138.3 (C-1"), 146.0 (d, $^{3}J_{C\text{-}F}$ = 3 Hz, C-8), 151.7 (C-2), 161.4 (d, $^{1}J_{C\text{-}F}$ = 242 Hz, C-6), 166.0 [C(3)-*C*O_2H], 168.1 [C(2")-*C*O_2H], 177.2 (d, $^{4}J_{C\text{-}F}$ = 3 Hz, C-4); EIMS *m/z* (%): 414 (M$^+$, 8), 396 (10), 370 (64), 352 (82), 323 (100), 295 (31), 217 (46), 189 (59), 154 (19), 136 (50), 108 (11); HRMS (EI): calcd. for $C_{20}H_{15}FN_2O_5S$: 414.06854; found: 414.07027; Anal. calcd. for $C_{20}H_{15}FN_2O_5S$ (414.41): C, 57.97; H, 3.65; N, 6.76; S, 7.74. Found: C, 57.68; H, 3.54; N, 6.72; S, 7.88.

1-cyclopropyl-6-fluoro-4,12-dioxo-1,4,12,13-tetrahydroquino[7,8-b]benzothiazepine-3-carboxylic acid (**6**)

Prepared from compound **11** (0.2 g, 0.48 mmol) by heating in PPA (7 g) at 145-150 °C for 2h. Work-up of the reaction mixture, as described for the preparation of **3,** produced a brown precipitate which was collected, washed with cold EtOH (1 mL) and dried. Yield 0.14 g (74 %) mp 317-319 °C (decomp*)*; IR (cm^{-1}) 3433, 3247, 3086, 2929, 1713, 1674, 1614, 1349, 1490, 1466, 1425, 1383, 1330, 1259, 1235, 1193; ^{1}H-NMR δ 0.36 , 1.06 (2m, 2H) and 0.91, 1.30 (2m, 2H) (2H-2' / 2H-3'), 4.37 (m, 1H, H-1'), 7.53 (m, 2H, H-9 + H-10), 7.62 (dd, *J* = 7.1, 1.4 Hz, 1H, H-8), 7.81 (dd, *J* = 7.3, 1.5 Hz, 1H, H-11), 7.90 (d, $^{3}J_{H\text{-}F}$ = 8.0 Hz, 1H, H-5), 8.80 (s, 1H, H-2), 10.99 (br s, 1H, N(1)-H), 13.30 (br s, 1H, CO_2H); ^{13}C-NMR δ 7.6, 11.9 (C-2' /C-3'), 40.9 (C-1'), 108.3 (d, $^{2}J_{C\text{-}F}$ = 26 Hz, C-5), 108.5 (C-3), 128.7 (d, $^{3}J_{C\text{-}F}$ = 8.2 Hz, C-4a), 130.7 (C-9), 132.0 (C-11), 132.4 (d, $^{2}J_{C\text{-}F}$ = 22.4 Hz, C-6a), 132.6 (d, $^{4}J_{C\text{-}F}$ = 1.7 Hz, C-13a), 132.9 (C-10), 133.0 (C-8), 134.2 (d, $^{4}J_{C\text{-}F}$ = 1.9 Hz, C-13b), 135.3 (C-11a), 138.3 (C-7a), 152.6 (C-2), 157.3 (d, $^{1}J_{C\text{-}F}$ = 245 Hz, C-6), 165.5 (*C*O_2H), 168.4 (C-12), 176.8 (d, $^{4}J_{C\text{-}F}$ = 2.9 Hz, C-4); EIMS *m/z* (%): 396 (M$^+$, 43), 378 (5), 352 (100),337 (6), 323 (19), 319 (46), 295 (16), 269 (10), 241 (9), 214 (11), 196 (6), 168 (5), 157 (4), 107 (11); HRMS (ESI): calcd. for

$C_{20}H_{14}FN_2O_4S^+$ $[M+H]^+$: 397.06583, found:397.06535; Anal. calcd. for $C_{20}H_{13}FN_2O_4S$ (396.36): C, 60.60; H, 3.31; N, 7.07; S, 8.09. Found: C, 60.48; H, 3.23; N, 7.02; S, 7.87.

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References and Notes

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