Heterocycles [*h*]-Fused onto 4-Oxoquinoline-3-carboxylic Acid. Part X [1]. Synthesis and X-Ray Structure of a Model 4-Oxo[1,4]benzoxazepino[2,3-*h*]quinoline-3-carboxylic Ester

Batool A. Farrayeh[a], Mustafa M. El-Abadelah[a], Jalal A. Zahra[a], Salim F. Haddad[a], and Wolfgang Voelter[b]

[a] Chemistry Department, Faculty of Science, The University of Jordan, Amman 11942, Jordan
[b] Interfakultäres Institut für Biochemie, Universität Tübingen, Hoppe-Seyler-Straße 4, 72076 Tübingen, Germany

Reprint requests to Prof. Dr. W. Voelter. E-mail: wolfgang.voelter@uni-tuebingen.de

Z. Naturforsch. **2013**, *68b*, 187 – 194 / DOI: 10.5560/ZNB.2013-2270
Received October 17, 2012

Direct interaction of salicylaldehyde oxyanion with ethyl 7-chloro-8-nitro-4-oxoquinoline-3-carboxylate (**2**) delivered the respective 7-(2-formyl-phenoxy)-8-nitro-4-oxoquinoline-3-carboxylic ester **3**. Reductive cyclization of **3** furnished the corresponding 4-oxo-[1,4]benzoxazepino[2,3-*h*]quinoline-3-carboxylic ester **5**. Acid-catalyzed hydrolysis of the esters **3/5** produced the respective acids **4/6**. Structural assignments for the new compounds **3** – **6** are supported by microanalytical and spectral (IR, HRMS, NMR) data and confirmed by X-ray structure determination for compound **5**. Interestingly, compound **6** exhibited good antifungal activity against *C. albicans*.

Key words: Salicylaldehyde Oxyanion in S_N(Ar) Reaction, 7-(2-Formylphenoxy)-8-nitro-4-oxoquinoline-3-carboxylic Ester, Reductive Cyclization, 4-Oxo[1,4]benzoxazepino-[2,3-*h*]quinoline-3-carboxylic Ester

Introduction

Synthetic fluoroquinolones (*e. g.* ciprofloxacin [2 – 5] Fig. 1) represent a successful achievement towards the design and development of potent antiinfectious drugs [2 – 12]. On the other hand, the tricyclic dibenz[*b*, *f*] [1,4]oxazepin-11(10*H*)-one ring system (**1a**, Fig. 1) is of natural occurrence and constitutes the skeleton of two dibenzo[*b*, *f*][1,4]oxazepin-11(10*H*)-one derivatives (**1b**, **1c**, Fig. 1) that have recently been isolated from the leaves of *Carex Distachya* Desf. (Cyperaceae), an herbaceous plant growing in the Mediterranean area. The latter compounds have been shown to possess antioxidant activity [13] (radical scavengers), while several other related species were prepared and patented as useful agents for the treatment and prevention of AIDS [14]. It is noteworthy that some [1,4]benzoxazepinone derivatives were reported to inhibit HIV-1 replication by interacting with the NNRTI binding pocket [15]. Furthermore, several members of the [1,4]benzoxazepinone class have been reported as monoanionic inhibitors of squalene syn-

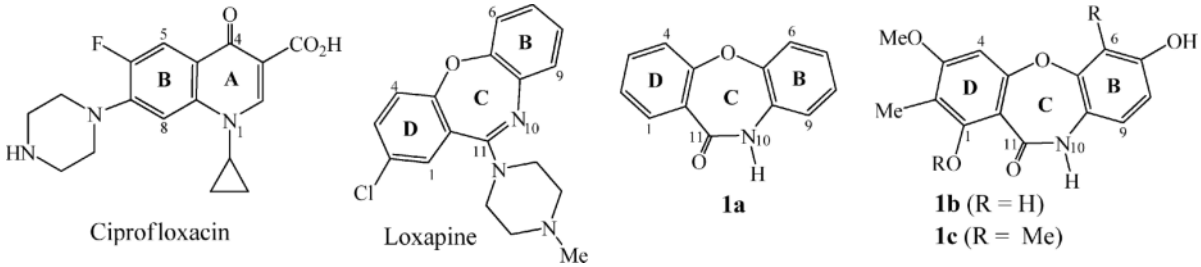


Fig. 1. Structures of ciprofloxacin, loxapine and the natural dibenzoxazepinones **1a – 1c**.

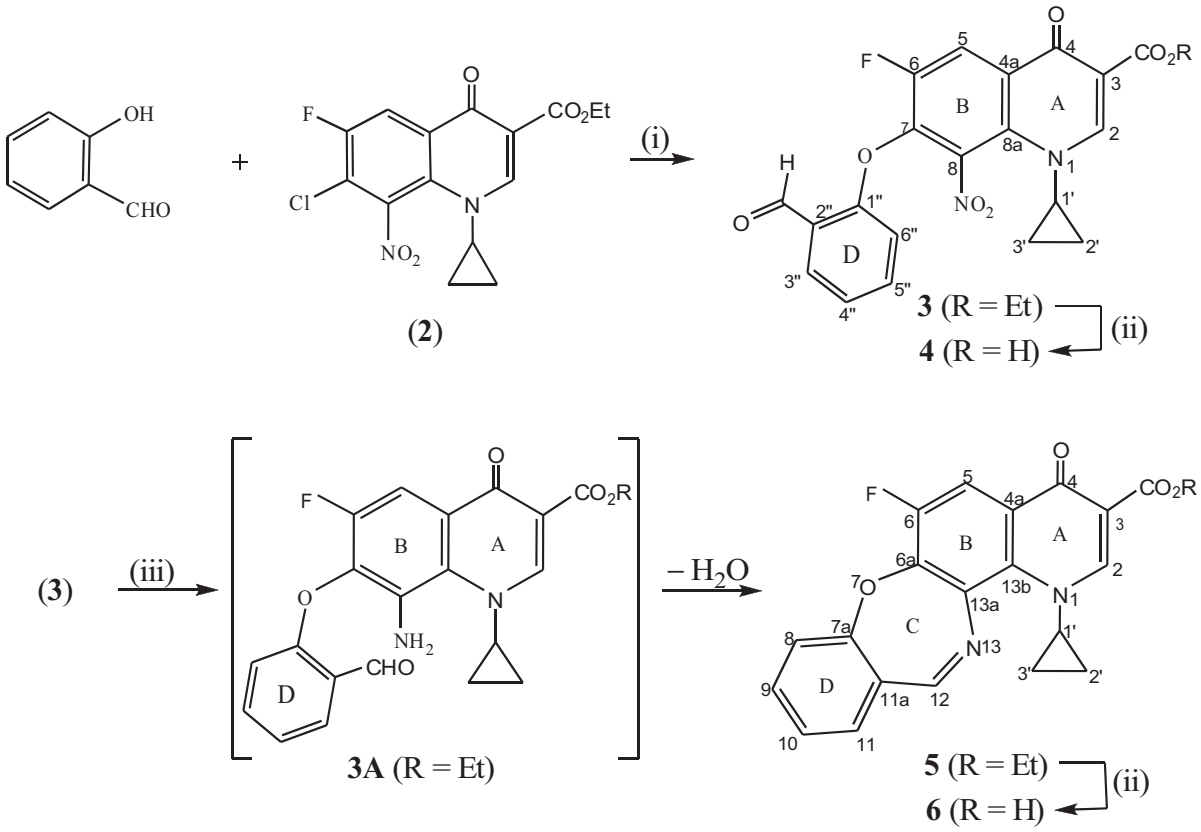
thetase in HMG-CoA reductase regulation [16] and as *y*-secretase inhibitors for the treatment of Alzheimer's disease [17], whereas 2-chloro-11-(4-methyl-1-piperazinyl)dibenz[*bf*][1,4]oxazepine (loxapine, Fig. 1) is an effective antipsychotic drug [18, 19].

Herein, we wish to report on the synthesis of the new tetracyclic system **5/6** incorporating a 4-oxopyridine entity condensed to dibenz[*bf*][1,4]oxazepine as depicted in Scheme 1. As a structural feature, the heterocyclic assembly in **5/6** encompasses fluoroquinolone (rings A, B) and dibenz[1,4]oxazepine (rings B, C, D) chemotypes. Such new hybrid heterocyclics, exemplified by **6**, might display interesting bioproperties.

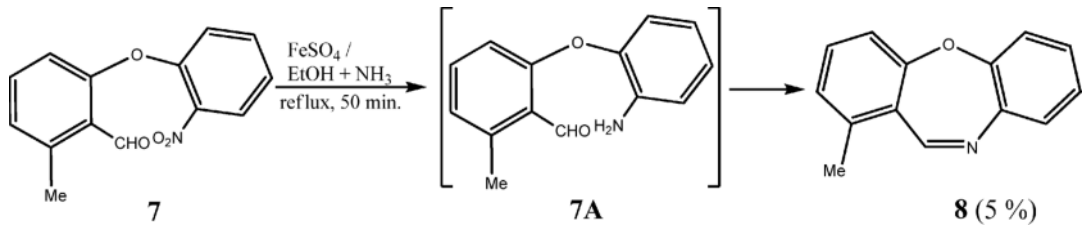
Results and Discussion

Synthesis

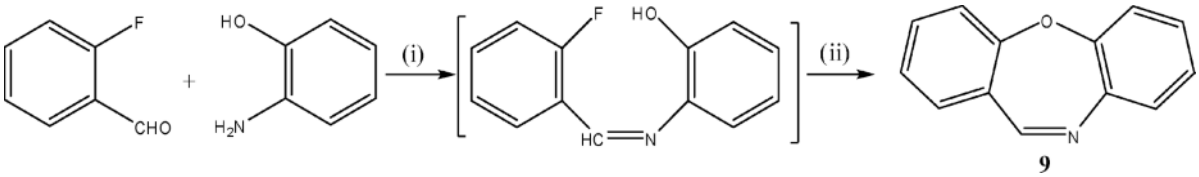
A feasible two-step synthetic route towards the target compound **6** was devised as depicted in



Scheme 1. Synthesis of 4-oxo[1,4]benzoxazepino[2,3-*h*]quinoline-3-carboxylic acid and ester (**5/6**): (i) 5 % aq. NaOH (1 equiv.); (ii) 6 N aq. HCl/reflux, 24 h; (iii) $SnCl_2$/conc. HCl, then 40 % aq. NaOH.



Scheme 2. Reductive cyclization of compound **7**.



9

Scheme 3. One-pot synthesis of dibenz[*b*, *f*][1,4]oxazepine: (i) polyethylene glycol, 50 °C, 10 h; (ii) K_2CO_3, 100 °C, 10 h.

Scheme 1. This approach is based upon annelation of the 1,4-benzoxazepine (rings C, D of compound **6**) onto the appropriately substituted 4-oxoquinoline system (rings A, B). The first step involves direct interaction between the salicyladehyde oxyanion and the 4-oxoquinoline-3-carboxylate **2** with ultimate displacement of the C(7)-chloride ion and consequent formation of the 7-(2-formylphenoxy)-8-nitro-4-oxoquinoline **3**. This nucleophilic aromatic substitution (S_N(Ar)) reaction, conducted at 60 – 65 °C, is facilitated by the presence of the neighboring electron-withdrawing 6-fluoro, 8-nitro and 4-keto entities. Related 6-fluoro-4-oxo-7-(substituted)phenoxyquinoline-3-carboxylic acids have recently been prepared in an analogous manner and evaluated as potential antitrypanosomal and antibacterial agents [20].

The second step involves reductive cyclization of compound **3** using $SnCl_2$/conc. HCl, and is initiated by the *in situ* generation of the 8-amino species **3A** (Scheme 1). This latter intermediate underwent spontaneous intramolecular cyclization involving the electrophilic formyl carbon (of ring B) and the suitably located nucleophilic amino group with ultimate construction of ring C in producing the [1,4]benzoxazepino[2,3-*h*]quinoline-3-carboxylate **5**. Acid-catalyzed hydrolysis of the latter ester furnished the corresponding carboxylic acid **6** as the target product. In this context, it is worth noting that com-

Table 1. Summary of the crystal data and structure refinement parameters for **5**.

Empirical formula	$C_{22}H_{17}FN_2O_4$
Formula weight M_r	392.38
Temperature, K	293(2)
Wavelength, Å	0.71073
Crystal system	orthorhombic
Space group	*Pbca*
Unit cell dimensions	
a, Å	18.1801(17)
b, Å	7.7376(8)
c, Å	26.418(3)
Volume, Å^3	371.6(3)
Z	8
Density (calcd.), mg m^{-3}	1.4
Absorption coefficient, mm^{-1}	0.1
F(000), e	1632
θ range for data collection, deg	2.96 – 25.03
Completeness to $\theta = 25.03°$, %	99.9
Index ranges *hkl*	$-20 \le h \le 21$, $-9 \le k \le 7$, $-31 \le l \le 15$
Reflections collected / independent	10102 / 3278
R_{int}	0.0332
Absorption correction	Semi-empirical from equivalents
Data / restraints / parameters	3278/ 0 / 272
*R*1 / *wR*2 [$I > 2\,\sigma(I)$][a,b]	0.0577 / 0.1214
*R*1 / *wR*2 (all data)[a,b]	0.1063 / 0.1479
Weight scheme[b], A / B	0.0588 / 0.8555
Goodness-of-fit on F^2 [c]	1.001
Largest difference peak / hole, e Å^{-3}	0.26 / −0.215

[a] $R1 = \Sigma|||F_o|| - ||F_c|||/\Sigma||F_o||$; [b] $wR2 = [\Sigma w(F_o^2 - F_c^2)^2/\Sigma w(F_o^2)^2]^{1/2}$, $w = [\sigma^2(F_o^2) + (AP)^2 + BP]^{-1}$, where $P = (\mathrm{Max}(F_o^2, 0) + 2F_c^2)/3$; [c] $\mathrm{GoF} = [\Sigma w(F_o^2 - F_c^2)^2/(n_{obs} - n_{param})]^{1/2}$.

Table 2. Selected bond lengths (Å) and angles (deg.) for **5**.

Bond lengths		Bond angles	
F(1)–C(6)	1.353(3)	C(2)–N(1)–C(13B)	119.7(2)
N(1)–C(2)	1.339(3)	C(2)–N(1)–C(1′)	116.4(2)
N(1)–C(13B)	1.408(3)	C(6A)–O(7)–C(7A)	115.1(2)
N(1)–C(1′)	1.463(3)	C(12)–N(13)–C(13A)	122.8(2)
O(7)–C(6A)	1.384(3)	N(1)–C(13B)–C(13A)	122.0(2)
O(7)–C(7A)	1.396(3)	C(7A)–C(11A)–C(12)	121.6(3)
N(13)–C(12)	1.276(3)	C(11)–C(11A)–C(12)	120.0(3)
N(13)–C(13A)	1.405(3)	C(6A)–C(13A)–N(13)	123.1(2)
O(14)–C(4)	1.241(3)	N(13)–C(13A)–C(13B)	118.6(2)
C(13B)–C(4A)	1.404(3)	C(4)–C(3)–C(15)	127.2(3)
C(4A)–C(4)	1.483(4)	O(7)–C(6A)–C(13A)	122.1(2)
C(11A)–C(7A)	1.382(4)	O(7)–C(6A)–C(6)	117.0(2)
C(11A)–C(12)	1.459(4)	N(1)–C(2)–C(3)	126.0(3)
C(13A)–C(6A)	1.388(4)	C(8)–C(7A)–O(7)	117.8(3)
C(3)–C(2)	1.364(4)	C(11A)–C(7A)–O(7)	119.5(3)
C(3)–C(4)	1.438(4)	O(14)–C(4)–C(3)	125.8(3)
C(3)–C(15)	1.485(5)	C(3)–C(4)–C(4A)	114.4(2)
O(17)–C(15)	1.329(4)	N(13)–C(12)–C(11A)	129.7(2)
O(17)–C(18)	1.476(5)		
O(16)–C(15)	1.199(4)		

pound **8** represents the first dibenz[*b*, *f*][1,4]oxazepine that was prepared by selective reduction of the appropriate nitro-aldehyde **7** to the respective amino-aldehyde **7A** which underwent spontaneous cyclization to give directly the desired Schiff base **8**, albeit in poor yield [21] (Scheme 2). Recent reinvestigation of this method has led to an improvement of the etherification procedure [22]. On the other hand, interaction of *o*-fluorobenzaldehyde with *o*-aminophenol, proceeding *via* initial imine formation followed by etherification (Scheme 3), represents an alternative one-pot synthesis of dibenz[*b*, *f*][1,4]oxazepine (**9**) [23].

Spectral properties

The IR, MS and NMR spectral and the microanalysis data for the new compounds **3** – **6** are in accordance with the assigned structures; details are given in the Experimental Section. Thus, the mass spectra display the correct molecular ion peaks for which the measured high resolution (HRMS) data are in good agreement with the calculated values. DEPT and 2D (COSY, HMQC, HMBC) experiments showed correlations that helped in the ^{1}H and ^{13}C signal assignments to the different carbons and the attached/neighboring hydrogens in compounds **3** – **6**. In the ^{13}C NMR spectra of **5** and **6**, the skeletal carbons of the benzo-fused entity (C-4, C-4a, C-5, C-6, C-6a) resonate as doublets due to scalar spin-spin coupling with the fluorine atom at C-6. Likewise, the skeletal carbons of ring B in compounds **3** and **4** are recognizable by their doublet signals originating from scalar (through bond) coupling with the

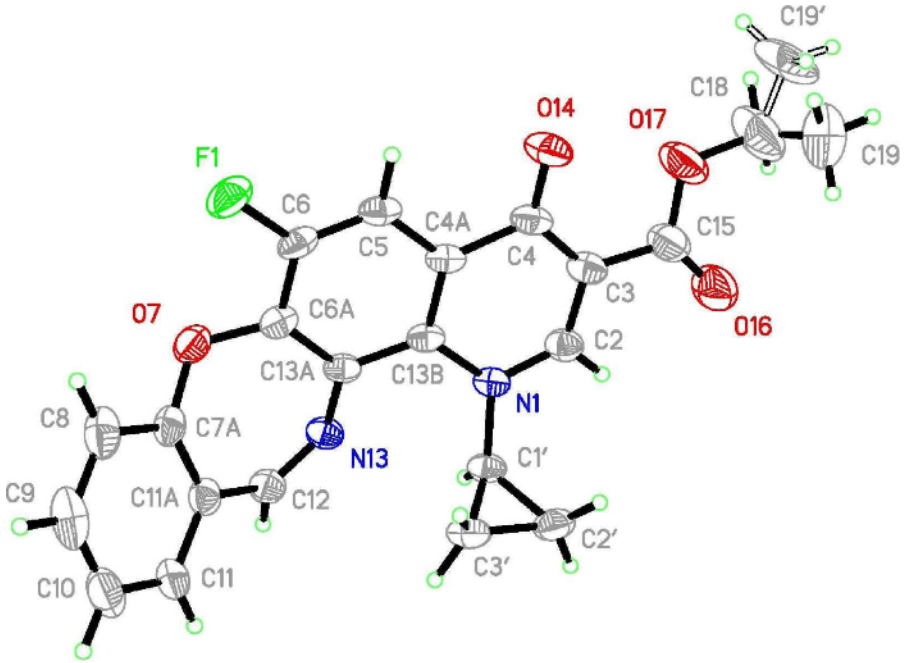


Fig. 2 (color online). An ORTEP plot of the molecular structure of **5**. Displacement ellipsoids are drawn at the 30 % probability level, H atoms with arbitrary radii. The methyl group C19 is disordered over two positions.

nearby fluorine atom. For compounds **5** and **6**, distinct "three-bond" (^{1}H, ^{13}C) correlations are observed between 5-H and each of C-4, C-6a and C-13b, between 2-H and each of C-4, C-13b and *C*O$_2$R, between 1′H and each of C-2 and C-13b, between 9-H/11-H and C-7a, between 8-H/10-H and C-11a, as well as between 12-H and each of C-7a and C-13a.

Molecular structure of ***5***

A crystal structure determination was performed to confirm the structure of **5** (and by inference that of **6**). A summary of data collection and refinement parameters is given in Table 1, while selected bond lengths and angles are provided in Table 2. The molecular structure of **5** in the crystal is displayed in Fig. 2. The three six-membered aromatic rings (A, B, D) in the molecular structure of **5** are planar and the dihedral angle between the plane containing the atoms N1-C2-C3-C4-C4A-C13B and the adjacent one containing atoms C6A-C13A-C4A-C5-C6-C13B-C4A is only 5.7(1)°. The dihedral angle between the two rings (B, D) spanning the seven-membered ring (C), namely C6A-C13A-C4A-C5-C6-C13B-C4A and C10-C11-C11A-C7A-C8-C9, is 44.0(1)°. As expected, the seven-membered ring is not planar with the dihedral angle between the fraction O7-C7A-C11A-C12 and the fraction O7-C6A-C13A-N13 being 57.7(1)°.

Preliminary pharmacological screening

Preliminary screening tests have indicated that compound **6** exhibit good activity against Candida Albicans clinical isolates, yet display moderate potency against Eschericia coli and Staphylococcus aureus. The preparation of several analogs of **6**, decorated with various substituents appended to ring D, for assessment of their biological properties is currently underway.

Experimental Section

The following chemicals, used in this study, were purchased from Acros and were used as received: 2,4-dichloro-5-fluoro-3-nitrobenzoic acid, ethyl 3-(*N,N*-dimethylamino)acrylate, cyclopropylamine, and salicylaldehyde. Melting points were determined on a Gallenkamp electrothermal melting apparatus in open capillary tubes. IR spectra were recorded as KBr discs on a Nicolet Impact-400 FT-IR spectrometer. Elemental analyses were performed on a Euro Vector elemental analyzer model EA 3000. ^{1}H and ^{13}C NMR spectra were recorded on a 500 MHz spectrometer (Bruker DPX-500) with TMS as the internal standard. Chemical shifts are expressed in δ units; J values for ^{1}H-^{1}H, ^{1}H-^{19}F and ^{13}C-^{19}F coupling constants are given in Hertz. Highresolution mass spectra (HRMS) were acquired (in positive mode) using the electrospray ion trap (ESI) technique by collision-induced dissociation on a Bruker APEX-4 (7 Tesla) 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^{-1}. External calibration was conducted using arginine cluster in a mass range m/z = 175 – 871.

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

This compound, required as starting material, was prepared from 2,4-dichloro-5-fluoro-3-nitrobenzoic acid, ethyl 3-(*N,N*-dimethylamino)acrylate, and cyclopropylamine, according to literature procedures [24 – 27].

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

To a stirred solution of compound **2** (1.1 g, 3 mmol) in DMF (20 mL) was added a freshly prepared solution of salicyldehyde (0.48 g, 4 mmol) in aqueous sodium hydroxide (0.16 g, 4 mmol), and the resulting mixture was heated at 60 – 65 °C for 4 – 5 h. Thereafter, the reaction mixture was cooled and poured onto ice water (100 mL); the precipitated product was collected by suction filtration, washed with water (3 × 10 mL), dried and recrystallized from ethanol. Yield: 1.2 g (90 %); m. p. 198 – 199 °C. – IR (KBr): ν = 3074, 2983, 2921, 2862, 1736, 1699, 1640, 1611, 1547, 1472, 1394, 1311, 1282, 1218, 1173, 1099, 1030 cm^{-1}. – HRMS ((+)-ESI): m/z = 441.10926 (calcd. 441.10980 for $C_{22}H_{18}FN_2O_7$ [M+H]$^+$); 463.09120 (calcd. 463.09175 for $C_{22}H_{17}FN_2O_7Na$ [M+Na]$^+$). – ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.14 (m, 2H) and 1.22 (m, 2H) (H_2-2′ + H_2-3′), 1.43 (t, J = 7.2 Hz, 3H, CH_3CH$_2$), 3.68 (m, 1H, H-1′), 4.43 (q, J = 7.2 Hz, 2H, OCH_2Me), 6.82 (d, J = 8.4 Hz, 1H, H-6″), 7.31 (dd, J = 7.7, 8.4 Hz, 1H, H-4″), 7.56 (ddd, J = 8, 8, 1 Hz, 1H, H-5″), 7.99 (dd, J = 7.7, 1.7 Hz, 1H, H-3″), 8.47 (d, $^3J_{H-F}$ = 10 Hz, 1H, H-5), 8.67 (s, 1H, H-2), 10.56 (s, 1H, -CHO). –^{13}C NMR (125 MHz, $CDCl_3$): δ = 10.9 (C-2′ + C-3′), 14.4 (CH_3), 38.0 (C-1′), 61.5 (-O*C*H$_2$Me), 112.2 (C-3), 115.1 (C-6″), 117.2 (d, $^2J_{C-F}$ = 20 Hz, C-5), 124.9 (C-4″), 125.5 (C-2″), 127.9 (d, $^3J_{C-F}$ = 5 Hz, C-4a), 129.3 (C-3″), 130.8 (d, $^4J_{C-F}$ = 1.3 Hz, C-8a), 135.8 (C-5″), 136.9 (d, $^3J_{C-F}$ = 1.2 Hz, C-8), 140.2 (d, $^2J_{C-F}$ = 17.5 Hz, C-7), 151.2 (d, $^1J_{C-F}$ = 255 Hz, C-6), 151.4 (C-2), 158.7 (C-1″), 164.2 (*C*O$_2$Et), 170.8 (d, $^4J_{C-F}$ = 1.2 Hz, C-4), 187.8 (HC=O). –

$C_{22}H_{17}FN_2O_7$ (440.38): calcd. C 60.00 H 3.89 N 6.36; found C 60.12 H 3.96 N 6.28.

*1-Cyclopropyl-6-fluoro-7-(2-formylphenoxy)-8-nitro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (**4**)*

A suspension of the ethyl ester **3** (0.5 g, 1.15 mmol) in 30 mL of 6 N aq. HCl was refluxed (oil bath 110 °C) for 48 h. Thereafter, the reaction mixture was cooled and poured onto ice water (30 mL); the precipitated product was collected by suction filtration, washed with water (3 × 4 mL), dried and recrystallized from ethanol. Yield: 0.35 g (84 %); m. p. 235 – 236 °C. – IR (KBr): $\nu =$ 3410, 3182, 3057, 2885, 1727, 1695, 1618, 1543, 1470, 1343, 1282, 1219, 1103, 1047, 1029 cm^{-1}. – HRMS ((+)-ESI): $m/z = 411.06340$ (calcd. 411.06285 for $C_{20}H_{12}FN_2O_7$ $[M-H]^+$). $-^1$H NMR (500 MHz, [D$_6$]DMSO): $\delta = 1.08$ (m, 2H) and 1.27 (m, 2H) (H_2-2′ + H_2-3′), 3.79 (m, 1H, H-1′), 7.17 (d, $J = 8.3$ Hz, 1H, H-6″), 7.42 (dd, $J = 7.6$, 7.7 Hz, 1H, H-4″), 7.72 (ddd, $J =$ 8.3, 7.7, 1.5 Hz, 1H, H-5″), 7.93 (dd, $J = 7.6$, 1.5 Hz, 1H, H-3″), 8.55 (d, $^3J_{H-F} = 10$ Hz, 1H, H-5), 8.89 (s, 1H, H-2), 10.44 (s, 1H, -CHO), 13.94 (s, 1H, exchangeable with D_2O, CO_2H). $-^{13}$C NMR (125 MHz, [D$_6$]DMSO): $\delta = 10.9$ (C-2′ + C-3′), 39.8 (C-1′), 109.6 (C-3), 116.5 (C-6″), 116.7 (d, $^2J_{C-F} =$ 20.4 Hz, C-5), 125.4 (C-2″), 125.6 (C-4″), 125.8 (d, $^3J_{C-F} = 7.5$ Hz, C-4a), 130.0 (C-3″), 132.2 (C-8a), 137.0 (C-5″), 137.2 (C-8), 141.2 (d, $^2J_{C-F} = 17.5$ Hz, C-7), 151.5 (d, $^1J_{C-F} = 253$ Hz, C-6), 153.2 (C-2), 158.4 (C-1″), 164.9 (*C*O_2H), 175.6 (d, $^4J_{C-F} = 2.2$ Hz, C-4), 188.9 (HC=O). – $C_{20}H_{13}FN_2O_7$ (412.32): calcd. C 58.26 H 3.18 N 6.79; found C 58.08 H 3.11 N 6.72.

*Ethyl 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo[1,4]benzoxazepino[2,3-h]quinoline-3-carboxylate (**5**)*

Anhydrous stannous chloride (1.25 g, 6.6 mmol) was added portionwise to a vigorously stirred and cooled (0 to 4 °C) solution of the ester **3** (4 mmol) in conc. HCl (10 mL). The reaction mixture was further stirred for additional 12 – 15 h at r. t. Thereafter, the solution was diluted with ice water (100 mL) and treated portionwise with a cold aqueous solution of sodium hydroxide (40 %, 25 mL) to pH ∼14. The resulting yellowish precipitate was collected by suction filtration, washed with water (4 × 10 mL), and dried. Yield: 1.36 g (87 %); m. p. 249 – 250 °C. – IR (KBr): $\nu =$ 3075, 2980, 2950, 2928, 2878, 1729, 1694, 1627, 1552, 1467, 1447, 1341, 1319, 1246, 1186, 1088, 1027 cm^{-1}. – HRMS ((+)-ESI): $m/z = 393.12451$ (calcd. 393.12506 for $C_{22}H_{18}FN_2O_4$ $[M+H]^+$); 415.10646 (calcd. 415.10700 for $C_{22}H_{17}FN_2O_4Na$ $[M+Na]^+$). $-^1$H NMR (500 MHz, [D$_6$]DMSO): $\delta = 0.84$ (m, 2H) and 1.03 (m, 2H) (H_2-2′ + H_2-3′), 1.24 (t, $J = 7$ Hz, 3H, C*H*$_3$CH$_2$), 4.22 (q, $J = 7$ Hz, 2H, CH$_3$C*H*$_2$), 4.25 (m, 1H, H-1′), 7.31 (d, $J = 8$ Hz, 1H, H-8), 7.47 (dd, $J = 7.4$, 7.6 Hz, 1H, H-10), 7.66 (dd, $J = 8$, 7.6 Hz, 1H, H-9), 7.73 (d, $J = 7.4$ Hz, 1H, H-11), 7.84 (d, $^3J_{H-F} = 10$ Hz, 1H, H-5), 8.54 (s, 1H, H-2), 8.94 (s, 1H, H-12). $-^{13}$C NMR (125 MHz, [D$_6$]DMSO): $\delta = 11.7$ (C-2′/C-3′), 14.7 (*C*H$_3$CH$_2$), 42.0 (C-1′), 60.4 (MeC*H*$_2$O), 110.2 (d, $^2J_{C-F} = 20$ Hz, C-5), 110.4 (C-3), 121.0 (C-8), 127.1 (d, $^3J_{C-F} = 6.7$ Hz, C-4a), 127.2 (C-10), 128.0 (C-13b), 130.4 (C-11), 133.2 (C-11a), 134.6 (C-9), 135.0 (C-13a), 145.2 (d, $^2J_{C-F} = 13.8$ Hz, C-6a), 150.8 (d, $^1J_{C-F} = 248$ Hz, C-6), 151.6 (C-2), 160.6 (C-7a), 161.2 (C-12), 164.5 (*C*O_2Et), 171.6 (C-4). – $C_{22}H_{17}FN_2O_4$ (392.38): calcd. C 67.34 H 4.37 N 7.14; found C 67.18 H 4.26 N 7.05.

*1-Cyclopropyl-6-fluoro-1,4-dihydro-4-oxo[1,4]benzoxazepino[2,3-h]quinoline-3-carboxylic acid (**6**)*

A suspension of the ethyl ester **5** (1.57 g, 4 mmol) in 30 mL of 6 N aq. HCl was refluxed (oil bath 110 °C) for 48 h. Thereafter, the reaction mixture was cooled and poured onto ice water (100 mL); the precipitated product was collected by suction filtration, washed with water (3 × 10 mL), dried and recrystallized from ethanol. Yield: 1.2 g (82 %); m. p. 305 – 306 °C (darkens around 250 °C). – IR (KBr): $\nu =$ 3412, 3074, 2973, 2921, 1762, 1695, 1613, 1547, 1444, 1320, 1272, 1194, 1090, 1029 cm^{-1}. – HRMS ((+)-ESI): $m/z = 365.09431$ (calcd. 365.09376 for $C_{20}H_{14}FN_2O_4$ $[M+H]^+$). $-^1$H NMR (500 MHz, [D$_6$]DMSO): $\delta = 0.92$ (m, 2H) and 1.10 (m, 2H) (H_2-2′ + H_2-3′), 4.42 (m, 1H, H-1′), 7.34 (d, $J = 8$ Hz, 1H, H-8), 7.49 (dd, $J =$7.6, 7.4 Hz, 1H, H-10), 7.69 (dd, $J = 8$, 7.6 Hz, 1H, H-9), 7.76 (d, $J = 7.4$ Hz, 1H, H-11), 8.03 (d, $^3J_{H-F} = 9.5$ Hz, 1H, H-5), 8.80 (s, 1H, H-2), 9.00 (s, 1H, H-12), 14.6 (br s, 1H, exchangeable with D_2O, CO_2H). $-^{13}$C NMR (125 MHz, [D$_6$]DMSO): $\delta = 11.8$ (C-2′/C-3′), 43.4 (C-1′), 108.2 (C-3), 109.6 (d, $^2J_{C-F} = 20.1$ Hz, C-5), 121.1 (C-8), 124.6 (d, $^3J_{C-F} = 7.5$ Hz, C-4a), 127.4 (C-10), 127.9 (C-13b), 130.6 (C-11), 133.7 (C-11a), 134.8 (C-9), 135.8 (C-13a), 146.4 (d, $^2J_{C-F} = 15$ Hz, C-6a) 151.5 (d, $^1J_{C-F} = 248$ Hz, C-6), 151.9 (C-2), 160.6 (C-7a), 162.0 (C-12), 165.7 (*C*O_2H), 176.9 (d, $^4J_{C-F} = 2.8$Hz, C-4). -$C_{20}H_{13}FN_2O_4$ (364.33): calcd. C 65.93 H 3.60 N 7.69; found C 65.76 H 3.52 N 7.61.

*X-Ray structure analysis of **5***

Crystals were grown by allowing a clear solution of **5** in DMSO in an open vessel to stand at room temperature for 4 – 5 days. A suitable needle-like fragment with approximate dimensions of $0.51 \times 0.09 \times 0.07$ mm^3, cut from a longer slightly yellowish crystal, was epoxymounted on a glass fiber. The data were collected at room temperature employing MoK_α radiation using a Calibur/Oxford diffractometer equipped with an Eos CCD detector. CrysAlis Pro soft-

ware was used for data collection, absorption correction and data reduction [28]. Three sets of ω scans were collected yielding 167 frames. Average exposure time was 65.8 s per frame. A one-degree scan width was used and the detector to crystal distance was 45 mm. A multi-scan absorption correction was applied with minimum and maximum transmission factors of 0.815 and 1.000, respectively. Cell parameters were refined using all observed reflections. The structure was solved by Direct Methods using OLEX 2 [29] and refined by full-matrix least-squares on F^2. Refinement was done using the SHELXTL program package [30, 31]. The terminal methyl group C19 of the ethyl ester group was found disordered and modeled over two positions with 0.67 and 0.33 occupancy, respectively. All nonhydrogen atoms were refined anisotropically with the hydrogen atoms placed constrained and assigned isotropic thermal parameters of 1.2 times that of the riding atoms. Molecular graphics and publication material were prepared using SHELXTL [30].

CCDC 882392 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

Acknowledgement

We wish to thank the Deanship of Scientific Research at The University of Jordan, Amman (Jordan), for financial support.

[1] Part IX: J. A. Zahra, H. I. Al-Jaber, M. M. El-Abadelah, M. M. Al-Abadleh, *Heterocycles* **2011**, *83*, 2165 – 2175.
[2] R. Wise, J. M. Andrews, L. J. Edwards, *Antimicrob. Agents Chemother.* **1983**, *23*, 559 – 564.
[3] D. Felmingham, M. D. O'Hare, M. J. Robbins, R. A. Wall, A. H. Williams, A. W. Cremer, G. L. Ridgeway, R. N. Gruneberg, *Drugs Exp. Clin. Res.* **1985**, *11*, 317 – 329.
[4] F. Maurer, K. Grohe, Ger. Offen. 3,435,392, **1986**; *Chem. Abstr.* **1986**, *105*, 97158e.
[5] U. Petersen, S. Bartel, K. D. Bremm, T. Himmler, A. Krebs, T. Schenke, *Bull. Soc. Chim. Belg.* **1996**, *105*, 683 – 699.
[6] T. Okada, K. Ezumi, M. Yamakawa, H. Sato, T. Tsuji, T. Tsushima, K. Motokawa, Y. Komatsu, *Chem. Pharm. Bul. Jpn.* **1993**, *41*, 126 – 131.
[7] K. Grohe, *Quinolone Antibacterials*, Springer Verlag, Berlin, Heidelberg, **1998**, pp. 13 – 62.
[8] Q. Li, L. A. Mitscher. L. L. Shen, *Med. Res. Rev.* **2000**, *20*, 231 – 293.
[9] G. G. Zhanel, K. Ennis, L. Vercaigne, A. Walkty, A. S. Gin, J. Embil, H. Smith, D. J. Hoban, *Drugs* **2002**, *62*, 13 – 59.
[10] A. D. Da Silva, M. V. De Almeida, M. V. N. De Souza, M. R. C. Couri, *Curr. Med. Chem.* **2003**, *10*, 21 – 39.
[11] M. Daneshtalab, *Topics in Heterocyclic Chemistry*, Vol. 2, *Heterocyclic Antitumor Antibiotics*, Springer Verlag, Berlin, Heidelberg, **2005**, pp. 153 – 173.
[12] L. A. Mitscher, *Chem. Rev.* **2005**, *105*, 559 – 592.
[13] A. Fiorentino, B. D'Abrosca, S. Pacifico, G. Cefarelli, P. Uzzo, P. Monaco, *Bioorg. Med. Chem. Lett.* **2007**, *17*, 636 – 639.
[14] K. D. Hargrave, G. Schmidt, W. Engel, K. Schromm, Can. Pat. Appl. CA 2024040 A1, **1991**; *Chem. Abstr.* **1991**, *115*, 183381.
[15] J. W. Corbett, *Curr. Med. Chem.-Anti-Infective Agents* **2002**, *1*, 119 – 140.
[16] S. F. Petras, S. Lindsey, H.J.Jr. Harwood, *J. Lipid Res.* **1999**, *40*, 24 – 38.
[17] G. Galley, R. A. Goodnow, J.-U. Peters, U. S. Pat. Appl. Publ., US 0235819 A1, **2004**; *Chem. Abstr.* **2004**, *141*, 1019771.
[18] H. Lacasse, M. M. Perreault, D. R. Williamson, *Annals of Pharmacotherapy* **2006**, *40*, 1966 – 1973.
[19] S. Jafari, F. Fernandez-Enright, X.-F. Huang, *J. Neurochem.* **2012**, *120*, 371 – 384.
[20] X. Ma, W. Zhou, R. Brun, *Bioorg. Med. Chem. Lett.* **2009**, *19*, 986 – 989.
[21] A. W. H. Wardrop, G. L. Sainsbury, J. M. Harrison, T. D. Inch, *J. Chem. Soc., Perkin Trans. 1* **1976**, 1279 – 1285.
[22] H. Fakhraian, Y. Nafary, A. Yarahmadi, H. Hadj-Ghanbary, *J. Heterocycl. Chem.* **2008**, *45*, 1469 – 1472, and refs. cited therein.
[23] H. Fakhraian, Y. Nafary, *J. Heterocycl. Chem.* **2009**, *46*, 988 – 992.
[24] K. Grohe, H. Heitzer, *Liebigs Ann. Chem.* **1987**, 29 – 37.
[25] U. Petersen, K. Grohe, T. Schenke, H. Hagemann, H. J. Zeiler, K. G. Metzger, Ger. Offen. 3 601 567, **1987**; *Chem. Abstr.* **1987**, *107*, P236747.
[26] R. M. Pulla, C. N. Venkaiah, PCT Int. Appl. WO 085 692, **2001**; *Chem. Abstr.* **2001**, *135*, P371649.
[27] Y. M. Al-Hiari, I. S. Al-Mazari, A. Shakya, K. Darwish, R. M. Abu-Dahab, *Molecules* **2007**, *12*, 1240 – 1258.
[28] CRYSALIS PRO (version 1.171.35.11; release 16-05-2011), Agilent Technologies, Yarnton, Oxfordshire (England) **2011**.
[29] O. V. Dolomanov, L. J. Bourhis, R. J. Gildea, J. A. K. Howard, H. Puschmann, *J. Appl. Cryst.* **2009**, *42*, 339 – 341.

[30] G. M. Sheldrick, SHELXTL (version 6.10), Bruker Analytical X-ray Instruments Inc., Madison, Wisconsin (USA) **2000**.

[31] G. M. Sheldrick, *Acta Crystallogr.* **2008**, *A64*, 112 – 122.