HETEROCYCLES, Vol. 83, No. 9, 2011, pp. 2165 - 2175. © The Japan Institute of Heterocyclic Chemistry
Received, 5th June, 2011, Accepted, 8th July, 2011, Published online, 20th July, 2011
DOI: 10.3987/COM-11-12274

HETEROCYCLES [*H*]-FUSED TO 4-OXOQUINOLINE-3-CARBOXYLIC ACID. PART IX.[1] SYNTHESIS OF 2,6-DIOXOTETRAHYDRO-1*H*-PYRROLO[3,2-*H*]QUINOLINE-7-CARBOXYLIC ACID

Jalal A. Zahra,[*a] Hala I. Al-Jaber,[b] Mustafa M. El-Abadelah,[a] and Mohammed M. Abadleh[c]

[a] Chemistry Department, Faculty of Science, The University of Jordan, Amman, Jordan

[b] Department of Basic sciences, Faculty of Engineering Technology, Al-Balqa Applied University, Marka, Amman, 1134, Jordan

[c] College of Pharmacy, Taibah University, Al Madinah, 41477, Saudia Arabia

[*]e-mail: zahra@ju.edu.jo

Abstract – Interaction of deprotonated malonic esters with 7-chloro-8-nitro-4-oxoquinoline-3-carboxylate (**1**) gave the respective 7-[bis(alkoxycarbonyl)-methyl] derivatives (**2**, **3**) which were converted into the corresponding 7-(carboxymethyl)-8-nitro-4-oxoquinoline-3-carboxylic acid (**4**). Reductive lactamization of the latter furnished the target tetrahydro-2,6-dioxo-1*H*-pyrrolo-[3,2-*h*]quinoline-7-carboxylic acid (**5**). Both compounds **4** and **5** exhibited broad spectrum of high antibacterial activity against representatives of Gram-negative and Gram-positive bacteria classes, but were less potent than the reference ciprofloxacin.

During the past three decades, several members of the fluoroquinolone family have emerged as highly potent anti-infective agents with broad spectrum against Gram-positive and Gram-negative bacteria.[2-5] Examples include ciprofloxacin,[3] levofloxacin[4] and moxifloxacin[5] (Figure 1).

On the other hand, the oxindole ring system is a privileged motif that constructs the core of a large family of bioactive natural products and a series of pharmaceutically active compounds.[6-13] Amongst these are the spiro[pyrrolidine-3,3-oxindole] alkaloids[7,8] e.g. horsfiline,[8] 3-substituted-3-hydroxyoxindoles[9,10] e.g. convolutamydine A,[10] and 3-alkenyl-oxindoles[11,12] e.g. soulieotine[12] and the synthetic antitumor drug sunitinib (sutent®)[13] (Figure 2).

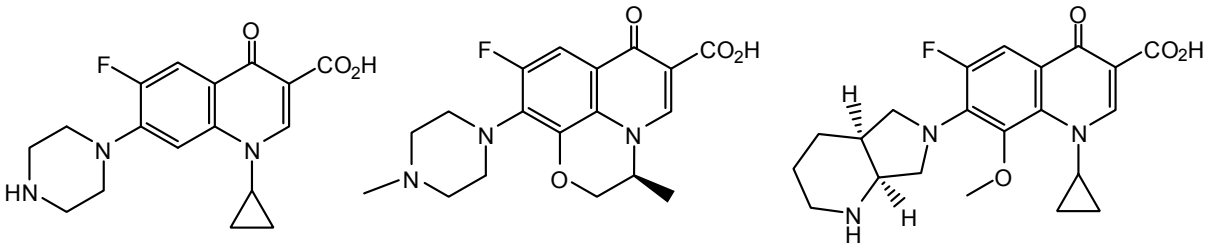


Figure 1. Structures of some fluoroquinolones in clinical use

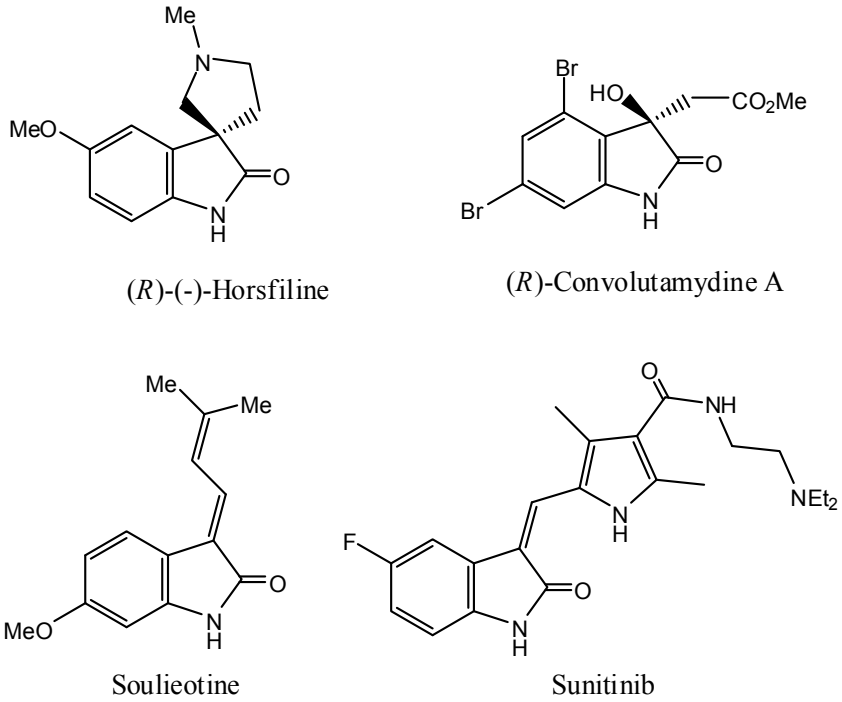
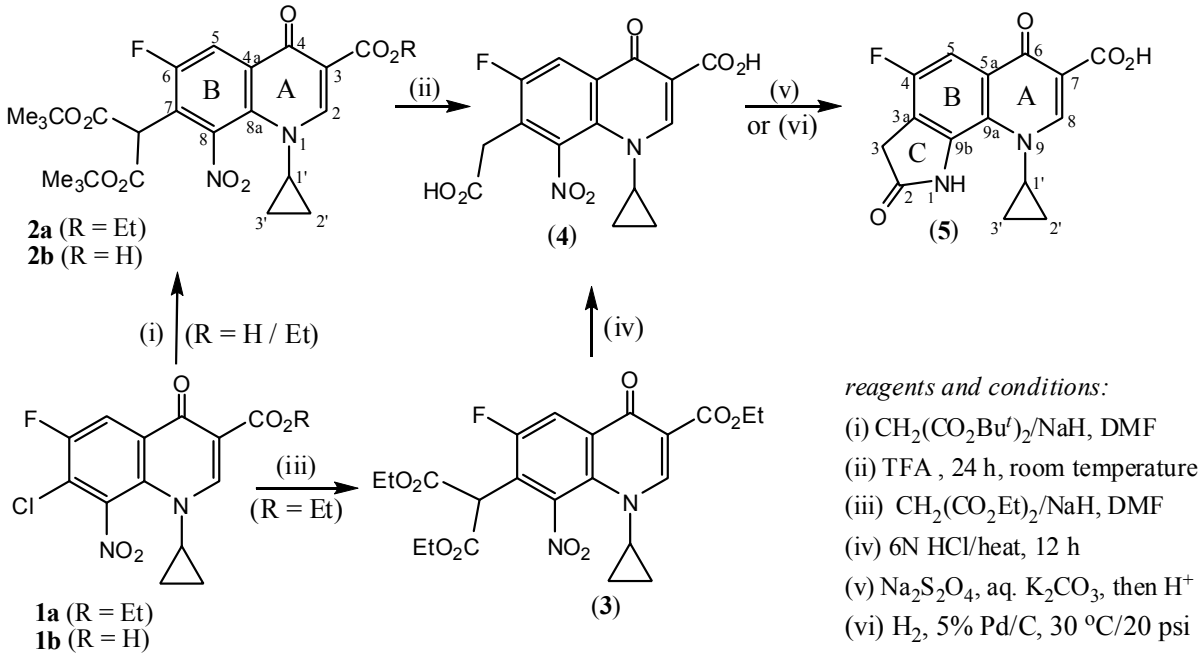


Figure 2. Representative natural products and bioactive compounds with 3,3-disubstituted- and 3-alkenyloxindole framework

As part of an ongoing program aimed at developing facile synthesis of novel heterocycles [*h*]-fused onto 1-cylopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid, we have recently explored the synthesis of some imidazo[4,5-*h*]quinolines,[14] of a [1,2,5]thiadiazolo[3,4-*h*]quinoline,[15] and of related tetracyclic fluoroquinolones[16] which are endowed with strong antibacterial activity. Along these lines, we have envisaged to construct a tricyclic sytem having a 2-pyrrolidinone ring [*h*]condensed with the fluoroquinolone partner. Accordingly, we report herein a synthesis of 2,6-dioxotetrahydro-1*H*-pyrrolo[3,2-*h*]quinoline-7-carboxylic acid (**5**) (Scheme 1), a new tricyclic hybrid combining the structural features of both fluoroquinolone (rings A, B) and oxindole (rings B, C) biophoric chemotype moieties. It is anticipated that **4** and/or **5** might possess interesting pharmacological properties.



Scheme 1. Synthesis of dioxo-1*H*-pyrrolo[3,2-*h*]quinoline-7-carboxylic acid (**5**)

Synthesis

The synthesis of 2,6-dioxotetrahydro-1*H*-pyrrolo[3,2-*h*]quinoline-7-carboxylic acid (**5**) is achieved by utilizing the appropriate 4-oxoquinoline-3-carboxylate (**1a**, **1b**), accessible from 2,4-dichloro-5-fluoro-3-nitrobenzoic acid,[17] and constructing the 2-pyrrolidinone nucleus thereupon through a series of conversions as illustrated in Scheme 1. Thus, displacement of the chloride from 7-chloro-1-cyclopropyl-6-fluoro-4-oxoquinoline-3-carboxylate (**1a**, **1b**) by deprotonated malonate (using NaH in DMF) produced the corresponding 7-[bis(alkoxycarbonyl)methyl]quinoline-3-carboxylic acid (**2b**) or the respective ethyl esters **2a**, **3** (Scheme 1). This nucleophilic aromatic substitution (S_N-Ar) reaction, conducted at room temperature, is facilitated by the presence of the neighboring electron-withdrawing 6-fluoro, 8-nitro and 4-keto entities. The methodology adopted herein is modeled on previous reports describing the preparation of related arylmalonates from their *ortho*-halonitroarene precursors.[18-23] In a subsequent step, acid-catalyzed ester hydrolysis of compounds **2a**, **2b** or **3** led to the generation of the corresponding 7-malonic acid-derived intermediate which then suffered monodecarboxylation to afford the respective 7-(carboxymethyl)-8-nitro-4-oxoquinoline-3-carboxylic acid (**4**) in moderate yield. Finally, reduction of the nitro group in compound **4** and spontaneous lactamization produced the corresponding 2,6-dioxo-1*H*-pyrrolo[3,2-*h*]quinoline-7-carboxylic acid (**5**). This reductive cyclization step was achieved in alkaline sodium dithionite,[24,25] and by catalytic hydrogenation. Yields are similar but the former dithionite method is being preferred whereby the obtained crude cyclized product **5** is highly pure, and the experimental procedure is very simple and fast.

Spectral properties

The new compounds **2–5** were characterized by elemental analyses, IR, MS and NMR spectral data. These data, detailed in the experimental part, are consistent with the suggested structures. 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 their attached, and/or neighboring hydrogens. For compounds **2-4**, long-range correlations are observed between H-5 and each of C-8a, C-4 and C-7; likewise, H-2 is correlated with C-8a, C-4, C-1', and CO$_2$Et/CO$_2$H. For compound **5**, similar long-range correlations are also observed between H-3, and each of C-4 and C-9b, between H-5 and each of C-3a, C-9a and C-6, as well as between H-8 and each of C-6, C-9a and CO$_2$H. In compounds **2-5**, the carbons of the benzo-fused ring B are readily identified by their doublet signals (with varying $J_{C\text{-}F}$-values) originating from spin-spin coupling with the nearby fluorine atom.

Antibacterial activity

In vitro antibacterial screening of compounds **4** and **5** were performed and compared with the reference ciprofloxacin. The results showed that **4** and **5** exhibited high antibacterial activity against representatives of Gram-negative and Gram-positive bacteria classes (Table 1). Interestingly, compound **4** displayed higher potency against *B*. *subtilis* and *E*. *coli*, while compound **5** showed higher potency against *S*. *aureu*s and *H*. *influenzae* . Both **4** and **5** were, however, less potent than the reference ciprofloxacin.

Table 1. *In vitro* antibacterial activity of compounds **4** and **5**, expressed as MIC (μg mL^{-1})

Compound No.	BS[a]	SA[a]	EC[b]	HI[b]
4	0.15	1.5	1.5	0.7
5	0.7	0.7	3	0.3
ciprofloxacin	0.03	0.3	0.015	0.15

[a]Gram positive bacteria: *Bacillus subtilis* ATCC 6633 (BS) and *Staphylococcus aureu*s ATCC 6538 (SA); [b]Gram negative bacteria: *Escherichia coli* ATCC 8739 (EC) and *Haemophilus influenzae* ATCC 19418 (HI).

An efficient and facile method is reported for the synthesis of 9-cyclopropyl-4-fluoro-2,3,6,9-tetrahydro-2,6-dioxo-1*H*-pyrrolo[3,2-*h*]quinoline-7-carboxylic acid (5) utilizing 7-chloro-8-nitro-4-oxoquinoline-3-carboxylate (1). Thus, an α-malonic ester moiety is introduced at C-7 locus of 1,

followed by transformation of the resulting derivatives (2, 3) into the respective 7-(carboxymethyl) analog 4. Reductive lactamization of the latter gave the target 5. Both compounds 4 and 5 exhibited broad spectrum of high antibacterial activity, but were less potent than the reference ciprofloxacin.

Our prime interest has been related to mixed aldol condensation reaction that the α-methylene (C-3) carbon of compound 5 would undergo with different 2-alkenals, aryl- and hetaryl carboxaldehydes. The preparation of various 3-alkenyl derivatives of 5 (congeners of soulieotine and sunitinib oxindolic drugs, Figure 2) for assessment of their biological properties and for comparative studies is currently underway.

EXPERIMENTAL

2,4-Dichloro-5-fluoro-3-nitrobenzoic acid, ethyl 3-(*N,N*–dimethylamino)acrylate, cyclopropyl- amine, sodium hydride (60% in mineral oil), diethyl malonate and di-*tert*-butyl malonate were purchased from Acros. Melting points (uncorrected) were determined on a Gallenkamp electrothermal melting-temperature apparatus. IR spectra were, in cm^{-1}, recorded as KBr discs on a Thermo Nicolet Nexus 670 FT-IR spectrophotometer. ^{1}H and ^{13}C NMR spectra were measured on a Bruker DPX-300 instrument. Chemical shifts are expressed in ppm with reference to *TMS* as internal standard. High-resolution mass spectra (HRMS) were measured (in positive or negative ion mode) using 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 (MeOH/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. Elemental analyses (C, H, N) were performed at the Microanalytical Laboratory of the Hashemite University, Zarqa-Jordan, and the results were found to be in good agreement (± 0.4%) with the calculated values.

Ethyl 7-chloro-1-cyclopropyl-6-fluoro-8-nitro-4-oxo-1,4-dihydroquinoline-3-carboxylate (1a) and the corresponding 3-carboxylic acid (1b)

These synthons were prepared from 2,4-dichloro-5-fluoro-3-nitrobenzoic acid, ethyl 3-(*N,N*-dimethylamino)acrylate and cyclopropylamine, according to literature procedures.[17]

Ethyl 7-[bis(*tert*-butoxycarbonyl)methyl]-1-cyclopropyl-6-fluoro-8-nitro-1,4-dihydro-4-oxoquinoline-3-carboxylate (2a)

To a stirred and cooled (0-5 °C) suspension of NaH (60% in mineral oil, 1.0 g, 25 mmol) in dry DMF (40 mL) was added di-*tert*-butyl malonate (5.4 g, 25 mmol) over 10 min. The mixture was maintained at 0-5 °C for additional 10 min, before the addition of **1a** (2.2 g, 6.2 mmol). The resultant orange-coloured reaction mixture was stirred at room temperature for 12 h, then poured into a mixture of ice-water (50

mL) and EtOAc (50 mL). The whole mixture was acidified with 6N HCl to pH 2, and the organic layer was separated, washed successively with water and saturated brine solution, then dried and evaporated. The residue was triturated with EtOH to afford the desired title product **2a** (2.2 g, 74%). An analytical sample was obtained by recrystallization from EtOH as faint yellow needles, mp 162-165 °C (dec). IR (KBr): ν 3093, 2979, 2934, 1732, 1637, 1605, 1541, 1473, 1393, 1367, 1337, 1260, 1150 cm^{-1}. ESI-HRMS: Calcd for $C_{26}H_{31}FN_2O_9Na$ $[M + Na]^+$: 557.19058. Found: 557.19024. ^1H NMR (300 MHz, $CDCl_3$): δ 0.80 (m, 2H) and 1.06 (m, 2H) (H_2-2'/H_2-3'), 1.33 (t, J = 7.1 Hz, 3H, CH_3CH_2O-), 1.46 [s, 18 H, $2C(CH_3)_3$], 3.66 (m, 1H, H-1'), 4.37 (q, J = 7.1 Hz, 2H, -OCH_2Me), 6.50 [br s, 1H, $CH(CO_2Bu^t)_2$], 7.81 (d, $^3J_{H\text{-}F}$ = 8.9 Hz, 1H, H-5), 8.52 (s, 1H, H-2). ^{13}C NMR (75 MHz, $CDCl_3$): δ 10.3 (C-2'/C-3'), 14.4 (CH_3CH_2O-), 28.0 [$2C(CH_3)_3$], 39.5 (C-1'), 52.0 [$CH(CO_2Bu^t)_2$], 61.3 (OCH_2Me), 82.6 [$2OC(CH_3)_3$], 113.7 (C-3), 117.3(d, $^2J_{C\text{-}F}$ = 30.8 Hz, C-5), 129.5 (d, $^2J_{C\text{-}F}$ = 14.8 Hz, C-7), 129.8 (d, $^3J_{C\text{-}F}$ = 3.4 Hz, C-4a), 132.3 (d, $^4J_{C\text{-}F}$ = 2.2 Hz, C-8a), 141.2 (d, $^3J_{C\text{-}F}$ = 9.1 Hz, C-8), 150.1 (C-2), 156.5 (d, $^1J_{C\text{-}F}$ = 250 Hz, C-6), 163.8 (CO_2Et), 166.4 ($2CO_2Bu^t$), 174.5 (d, $^4J_{C\text{-}F}$ = 2.3 Hz, C-4). Anal. Calcd for $C_{26}H_{31}FN_2O_9$ (534.53 g mol^{-1}): C, 58.42; H, 5.85; N, 5.24. Found: C, 58.33; H, 5.76; N, 5.21.

7-[Bis(*tert*-butoxycarbonyl)methyl]-1-cyclopropyl-6-fluoro-8-nitro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (2b)

To a stirred and cooled (0-5 °C) suspension of NaH (60% in mineral oil, 2.0 g, 50 mmol) in dry DMF (40 mL) was added di-*tert*-butyl malonate (5.4 g, 25 mmol) over 10 min. The mixture was allowed to warm to room temperature before the addition of **1b** (2.0 g, 6.1 mmol). The resultant reaction mixture was stirred at room temperature for 24 h and worked up as described for **2a** above to afford **2b** (2.2 g, 71%). An analytical sample was obtained by recrystallization from MeOH as faint yellow needles, mp 212-214 °C. ESI-HRMS: Calcd for $C_{24}H_{26}FN_2O_9$ $[M - H]^-$: 505.16169. Found: 505.16212. ^1H NMR (300 MHz, $CDCl_3$): δ 0.88 (m, 2H) and 1.16 (m, 2H) (H_2-2'/H_2-3'), 1.45 [s, 18 H, $2C(CH_3)_3$], 3.81 (m, 1H, H-1'), 6.01 [br s, 1H, $CH(CO_2Bu^t)_2$], 7.95 (d, $^3J_{H\text{-}F}$ = 8.6 Hz, 1H, H-5), 8.91 (s, 1H, H-2), 13.87 (br s, 1H, CO_2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 10.6 (C-2'/C-3'), 27.9 [$2C(CH_3)_3$], 40.8 (C-1'), 52.2 [$CH(CO_2Bu^t)_2$], 83.1 [$2OC(CH_3)_3$], 111.0 (C-3), 119.1(d, $^2J_{C\text{-}F}$ = 31.6 Hz, C-5), 127.8 (d, $^3J_{C\text{-}F}$ = 3.7 Hz, C-4a), 129.1 (d, $^2J_{C\text{-}F}$ = 14.4 Hz, C-7), 132.7 (d, $^4J_{C\text{-}F}$ = 2.3 Hz, C-8a), 141.9 (d, $^3J_{C\text{-}F}$ = 9.2 Hz, C-8), 151.5 (C-2), 156.6 (d, $^1J_{C\text{-}F}$ = 251 Hz, C-6), 165.1 ($2CO_2Bu^t$), 165.6 (CO_2H), 178.8 (d, $^4J_{C\text{-}F}$ = 2.8 Hz, C-4). Anal. Calcd for $C_{24}H_{27}FN_2O_9$ (506.48 g mol^{-1}): C, 56.91; H, 5.37; N, 5.53. Found: C, 56.73; H, 5.26; N, 5.48.

Ethyl 7-[bis(ethoxycarbonyl)methyl]-1-cyclopropyl-6-fluoro-8-nitro-1,4-dihydro-4-oxoquinoline-3-carboxylate (3)

To a stirred and cooled (0-5 °C) suspension of NaH (60% in mineral oil, 1.0 g, 25 mmol) in dry DMF (40 mL) was added diethyl malonate (4.0 g, 25 mmol) over 10 min. The mixture was maintained at 0-5 °C for additional 10 min, before the addition of **1a** (2.2 g, 6.2 mmol). The resultant orange-coloured reaction mixture was stirred at room temperature for 12 h and worked up as described above for **2a** above to afford **3** (2.4 g, 81%). An analytical sample was obtained by recrystallization from EtOH as faint yellow needles, mp 176-178 °C. (KBr): ν3103, 2941, 2924, 2855, 1781, 1729, 1611, 1541, 1465, 1370, 1312, 1266, 1222, 1134, 1031 cm^{-1}. ESI-HRMS: Calcd for $C_{22}H_{24}FN_2O_9$ $[M+H]^+$: 479.14603. Found: 479.14618; Calcd for $C_{22}H_{23}FN_2O_9$ Na $[M+Na]^+$: 501.12798. Found: 501.12817. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.97 (m, 2H) and 1.10 (m, 2H) (H_2-2'/H_2-3'), 1.26 (t, J = 7.1 Hz, 6H, $CH(CO_2CH_2CH_3)_2$), 1.38 (t, J = 7.1 Hz, 3H, C(3)-$CO_2CH_2CH_3$), 3.60 (m, 1H, H-3'), 4.26 (q, J = 7.1 Hz, 4H, $CH(CO_2CH_2Me)_2$), 4.37 (q, J = 7.1 Hz, 2H, C(3)-CO_2CH_2Me), 4.63 (s, 1H, $CH(CO_2Et)_2$), 8.35 (d, $^3J_{H\text{-}F}$ = 9.7 Hz, 1H, H-5), 8.63 (s, 1H, H-2). ^{13}C NMR (75 MHz, $CDCl_3$): δ 10.9 (C-2'/C-3'), 14.0 $(CO_2CH_2CH_3)_2$, 14.4 (C(3)-$CO_2CH_2CH_3$), 38.3 (C-1'), 50.7 ($CH(CO_2Et)_2$), 61.5 (CO_2CH_2Me), 62.9 $(CO_2CH_2Me)_2$, 112.0 (C-3), 116.4 (d, $^2J_{C\text{-}F}$ = 24.8 Hz, C-5), 122.6 (d, $^4J_{C\text{-}F}$ = 20.5 Hz, C-7), 130.6 (d, $^4J_{C\text{-}F}$ = 2.3 Hz, C-8a), 132.1 (d, $^3J_{C\text{-}F}$ = 7.3 Hz, C-4a), 141.6 (d, $^3J_{C\text{-}F}$ = 2.9 Hz, C-8), 152.0 (C-2), 157.0 (d, $^1J_{C\text{-}F}$ = 252 Hz, C-6), 164.3 (CO_2Et), 165.1 $(CO_2Et)_2$, 171.1 (d, $^4J_{C\text{-}F}$ = 1.8 Hz, C-4). Anal. Calcd for $C_{22}H_{23}FN_2O_9$ (478.42 g mol^{-1}): C, 55.23; H, 4.85; N, 5.86. Found: C, 55.06; H, 4.82; N, 5.90.

7-(Carboxymethyl)-1-cyclopropyl-6-fluoro-8-nitro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (4)

Method (a): Trifluoroacetic acid (TFA) (2 mL) was added to a solution of **2b** (1.0 g, 2.0 mmol) in CH_2Cl_2 at room temperature. The reaction mixture was stirred overnight, then concentrated under reduced pressure and the residue treated with Et_2O (10 mL) to induce crystallization. The crystals were collected by suction filtration to give the title compound **4** (0.44 g, 63%). This product was recrystallized from DMF as yellowish needles, mp 275-278 °C (dec). Likewise, treatment of **2a** (1.6 g, 3 mmol) in CH_2Cl_2 with TFA (3 ml) for 24 h, and work-up of the reaction mixture as noted for **2b** above, produced **4** (0.71 g, 68%). (KBr): ν 3410, 3168, 3091, 3060, 2924, 2854, 1743, 1711, 1608, 1544, 1463, 1329, 1266, 1190, 1031 cm^{-1}. ESI-HRMS: Calcd for $C_{15}H_{10}FN_2O_7$ $[M-H]^-$: 349.04666. Found: 349.04775. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.02 (m, 4H, H_2-2'/H_2-3'), 3.71 (m, 1H, H-1'), 3.80 (d, $^4J_{H\text{-}F}$ = 1.5 Hz, 2H, CH_2CO_2H), 8.31 (d, $^3J_{H\text{-}F}$ = 8.8 Hz, 1H, H-5), 8.81 (s, 1H, H-2), 13.15 (br s, 1H, CH_2CO_2H), 13.80 (br s, 1H, C(3)-CO_2H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 10.9 (C-2'/C-3'), 32.5 (d, $^3J_{C\text{-}F}$ = 2.9 Hz, CH_2CO_2H), 40.1 (C-1'), 109.3 (C-3), 114.3 (d, $^2J_{C\text{-}F}$ = 24.7 Hz, C-5), 125.8 (d, $^2J_{C\text{-}F}$ = 22.4 Hz, C-7), 128.6 (d, $^3J_{C\text{-}F}$ = 7.9 Hz, C-4a), 131.4 (d, $^4J_{C\text{-}F}$ = 2.7 Hz, C-8a), 142.2 (d, $^3J_{C\text{-}F}$ = 3.6 Hz, C-8), 153.4 (C-2), 157.3 (d, $^1J_{C\text{-}F}$ = 249 Hz, C-6), 165.0 (C(3)-CO_2H), 169.6 (CH_2CO_2H), 175.9 (d, $^4J_{C\text{-}F}$ = 2.5 Hz, C-4). Anal. Calcd for $C_{15}H_{11}FN_2O_7$ (350.26 g mol^{-1}): C, 51.44; H, 3.17; N, 8.00. Found: C, 51.28; H, 3.20; N, 7.93.

Method (b): Compound **3** (2.87 g, 6 mmol) and 6 N HCl (50 mL,) were heated at ~105 ^{o}C (oil bath, 110 ^{o}C) for 20-30 min, and then at ~ 90 ^{o}C for 12 h. Thereafter, the reaction mixture was cooled to room temperature, the resultant yellow solid product was collected, washed with water, and dried in vacuo. Yield 1.22 g (58%). This product was identical in all respects with **4** as previously described in method (a) above.

9-Cyclopropyl-4-fluoro-2,3,6,9-tetrahydro-2,6-dioxo-1*H*-pyrrolo[3,2-*h*]quinoline-7-carboxylic acid (5)

Method (a): To a stirred and cooled (0-5 °C) solution of compound **4** (0.7 g, 2.0 mmol) in aqueous K_2CO_3 (3.85 g, 28 mmol/80 mL) was added, portionwise, a solution of $Na_2S_2O_4$ (2.6 g, 15 mmol/20 mL) in water (20 mL). Following each addition, the solution acquired a dark brown color which shortly faded away (1-2 min). Thereafter, the reaction mixture was stirred at room temperature for 15-20 min, and acidified with 6 N HCl to pH 2-3. The precipitated solid product was collected by suction filtration, washed successively with water, ethanol, CH_2Cl_2 and recrystallized from DMSO. Yield 0.38 g (63%); mp 278-280 ^{o}C. (KBr): ν 3458, 3284, 3085, 2922, 1743, 1722, 1618, 1533, 1464, 1339, 1273, 1195, 1079, 1050 cm^{-1}. ESI- HRMS: Calcd for $C_{15}H_{10}FN_2O_4$ $[M-H]^-$: 301.06301. Found: 301.06301. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.18 (m, 2H) and 1.26 (m, 2H) (H_2-2'/H_2-3'), 3.81 (s, 2H, H_2-3), 4.37 (m, 1H, H-1'), 7.69 (d, $^3J_{H\text{-}F}$ = 8.4 Hz, 1H, H-5), 8.67 (s, 1H, H-8), 10.61 (s, 1H, N(1)-H), 14.69 (s, 1H, CO_2H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 10.1 (C-2'/C-3'), 33.1 (C-3), 38.8 (C-1'), 104.3 (d, $^2J_{C\text{-}F}$ = 22.7 Hz, C-5), 106.8 (C-7), 120.4 (d, $^2J_{C\text{-}F}$ = 25.3 Hz, C-3a), 125.1 (d, $^4J_{C\text{-}F}$ = 1.8 Hz, C-9a), 128.0 (d, $^3J_{C\text{-}F}$ = 7.9 Hz, C-5a), 136.6 (d, $^3J_{C\text{-}F}$ = 9.2 Hz, C-9b), 150.2 (C-8), 156.0 (d, $^1J_{C\text{-}F}$ = 244 Hz, C-4), 165.9 (CO_2H), 176.0 (C-2), 177.3 (d, $^4J_{C\text{-}F}$ = 2.6 Hz, C-6). Anal. Calcd for $C_{15}H_{11}FN_2O_4$ (302.26 g mol^{-1}): C, 59.61; H, 3.67; N, 9.27. Found: C, 59.68; H, 3.58; N, 9.22.

Method (b): A solution of **4** (1.75 g, 5 mmol) in EtOH (50 mL) was hydrogenated at 30 °C and 20 psi in the presence of 5% Pd/C. Under these conditions, **4** was completely converted into the corresponding title product **5** within 1.5-2 h. Thereafter, the catalyst was removed by filtration, and the solution was evaporated to dryness. The residue was triturated with cold EtOH (5 mL) and the solid suspension was collected by suction filtration, washed with water and dried. Yield 0.92 g (61%). This product was identical in all respects with **5** as previously described in method (a) above.

ANTIBACTERIAL TESTS

The minimal inhibitory concentrations (MICs) were determined by the conventional broth dilution method using the two-serial dilution technique. The standardization of bacterial test suspension was

carried out according to *McFarland* standard method as described by the National Committee for Clinical Laboratories Standard (NCCLS, 1993). Stock solutions of the test compounds were prepared using DMSO as the solvent. Serial dilutions were prepared to obtain test concentrations ranging from 100 μg mL^{-1} - 0.015 μg mL^{-1}. Each tube was then inoculated with 0.1 mL of the cultured bacteria (containing approximately 1-2 x 10^8 CFU mL^{-1}), mixed and incubated at 37 °C for 24 h. Growth inhibition with concentrations at 128 μg mL^{-1} or lower was carried out in duplicates. All test tubes showing positive/negative growth were confirmed by the agar plate method. The results were recorded according to presence and absence of growth. The MICs were calculated as the average concentration of the test agent in the broth tubes showing consecutive positive and negative growth.

ACKNOWLEDGEMENTS

We wish to thank the Deanship of Scientific Research at The University of Jordan, Amman- Jordan, for financial support. We also thank Prof. P. Vicini (Università degli Studi di Parma, Italy) for obtaining the antibacterial data.

REFERENCES

1. Part VIII: Y. M. Al-Hiari, R. Abu-Dahab, and M. M. El-Abadelah, *Molecules*, 2008, **13**, 2880.
2. (a) A. S. Wagman and M. P. Wentland, '*Comprehensive Medicinal Chemistry* **II**,' ed. by J. B. Taylor and D. J. Triggle, Elsevier Ltd., Oxford, 2007, vol. 7, pp. 567–596; (b) A. Bryskier, '*Antimicrobial agents: Antibacterials and Antifungals*,' ed. by A. Bryskier, ASM Press: Washington, 2005, pp. 668–788; (c) A. Dalhoff and F.- J. Schmitz, *Eur. J. Clin. Microbiol. Infect. Dis.*, 2003, **22**, 203; (d) A. D. Da Silva, M. V. De Almeida, M. V. N. De Souza, and M. R. C. Couri, *Curr. Med. Chem.*, 2003, **10**, 21; (e) G. G. Zhanel, K. Ennis, L. Vercaigne, A. Walkty, A. S. Gin, J. Embil, H. Smith, and D. J. Hoban, *Drugs*, 2002, **62**, 13; (f) L. R. Peterson, *Clin. Infect. Dis*., 2001, **33**, S180; (g) P. C. Appelbaum and P. A. Hunter, *Int. J. Antimicrob. Agents*, 2000, **16**, 5; (h) Q. Li, L. A. Mitscher, and L. L. Shen, *Med. Res. Rev*., 2000, **20**, 231; (i) K. Grohe, '*Quinolone Antibacterials*,' Springer- Verlag, Berlin, Heidelberg, 1998, pp. 13-62.
3. (a) R. Wise, J. M. Andrews, and L. J. Edwards, *Antimicrob. Agents Chemother*., 1983, **23**, 559; (b) D. Felmingham, M. D. O'Hare, M. J. Robbins, R. A. Wall, A. H. Williams, A.W. Cremer, G. L. Ridgeway, and R. N. Gruneberg, *Drugs Exp. Clin. Res*., 1985, **11**, 317; (c) F. Maurer and K. Grohe, *Ger. Offen*., **1986**, 3 435 392 (*Chem. Abstr.*, 1986, **105**, P97158e); (d) U. Petersen, S. Bartel, K.-D. Bremm, T. Himmler, A. Krebs, and T. Schenke, *Bull. Soc. Chim. Belg.*, 1996, **105**, 683.
4. (a) T. Fujimoto and S. Mitsuhashi, *Chemotherapy* (Basel, Switz.), 1990, **36**, 268; (b) K. P. Fu, S. C.

Lafredo, B. Foleno, D. M. Isaacson, J. F. Barrett, A. J. Tobia, and M. E. Rosenthale, *Antimicrob. Agents Chemother*., 1992, **36**, 860; (c) N. Mor, J. Vanderkolk, and L. Heifets, *Antimicrob. Agents Chemother*., 1994, **38**, 1161.

5. (a) O. G. Cardenosa and J. L. Soto-Hernandez, *Chemotherapy* (Basel, Switz.), 2000, **46**, 379; (b) J. A. B. Balfour and H. M. Lamb, *Drugs*, 2000, **59**, 115.
6. (a) F. Zhou, Y.-L. Liu, and J. Zhou, *Adv. Synth. Catal.*, 2010, **352**, 1381; (b) G. Cerchiaro and A. M. D. C. Ferreira, *J. Braz. Chem. Soc*., 2006, **17**, 1473.
7. (a) C. Marti and E. M. Carreira, *Eur. J. Org. Chem*., 2003, 2209; (b) B. M. Trost and M. K. Brennan, *Synthesis,* 2009, **18**, 3003; (c) C. V. Galliford and K. A. Scheidt, *Angew. Chem. Int. Ed*., 2007, **46**, 8748; (d) M. Ghandi, A. Taheri, and A. Abbasi, *Tetrahedron*, 2010, **66**, 6744.
8. (a) A. Jossang, P. Jossang, H. A. Hadi, T. Sévenet, and B. Bodo, *J. Org. Chem*., 1991, **56**, 6527; (b) G. Palmisano, R. Annunziata, G. Papeo, and M. Sisti, *Tetrahedron: Asymmetry*, 1996, **7**, 1.
9. S. Peddibhotla, *Curr. Bioact. Compd.*, 2009, **5**, 20.
10. (a) G. Cravotto, G. B. Giovenzana, G. Palmisano, A. Penoni, T. Pilati, M. Sistic, and F. Stazic, *Tetrahedron: Asymmetry*, 2006, **17**, 3070; (b) Y. Kamano, H.-P. Zhang, Y. Ichihara, H. Kizu, K. Komiyama, and G. R. Pettit, *Tetrahedron Lett.*, 1995, **36**, 2783; (c) G. R. Pettit, Y. Kamano, R. Herald, C. L. Aoyagi, D. L. Doubek, J. M. Schmidt, and J. J. Rudloe, *Tetrahedron*, 1985, **41**, 985.
11. A. Millemaggi and R. J. K. Taylor, *Eur. J. Org. Chem.*, 2010, 4527.
12. (a) A. Millemaggi, A. Perry, A. C. Whitwood, and R. J. K. Taylor, *Eur. J. Org. Chem.*, 2009, 2947; (b) L. Zhou, J.-S. Yang, X. Wu, J.-H. Zou, X.-D. Xu, and G.-Z. Tu, *Heterocycles*, 2005, **65**, 1409.
13. (a) P. C. Tang, T. A. Miller, X. Li, L. Sun, C. C. Wei, S. Shirazian, C. Liang, T. Vojkovsky, A. S. Nematalla, and M. Hawley, *PCT Int. Appl.*, 2001, *WO 2001060814* A2 (*Chem. Abstr.*, 2001, **135**, P195497); (b) L. Sun, C. Liang, S. Shirazian, Y. Zhou, T. Miller, J. Cui, J. Y. Fukuda, Y.-Yu. Chu, A. S. Nematalla, X. Wang, H. Chen, A. Sistla, T. C. Luu, F. Tang, J. Wei, and C. Tang, *J. Med. Chem*., 2003, **46**, 1116; (c) C. Le Tourneau, E. Raymond, and S. Faivre, *Ther. Clin. Risk. Manag*., 2007, **3**, 341.
14. M. R. Al-Dweik, J. A. Zahra, M. A. Khanfar, M. M. El-Abadelah, K.-P. Zeller, and W. Voelter, *Monatsh. Chem.*, 2009, **140**, 221.
15. R. A. Al-Qawasmeh, J. A. Zahra, F. Zani, P. Vicini, R. Boese, and M. M. El-Abadelah, *ARKIVOC*, 2009, **xii**, 322.
16. S. A. Al-Trawneh, J. A. Zahra, M. R. Kamal, M. M. El-Abadelah, F. Zani, M. Incerti, A. Cavazzoni, R. R. Alfieri, P. G. Petronini, and P. Vicini, *Bioorg. Med. Chem*., 2010, **18**, 5873.
17. (a) K. Grohe and H. Heitzer, *Liebigs Ann. Chem*., 1987, 29; (b) U. Petersen, K. Grohe, T. Schenke, H. Hagemann, H. J. Zeiler, and K. G. Metzger, *Ger. Offen*., 1987, *3 601 567* (*Chem. Abstr.*, 1987, **107**,

P236747); (c) R. M. Pulla and C. N. Venkaiah, *PCT Int. Appl*., 2001, *WO 085 692* (*Chem. Abstr.*, 2001, **135**, P371649); (d) Y. M. Al-Hiari, I. S. Al-Mazari, A. Shakya, K. Darwish, and R. M. Abu-Dahab, *Molecules*, 2007, **12**, 1240.

18. I. Gruda, *Can. J. Chem.*, 1972, **50**, 18.
19. J. Cao, H. Gao, G. Bemis, F. Salituro, M. Ledeboer, E. Harrington, S. Wilke, P. Taslimi, S. Pazhanisamy, X. Xie, M. Jacobs, and J. Green, *Bioorg. Med. Chem. Lett.*, 2009, **19**, 2891.
20. D. A. Walsh, H. W. Moran, D. A. Shamblee, I. M. Uwaydah, W. J. Welstead, L. F. Sancilio, and W. N. Dannenburg, *J. Med. Chem*., 1984, **27**, 1379.
21. E. A. Kraynack, J. E. Dalgard, and F. C. A. Gaeta, *Tetrahedron Lett*., 1998, **39**, 7679.
22. A. Fensome, W. R. Adams, A. L. Adams, T. J. Berrodin, J. Cohen, C. Huselton, A. Illenberger, J. C. Kern, V. A. Hudak, M. A. Marella, E. G. Melenski, C. C. McComas, C. A. Mugford, O. D. Slayden, M. Yudt, Z. Zhang, P. Zhang, Y. Zhu, R. C. Winneker, and J. E. Wrobel, *J. Med. Chem*., 2008, **51**, 1861.
23. N. Kammasud, C. Boonyarat, K. Sanphanya, M. Utsintong, S. Tsunoda, H. Sakurai, I. Saiki, I. André, D. S. Grierson, and O. Vajragupta, *Bioorg. Med. Chem. Lett.*, 2009, **19**, 745.
24. R. Chicharro, S. de Castro, J. L. Reino, and V. J. Arán, *Eur. J. Org. Chem*., 2003, 2314.
25. (a) M. Abou-Gharbia, M. E. Freed, R. J. McCaully, P. J. Silver, and R. L. Wendt, *J. Med. Chem.*, 1984, **27**, 1743; (b) B. I. Alo, A. G. Avent, J. R. Hanson, and A. E. Ode, *J. Chem. Soc.*, *Perkin Trans. 1*, 1988, 1997; (c) M. Y. A. Shuheil, M. R. Hassuneh, Y. M. Al-Hiari, A. M. Qaisi, and M. M. El-Abadelah, *Heterocycles*, 2007, **71**, 2155; (d) L. F. Fieser and M. Fieser, *J. Am. Chem. Soc.*, 1934, **56**, 1565.