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Antibacterial and Anticancer Properties of New Fluoroquinolones

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Fluoroquinolones are clinically successful antibacterial agents. In this work a series of novel 7-substituted anilino-8-nitrofluoroquinolone esters (**3-9**), acids (**10-16**) and 8-amino reduced derivatives (**17-23**) of the later compounds were successfully prepared and characterized using spectroscopic techniques. All the compounds tested (**10-23**) showed good antibacterial activity against both Gram-positive and Gram- negative standard bacterial strains. Interestingly, 8-amino reduced derivatives (**17-22**) were more active against both standard strains than their 8-nitro acid analogues (**10-15**). Moreover, some targeted compounds have shown reasonable activity mainly against resistant gram positive bacteria. In particular compounds **10**, **12** and **16** displayed a potent activity against methicillin resistant *S. aureus* (MRSA) with MIC values of 4.7, 2.3 and 1.2 µg/mL, respectively. Lipophilicity could be a plausible explanation of such higher activity against the gram positive resistant strain (MRSA). Biological screening of cytotoxic activity against five cancer cell lines using an *in vitro* cell culture system was achieved for all tested compounds. These derivatives have shown weak activity for most of them. Interestingly, more lipophilic nitroacids (**10-15**) were more active than their analogous reduced acids (**17-22**).

Keywords: Fluoroquinolones, Antibacterial activity, Anticancer activity, Cell lines, MRSA.

INTRODUCTION

Many antibacterial agents have been introduced into clinical use with a significant improvement in their antibacterial spectrum and activity [1,2]. Fluoroquinolone antibacterial agents, such as ciprofloxacin and norfloxacin are among the most successful clinically active drugs in the anti-infective chemotherapy field and constitute a major class of broad spectrum antibacterial agents against both Gram-positive and Gram-negative strains [3,4]. However, the extensive and naive misuse of these drugs led to the emergence of bacterial resistance against these agents [5-7].

Although antibacterial quinolones are known as potent inhibitors of bacterial DNA gyrase and topoisomerase IV needed for DNA replication and transcription, new quinolone derivatives have inhibitory effect against eukaryote topoisomerase II leading to cytotoxic activity against some cancerous cells [8,9]. Despite great advances in modes of treatment in cancer therapy, cancer remains a major leading cause of morbidity and mortality throughout the world and therefore there is considerable recent interest in developing new anticancer agent with new mode of action to overcome increased resistance against current anticancer drugs [10]. Fluoroquinolones were recently introduced as anticancer agents with new mode of action that will overwhelmed resistance and side effects of available therapies including chemotherapy, surgery and radiotherapy [9].

Vasoroxin (voreloxin) is an anticancer quinolone that inhibits topoisomerase-II leading to cell cycle arrest and apoptosis [11]. Vasoroxin has currently completed phase III clinical trial for acute myelocytic leukemia (AML) [12]. Owing to the potential biological interest of these fluoroquinolones including anticancer and antibacterial activity and to overcome the problem of resistance, a new series of lipophilic fluoroquinolones were designed to exhibit substituted anilines on C-7; mainly methyl and methoxy aniline derivatives. All these derivatives will be screened for their antibacterial activity against standard and resistant gram positive and negative strains. Due to availability of cancer cell lines and potential anticancer activity of anti-

bacterial fluoroquinolones, new acid (**10-15**) and reduced (**17-22**) derivatives will be screened for their anticancer activity against five cancer cell lines (T47D, MCF-7, A498, HeLa and PC-3).

This work involves the preparation and characterization of a series of novel 7-substituted anilino-8-nitrofluoroquinolone esters (ethyl 7-substituted anilino-1-cyclopropyl-6-fluoro-8-nitro-4-oxo-1,4-dihydroquinoline-3-carboxylate (**3-9**), their hydrolyzed acids (7-substituted anilino-1-cyclopropyl-6-fluoro-8-nitro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid) (**10-16**); and their reduced 8-amino derivatives (8-amino-7-substituted anilino-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid) (**17-23**).

7-Aniline derivatives (**3**, **10** and **17**), 2-methyl phenyl derivatives (**6**, **13** and **20**), 3-methoxy phenyl derivatives (**8**, **15** and **22**) and 2-methoxyphenyl derivatives (**9**, **16** and **23**) were synthesized for the first time and their experimental data are within the experimental data. Whereas, 4-methyl aniline derivatives (**4**, **11** and **18**), 3-methyl aniline derivatives (**5**, **12** and **19**) and 4-methoxy aniline (**7**, **14** and **21**) were previously reported by our group [13,14]. Synthesis of cipro ester (**2**) has been reported in the literature and was followed in this work with minor modifications [13,15].

A simple, optimized and efficient pathway was used to synthesize substituted aniline derivatives in which aniline derivatives were introduced starting from synthone **2** (ester pathway) using DMSO as a solvent and few drops of pyridine under reflux and anhydrous conditions. The ester pathway furnished 7-anilino esters (**3-9**) with high yield and good purity for most compounds. Crystallization was enough to get pure crystalline solids of target esters and simple dispersion from hexane or petroleum ether produced pure products of most esters without the need for purification or chromatographic separation (**3-9**).

The esters (**3-9**) were hydrolyzed successfully in ethanol and 12 N HCl (3:7), under reflux at 80-90 ºC for 24-48 h; providing high yield upon precipitation. Then the resulting acid derivatives (**10-16**) were further reduced using aqueous $SnCl_2$/HCl at room temperature to get 8-amino acid analogues (**17-23**). All intermediates and targets were successfully purified and characterized by NMR, MS and IR. Screening of the biological activity of obtained pure acid and reduced fluoroquinolone acid derivatives against both standard and resistant strains of bacteria and five human cancer cell lines was then carried out. The intermediates **3-9** were not tested due to negligible activity in their ester form.

EXPERIMENTAL

All chemicals, reagents and solvents were of analytical grade and used without further purification. The starting materials involved in this work are: aniline, *o*-anisidine, *o*-toluidine from Merck, (Darmstadt, Germany); *m*-anisidine and *m*-toludine from Aldrich Chemicals (England); *p*-toluidine, *p*-anisidine from Fluka (Switzerland). Reducing agents used are stannous chloride dihydrate crystals from Fluka (Switzerland), sodium dithionate from Loba Chemie (India).

Nutrient broth, Mueller-Hinton broth and 0.5 McFarland suspension were obtained from Oxoid (England); agar, broth and suspension were prepared as described by the manufacturer and autoclaved (Raypa Steam Sterilizer, Spain) at 121 ºC for 15 min. Universal Microplate Reader, ELx 800UV, Biotech Instruments (USA) were used. *Staphylococcus aureus* ATCC 6538P, *Escherichia coli* ATCC 8739 and methicillin resistant *Staphylococcus aureus* ATCC 43300 (MRSA), *Acinetobacter baumannii* F24 (environmental strain) and clinical Resistant *Escherichia coli* strains (1122, 1058 & 990) were receieved as a kind gift from Prof. Asem Shehabi, Faculty of Medicine, University of Jordan. Ciprofloxacin hydrochloride was gifted from Al-Hikma Pharmaceutical company.

NMR were recorded on Bruker, Avance DPX-300 spectrometer and Bruker Avance 500 MHz Ultrashield spectrometer at The University of Jordan. Chemical shifts are reported in ppm related to tetramethylsilane (TMS) as the internal standard using DMSO-d_6 and $CDCl_3$. Infrared (IR) spectra were recorded using Shimadzu 8400F FT-IR spectrophotometer. Samples were prepared as KBr (Merck, Dermstadt, Germany) discs.

Melting points were determined in open capillaries on a Stuart scientific electro-thermal melting point apparatus, and are uncorrected. High resolution mass spectra (HRMS) were measured in positive ion mode using electrospray ionization (ESI) technique by collision-induced dissociation on a Bruker APEX-4 (7 Tesla) instrument at The University of Jordan. 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 arginine cluster in a mass range *m/z* 175-871.

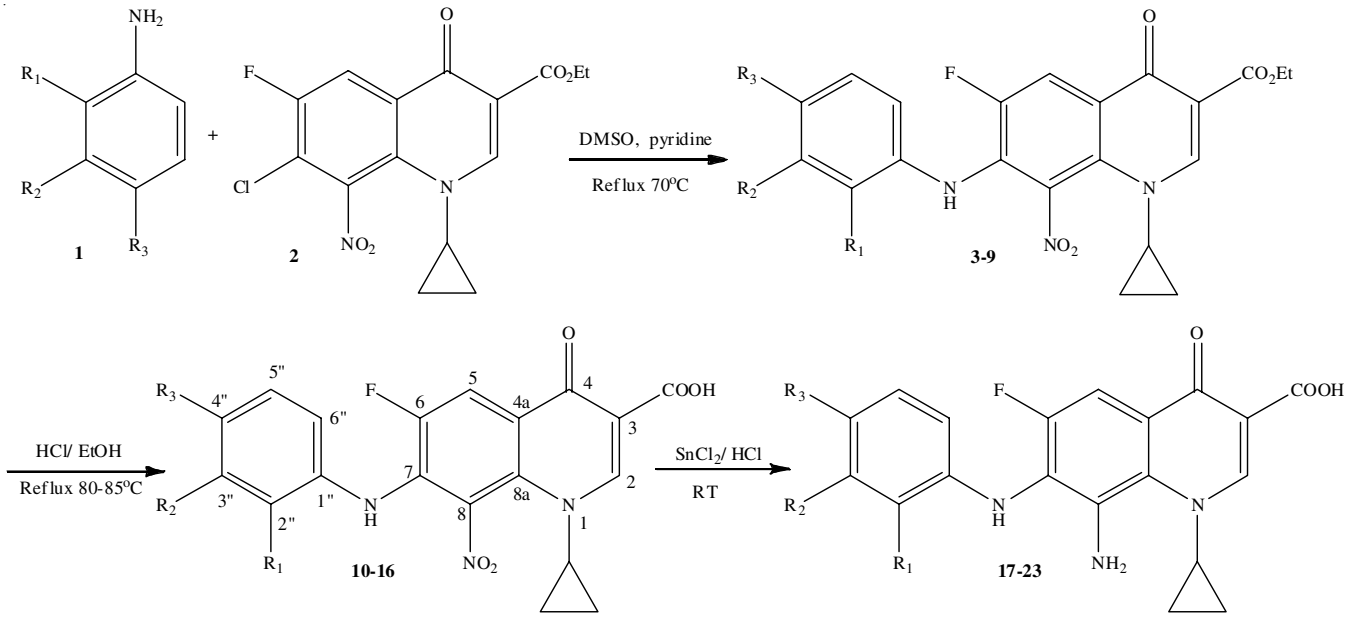
Thin layer chromatography (TLC) was performed on aluminum plates pre-coated with fluorescent silica gel GF_{254} from ALBET (Germany) and were visualized under UV lamp, Spectroline cabinet, Model CX-20 (USA).

Mobile phase mixtures were as follows: system 1: $CHCl_3$: MeOH: FA) (94: 5: 1); system 2: $CHCl_3$:MeOH:FA (90:10:1), system 3: Hexane:ethyl acetate (50:50) and; system 4: system 1:system 3 (50: 50).

7-Chloro-1-cyclopropyl-6-fluoro-8-nitro-4-oxo-1,4-dihydroquinoline-3-carboxylate ester (**2**) was synthesized according to the reported method (**Scheme-I**) [13,14].

General procedure for ester pathway to synthesized compounds (3, 6, 8 and 9): Initially, 2 M equivalents of substituted aniline derivatives **1** were added into a solution containing ethyl-7-chloro-1-cyclopropyl-6-fluoro-8-nitro-4-oxo-1,4-dihydroquinoline-3-carboxylate (**2**) (1 g, 2.83 mmol) and 10-15 mL of DMSO as a solvent and few drops of pyridine. The mixture was refluxed for 65-70 ºC under anhydrous conditions. Additional (0.5 molar equivalent) of aniline derivative was added according to the TLC. The reaction mixture was monitored until no starting material remained. The reaction was completed within 2-7 days. Then, cooled mixture was left to crystallize at room temperature and the product was filtered and left to dry in a dark place. In this work, compounds **3, 6, 8** and **9** are reported for the first time, whereas compounds **4**, **5** and **7** were synthesized according to the reported method [13].

Ethyl 7-anilino-1-cyclopropyl-6-fluoro-8-nitro-4-oxo-1,4-dihydroquinoline-3-carboxylate (3): Dark orange, yield: 51.7 % (0.6 g); m.p. 210-212 ºC (decomp.); R_f value in system



Compounds	7-Derivative	R_1	R_2	R_3
3,10,17	Aniline	H	H	H
4,11,18	*p*-Toluidine	H	H	CH_3
5,12,19	*m*-Toluidine	H	CH_3	H
6,13,20	*o*-Toluidine	CH_3	H	H
7,14,21	*p*-Anisidine	H	H	OCH_3
8,15,22	*m*-Anisidine	H	OCH_3	H
9,16,23	*o*-Anisidine	OCH_3	H	H

Scheme-I: Synthesis of fluoroquinolone targets (**3-23**)

4 = 0.71. IR (KBr, ν_{max}, cm^{-1}): 3400, 3367, 1735, 1620, 1512, 1450, 1319, 1234. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.93, 1.14 (2m, 4H, H_2-2′/H_2-3′), 1.42 (t, *J* = 7.1 Hz, OCH_2CH_3), 3.65 (m, 1H, H-1′), 4.42 (q, *J* = 7.1 Hz, 2H, OCH_2CH_3), 7.03 (d, *J* = 7.5 Hz, 2H, H-2″/H-6″), 7.17 (d,d, *J* = 7.4, 7.4 Hz, 1H, H-4″), 7.34 (d, d, *J* = 7.7, 7.8 Hz, 2H, H-3″/H-5″), 7.85 (br s, 1H, NH, exch.), 8.25 (d, $^3J_{H\text{-}F}$ = 12.0 Hz, 1H, H-5), 8.63 (s, 1H, H-2). ^{13}C NMR (75 MHz, $CDCl_3$): δ 10.16 (C-2′/C-3′), 14.4 (CH_3CH_2), 38.78 (C-1′), 61.33 (CH_2CH_3), 112.88 (C-3), 117.1 (d, $^2J_{C\text{-}F}$ = 21.2 Hz, C-5), 118.28 (Ar-C), 122.59 (Ar-C), 124.78, 131.14, 133.23, 129.49 (Ar-C), 131.8 (d, $^2J_{C\text{-}F}$ = 14.4 Hz, C-7), 143.17 (N-CAr), 150.9 (d, $^1J_{C\text{-}F}$ = 254 Hz, C-6), 151.23 (C-2), 164.54 (CO_2Et), 171.19 (C-4). HRMS (ESI, +ve): calculated for $C_{21}H_{18}N_3O_5FNa$ $[M+Na]^+$: 434.11282. Found: 434.11227

Ethyl-1-cyclopropyl-6-fluoro-7-[(2-methyl phenyl)-amino]-8-nitro-4-oxo-1,4-dihydroquinoline-3-carboxylate (6): Orange, yield: 38% (0.45 g); m.p.: 242-244 ºC (decomp.); R_f value in system 1 = 0.75. IR (KBr, ν_{max}, cm^{-1}): 3459, 3355, 3071, 2924, 2931, 1727, 1620, 1527, 1464, 1337, 1310, 1232, 1153, 1045. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.12, 1.21 (2m, 4H, H_2-2′/H_2-3′), 1.42 (t, *J* = 7.4 Hz, 3H, OCH_2CH_3), 2.25 (s, 3H, CH_3), 3.68 (m,1H, H-1′), 4.20 (q, *J* = 7.8 Hz, 2H, OCH_2CH_3), 6.89-7.51 (m, 4H, Ar-H), 8.48 (d, $^3J_{H\text{-}F}$ = 13 Hz, 1H, H-5), 8.72 (br s, 1H, NH, exch.), 8.85 (s, 1H, H-2). ^{13}C NMR (75 MHz, DMSO-d_6): δ 10.31 (C-2′/C-3′), 14.35 (OCH_2CH_3), 21.22 (Ar-CH_3), 39.21 (C-1′), 55.56 (OCH_2CH_3), 110.42 (C-3), 115.57 (d, $^2J_{C\text{-}F}$ = 21.83 Hz, C-5), 118.12, 120.0, 121.36 (d, $^3J_{C\text{-}F}$ = 7.9 Hz, C-4a), 127.33, 129.7,131.24, 134.52 (C-8a), 133.35 (d, $^2J_{C\text{-}F}$ = 15.4 Hz, C-7), 135.23 (C-8), 141.54 (C-1″), 151.25 (C-2), 152.53 (d, $^1J_{C\text{-}F}$ = 253 Hz, C-6), 165.45 (C(3)-CO_2Et), 176.78 (C-4). HRMS: calculated for $C_{22}H_{20}N_3O_5F$ $[M]^+$: 425.13870. Found $C_{22}H_{21}N_3O_5F$ $[M+1]^+$: 426.14598.

Ethyl-1-cyclopropyl-6-fluoro-7-[(3-methoxy phenyl)-amino]-8-nitro-4-oxo-1,4-dihydroquinoline-3-carboxylate (8): Orange, yield: 43% (0.80 g); m.p.: 234-237 ºC (decomp.); R_f value in system 4 = 0.71. IR (KBr, ν_{max}, cm^{-1}): 3363, 2978, 2931, 1728, 1604, 1512, 1465, 1165, 1087, 1033. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.04 (m, 4H, H_2-2′/H_2-3′), 1.29 (t, *J* = 7.4 Hz, 3H, OCH_2CH_3), 3.65 (m, 1H, H-1′), 3.75 (s, 3H, OCH_3), 4.32 (q, *J* = 7.5 Hz, 2H, OCH_2CH_3), 6.57-6.62 (m, *J* = 8.5, 7.5 Hz, 3H, Ar-H), 7.76 (d,d, *J* = 4.0, Hz, 1H, Ar-H), 8.22 (d, $J_{H\text{-}F}$ = 11.4 Hz, 1H, H-5), 8.84 (s, 1H, H-2), 8.96 (br s, 1H, NH, exch.). ^{13}C NMR (75 MHz, $CDCl_3$): δ 10.14 (C-2′/C-3′), 14.33 (OCH_2CH_3), 38.70 (C-1′), 55.33 (OCH_3), 61.19 (OCH_2-CH_3), 106.17 (C-3), 112.42 (d, $J_{C\text{-}F}$ = 3 Hz, C-4a), 112.91, 116.79 (d, $^2J_{C\text{-}F}$ = 21.0 Hz, C-5), 122.34, 127.82, 129.79, 131.20, 132.99, 133.38, 133.86, 150.91 ($^1J_{C\text{-}F}$ = 250 Hz, C-6), 151.15 (C-2), 158.25 (C- 3″), 164.59 (CO_2Et), 172.52 (C-4). HRMS (ESI, +ve): calculated for $C_{22}H_{20}N_3O_6FNa$ $[M+Na]^+$: 464.12338. Found: 464.12283.

Ethyl-1-cyclopropyl-6-fluoro-7-[(2-methoxyphenyl)-amino]-8-nitro-4-oxo-1,4-dihydroquinoline-3-carboxylate (9): Dark orange, yield: 24.1 % (0.45 g); m.p.: 200-205 ºC (decomp.); R_f value in system 4 = 0.71. IR (KBr, ν_{max}, cm^{-1}): 3379, 2924, 2931, 1620, 1527, 1465, 1327, 1242, 1172, 1035. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.02 (m, 4H, H_2-2′/H_2-3′), 1.32

(t, J = 7.4 Hz, 3H, OCH_2CH_3), 3.60 (m,1H, H-1′), 3.77 (s, 3H, OCH_3), 4.28 (q, J = 7.6 Hz, 2H, OCH_2CH_3), 7.0-7.41 (m, 4H, Ar-H), 7.98 (d, $^3J_{H\text{-}F}$ = 12 Hz, 1H, H-5), 8.78 (br s, 1H, NH, exch.), 8.79 (s, 1H, H-2). ^{13}C NMR (75 MHz, $CDCl_3$): δ 10.10 (C-2′/C-3′), 14.52 (OCH_2CH_3), 39.82 (C-1′), 55.33 (OCH_3), 61.95 (OCH_2CH_3), 102.21 (d, $^2J_{C\text{-}F}$ = 20.10 Hz, C-5), 107.25 (C-3), 108.92, 112.72, 116.21, 121.29,126.15, 127.45, 127.61, 140.22 (C-1″), 140.89 (C-8), 151.23 (C-2), 151.59 (d, $^1J_{C\text{-}F}$ = 254 Hz, C-6), 154.62 (C-2″), 167.92 (CO_2Et), 175.98 (C-4). HRMS (ESI, +ve): EA calculated for $C_{22}H_{20}N_3O_6FNa$ [M+Na]$^+$: 464.12338. Found: 464.12278.

Synthesis of compounds (10, 13, 15 and 16) by hydrolysis of compounds (3, 6, 8 and 9): In this work, compounds **10**, **13**, **15** and **16** are reported for the first time, whereas compounds **11**, **12** and **14** were previously reported [13] and resynthesized for biological screening

General procedure: The resulting compounds, ethyl-7-(substituted anilino)-1-cyclopropyl-6-fluoro-8-nitro-4-oxo-1,4-dihydroquinoline-3-carboxylate (**3**, **6**, **8**, **9**) were dissolved in a mixture of absolute ethanol and 12 N HCl (3:7), under reflux at 80-90 ºC for 24-48 h. The reaction was monitored by TLC. At the end of reaction, the reaction mixture was poured onto a crushed ice and the pure precipitate was collected by filtration and dried at room temperature.

7-Anilino-1-cyclopropyl-6-fluoro-8-nitro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (10): Bright orange, yield: 76.1 % (0.245 g); m.p. 210-214 ºC (decomp.); R_f value in system 4 = 0.55. IR (KBr, ν_{max}, cm^{-1}): 3448, 3363, 3055, 2399, 1735, 1620, 1512, 1450, 1319, 1234, 1026. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.07 (2m, 4H, H_2-2′/H_2-3′), 3.75 (m, 1H, H-1′), 7.05 (m, 2H, Ar-H), 7.27 (d, d, J = 7.4, 7.5 Hz, 2H, Ar-H), 7.43 (d, J = 4.2 Hz, 1H, Ar-H), 8.20 (d, $^3J_{H\text{-}F}$ = 11.6 Hz, 1H, H-5), 8.85 (s, 1H, H-2), 9.05 (br s, 1H, NH, exch.), 14.52 (br s, 1H, COOH). ^{13}C NMR (75 MHz, DMSO-d_6): δ 10.57 (C-2′/C-3′), 39.65 (C-1′), 110.4 (d, $^1J_{C\text{-}F}$ = 21.5 Hz, C-5), 119.3, 121.27, 121.88,122.23, 124.41, 126.19, 126.65, 129.9, 132.97, 133.129, 148.25, 151.9 (C-2), 152.52 (d, $J_{C\text{-}F}$ = 253 Hz, C-6), 165.26 (COOH), 175.84 (C-4). HRMS (ESI, +ve): EA calculated for $C_{19}H_{14}N_3O_5FNa$ [M+Na]$^+$: 406.08152. Found: 406.08097.

1-Cyclopropyl-6-fluoro-7-[(2-methylphenyl)amino]-8-nitro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (13): Faint orange, yield: 67 % (0.28 g); m.p. 234-236 ºC (decomp.); R_f value in system 4: 0.62. IR (KBr, ν_{max}, cm^{-1}): 3465-3374 br, 3092, 2935, 2923, 1735, 1645, 1552, 1477, 1345, 1301, 1222, 1095, 1025. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.02, 1.03 (2m, 4H, H_2-2′/H_2-3′), 2.25 (s, 3H, CH_3), 3.74 (m, 1H, H-1′), 7.02 (d, J = 7.65Hz, Ar-H), 7.13 (m, 2H, Ar-H), 7.25 (dd, J = 7.4, 5.5 Hz, Ar-H), 8.10 (d, $^3J_{H\text{-}F}$ = 11.9 Hz, 1H, H-5), 8.59 (br s, 1H, NH, exch.), 8.83 (s, 1H, H-2), 14.53 (brs, 1H, COOH). ^{13}C NMR (125 MHz, DMSO-d_6): δ 10.54 (C-2′/C-3′), 18.25 (Ar-CH_3), 40.36 (C-1), 109.29 (C-3), 114.13 (d, $^2J_{C\text{-}F}$ = 21.21 Hz, C-5), 119.15 (d, J=6.8Hz, C-8a), 123.95 (CH-Ar), 126.07 (CH-Ar), 126.76 (CH-Ar), 130.92 (CH-Ar), 131.59 (C-4a), 132.56 (C-2″), 134.38 (C-8), 135.58 (d, $^2J_{C\text{-}F}$ = 14.2 Hz, C-7), 139.63 (C-1″), 151.72 (d, $^1J_{C\text{-}F}$ = 251.46 Hz, C-6), 152.36 (C-2), 165.29 (C(3)-CO_2H), 175.72 (C-4). HRMS: calculated for $C_{20}H_{17}N_3O_5F$ [M+1]$^+$: 398.11523. Found: 398.11535.

1-Cyclopropyl-6-fluoro-7-[(3-methoxyphenyl)amino]-8-nitro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (15): Dark yellow to faint brown. Yield: 78 % (0.28 g); m.p. 245-247 ºC (decomp.); R_f value in system 4 = 0.65. IR (KBr, ν_{max}, cm^{-1}): 3448, 3363, 3063, 2924, 2854, 2360, 1728, 1612, 1512, 1319, 1280, 1157, 1049. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.06 (m, 4H, H_2-2′/H_2-3′), 3.71 (s, 3H, OCH_3), 3.78 (m, 1H, H-1′), 6.55-6.44 (m, J = 8.6, 7.6 Hz, 3H, Ar-H), 7.76 (d, d, J = 8.1, 7.9 Hz, 1H, Ar-H), 8.22 (d, $J_{H\text{-}F}$ = 11.5 Hz, 1H, H-5), 8.84 (s, 1H, H-2), 8.96 (br s, 1H, NH, exch.), 13.25 (s, 1H, COOH). ^{13}C NMR (75 MHz, DMSO-d_6): δ 10.58 (C-2′/C-3′), 40.92 (C -1′), 55.52 (OCH_3), 105.01 (Ar-C), 108.80 (Ar-C), 109.39 (C-3), 111.32 (Ar-C), 114.82 (d, d, $^2J_{C\text{-}F}$ = 21.3 Hz, C-5), 121.77 (d, $^3J_{C\text{-}F}$ = 7.2 Hz, C-4a), 130.03 (Ar-C), 132.66 (d, $^1J_{C\text{-}F}$ = 16 Hz, C-7), 133.81 (C-8a), 135.41 (C-8), 143.56 (C-1″), 152.56 (C-2), 153.32 (d, $^1J_{C\text{-}F}$ = 253 Hz, C-6), 160.25 (C-3″), 165.25 (COOH), 175.89 (d, $^4J_{C\text{-}F}$ = 2.5 Hz, C-4). HRMS (ESI +ve): EA calculated for $C_{20}H_{16}N_3O_6FNa$ [M+Na]$^+$: 436.09208. Found: 436.09153.

1-Cyclopropyl-6-fluoro-7-[(2-methoxyphenyl)amino]-8-nitro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (16): Dark brown, yield: 51.78 % (0.145 g); m.p. 239-244 ºC (decomp.); R_f value in system 4 = 0.65. IR (KBr, ν_{max}, cm^{-1}): 3410, 3078, 3016, 2926, 2839, 2492, 1728, 1627, 1519, 1465, 1311, 1249, 1095, 1026. ^{1}H NMR (500 MHz, DMSO-d_6): 1.04 (2m, 4H, H_2-2′/H_2-3′), 3.71 (s, 1H, OCH_3), 3.76 (m, 1H, H-1′), 6.92 (d, d, J = 7.55, 7.55 Hz, 1H, H-4″), 7.04 (d, J = 8.05 Hz, 1H, H-3″), 7.15 (m, 2H, H-5″ & 6″), 8.10 (d, $J_{H\text{-}F}$ = 12.1 Hz, 1H, H-5), 8.61 (br s, 1H, NH, exch.), 8.83 (s, 1H, H-2, 14.54 (s, 1H, COOH). ^{13}C NMR (125 MHz, DMSO-d_6): δ 10.42 (C-2′/C-3′), 40.44 (C-1′), 56.14 (OCH_3), 113.81 (d, $^2J_{C\text{-}F}$ = 21.54 Hz, C-5), 109.46 (C-3), 111.97 (Ar-CH), 119.59 (d, J = 7.03 Hz, C-4a), 120.84 (Ar-CH), 122.77 (Ar-CH), 125.89 (Ar-CH), 129.45 (C-8), 132.17 (C-8a), 134.34 (C-1″), 134.86 (d, J = 14.6 Hz, C-7), 152.06 (C-2″), 152.15 (d, $^1J_{C\text{-}F}$ = 252.46 Hz, C-6), 152.36 (C-2), 165.29 (COOH), 175.74 (C-4). HRMS (ESI +ve): EA calculated for $C_{20}H_{16}N_3O_6NaF$ [M+Na]$^+$: 436.09208. Found: 436.09211.

Preparation of Compounds (17, 20, 22 and 23) by reduction of compounds (10, 13, 15 and 16): In this work, compounds **17, 20, 22** and **23** are reported for the first time, whereas compounds **18**, **19** and **21** were previously reported [13,14] and re-synthesized in this work for biological screening.

Main procedure: Stannous chloride/HCl method (major): A mixture of the resulting acid derivatives (**10, 13, 15** and **16**) in a 5-10 mL of 12 N HCl was left stirring in an ice-bath (2-5 ºC) for 15 min. After that an ice bath was removed, excess $SnCl_2$ was added portion-wise, and the reaction mixture was left stirring overnight and monitored by TLC until completion. Then, the reaction mixture was poured onto a crushed ice to precipitate the product which was collected by filtration and dried. This reduction method was successful in reducing most of the target models with good yield.

Sodium dithionate/K_2CO_3 method: To a stirred solution of resulting acid derivatives (**10**, **13**, **15** and **16**), potassium carbonate in 5 mL water; an aqueous solution of sodium dithionite (2 mmol) in 5 mL water was added dropwise. The reaction mixture left stirring at room temperature overnight and monitored by TLC. At the end of reaction, pH of the solution

was adjusted to about 4 by gradual addition of 3 N HCl. The precipitate product was filtered, washed with water and left to dry. This reduction method produced the compounds in low yield and with some side products that needed chromatographic separation.

8-Amino-7-anilino-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (17): Dark yellow, yield: 73.06 % (0.08 g); m.p. 175-180 ºC (decomp.); R_f value in system 4 = 0.25. IR (KBr, ν_{max}, cm^{-1}): 3450, 3006, 2893, 2816, 1720, 1604, 1504, 1450, 1334, 1180, 1087. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.20 (2m, 4H, H2-2′/H2-3′), 4.53 (m,1H, H-1′), 5.75 (br s, 2H, NH_2), 6.68 (m, 2H, Ar-H), 7.16 (m, 2H, Ar-H), 7.37 (m, 1H, Ar-H), 7.81 (br d, 1H, H-5), 8.76 (s, 1H, H-2), 9.10 (br s, 1H, NH, exch.), 15.12 (br s, 1H, COOH). ^{13}C NMR (75 MHz, DMSO-d_6): δ 10.63 (C-2′/C-3′), 40.93 (C-1′), 97.76 (C-3), 98.15 (d, $^2J_{C\text{-}F}$ = 23 Hz, C-5), 106.66, 114.6 (C-2″/C- 6″), 119.23 (C- 4″), 120.75, 125.28, 127.73, 129.34 (C-3″/C-5″), 139.40, 145.02 (C-1″), 151.1 (C-2), 152.3 (d, $^1J_{C\text{-}F}$ = 251 Hz, C-6), 166.27 (COOH), 177.32 (C-4). HRMS (ESI, +ve): EA calculated for $C_{19}H_{17}N_3O_3F$ $[M+H]^+$: 354.1254. Found: 354.1249.

8-Amino-1-cyclopropyl-6-fluoro-7-[(2-methylphenyl)-amino]-8-nitro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (20): Faint yellow, yield: 68 % (0.31 g); m.p. 190-195 ºC (decomp.); R_f value in system 4 = 0.31. IR (KBr, ν_{max}, cm^{-1}): 3460-3343, 3085, 2922, 2905, 1745, 1655, 1556, 1480, 1375, 1275, 1075. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.17, 1.28 (2m, 4H, H_2-2′/H_2-3′), 2.35 (s, 3H, CH_3), 4.56 (m, 1H, H-1′), 5.81 (br s, 2H, NH_2), 6.27 (d, *J* = 7.95 Hz, 1H, H-6″), 6.73 (d, d, *J* = 7.25, 7.3 Hz, 1H, H-4″), 6.88 (br s, 1H, NH, exch.), 6.96 (d, d, *J* = 7.55, 7.6 Hz, 1H, H-5″), 7.12 (d, *J* = 7.25 Hz, 2H, H-3″), 7.36 (d, $^3J_{H\text{-}F}$ = 9.6 Hz, 1H, H-5), 8.77 (s, 1H, H-2), 15.03 (brs, 1H, COOH). ^{13}C NMR (125 MHz, DMSO-d_6): δ 10.66 (C-2′/C-3′), 18.41 (Ar-CH_3), 39.89 (C-1′), 98.24 (d, $^2J_{C\text{-}F}$ = 23.4 Hz, C-5), 106.61 (C-3), 113.19 (C-6″), 119.64 (C-4″), 121.33 (d, $^2J_{C\text{-}F}$ = 17.2 Hz, C-7), 125.00 (C-8a), 125.47 (d, *J* = 9.7 Hz, C-4a), 126.88 (C-5″), 127.62 (C-8), 130.84 (C-3″), 139.70 (d, *J* = 4.0 Hz, C-1″), 143.38 (C-2″-Me), 151.09 (C-2), 157.31 (d, $^1J_{C\text{-}F}$ = 244 Hz, C-6), 166.29 (C(3)-*C*O_2H), 177.34 (C-4). HRMS: calculated for $C_{20}H_{19}N_3O_3F$ $[M+1]^+$: 368.14105. Found $C_{20}H_{17}N_3O_5F$: 368.14120.

8-Amino-1-cyclopropyl-6-fluoro-7-[(3-methoxyphenyl)-amino]-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (22): Faint green, yield: 98.04 % (0.15 g); m.p. 176-180 ºC (decomp.); R_f value in system 4 = 0.26. IR (KBr, ν_{max}, cm^{-1}): 3487-3363, 3099, 2931, 2360, 1604, 1512, 1450, 1273, 1157, 1067, 1041. ^{1}H NMR (300 MHz, DMSO-d_6): 1.03 (m, 4H, H_2-2′/H_2-3′), 3.66 (s, 3H, OCH_3), 4.75 (br s, 1H, H-1′), 5.53 (br s, 2H, NH_2), 6.89 (s, 1H, H2″), 6.92-7.78 (2m, 3H, Ar-H), 7.85 (br m, 1H, H-5), 8.23 (br m, 2H, H-2), 8.75 (br s, 1H, NH, exch.), 13.52 (br s, 1H, COOH). ^{13}C NMR (75 MHz, DMSO-d_6): δ 11.22 (C-2′/C-3′), 42.25 (C-1′), 57.84 (OCH_3), 107.21 (Ar-C-2″), 109.42 (C-3), 110.01 (Ar-C-6″), 112.22 (Ar-C-4″), 115.32 (d, $^2J_{C\text{-}F}$ = 22 Hz, C-5), 122.12 (d, $^3J_{C\text{-}F}$ = 6.5 Hz, C-4a), 129.27 (Ar-C-5″), 131.84 (d, $^1J_{C\text{-}F}$ = 16 Hz, C-7), 134.91 (C-8a), 136.23 (C-8), 141.25 (C-1″), 150.01 (C-2), 154.51 (d, $^1J_{C\text{-}F}$ = 249 Hz, C-6), 161.12 (C-3″), 166.55 (COOH), 176.24 (d, $^4J_{C\text{-}F}$ = 2.0 Hz, C-4). HRMS (ESI +ve): calculated for $C_{20}H_{18}N_3O_4FNa$ $[M+Na]^+$: 406.11790. Found: 4306.11788.

8-Amino-1-cyclopropyl-6-fluoro-7-[(2-methoxyphenyl)-amino]-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (23): Dark greenish, yield: 95 % (0.145 g); m.p. 187-192 ºC (decomp.); R_f value in system 4 = 0.26. IR (KBr, ν_{max}, cm^{-1}): 3475-3324, 3084, 2925, 2347, 1610, 1522, 1462, 1275, 1167, 1087, 1055. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.17, 1.23 (2m, 4H, H_2-2′/H_2-3′), 3.89 (s, 1H, OCH_3), 4.54 (br s, 1H, H-1′), 5.80 (br s, 2H, NH_2), 6.29 (d, *J* = 7.25 Hz, 1H, H-3″), 6.76 (m, *J* = 8.3 Hz, 2H, H-4″/H-5″), 6.94 (br s, 1H, NH, exch.), 6.98 (d, *J* = 7.5 Hz, 1H, H-6″), 7.34 (d, $^3J_{H\text{-}F}$ = 9.6 Hz, 1H, H-5), 8.76 (s, 1H, H-2), 15.07 (s, 1H, COOH). ^{13}C NMR (125 MHz, DMSO-d_6): δ 10.73 (C-2′/C-3′), 40.35 (C-1′), 56.15 (OCH_3), 98.31 (d, $^2J_{C\text{-}F}$ = 23.4 Hz, C-5), 106.62 (C-3), 111.37 (Ar-CH), 112.74 (Ar-CH), 119.48 (Ar-CH), 120.95 (d, $^2J_{C\text{-}F}$ = 17.13 Hz, C-7), 121.16 (Ar-CH), 125.52 (d, *J* = 9.6 Hz, C-4a), 127.65 (C-8a), 134.28 (C-8), 139.88 (d, *J* = 3.95 Hz, C-1″), 148.10 (C-2″), 151.07 (C-2), 157.21 (d, $^1J_{C\text{-}F}$ = 243.58 Hz, C-6), 166.28 (COOH), 177.32 (C-4). HRMS (ESI +ve): calculated for $C_{20}H_{18}N_3NaO_4F$ [M+Na]+: 406.11790. Found: 4306.11794.

in vitro Antibacterial analysis

Broth microdilution method: The minimum inhibitory concentration (MIC) was determined according to the broth microdilution susceptibility assay, which was described by the National Committee of Clinical Laboratory Standards (NCCLS, 2005) with some modifications. MIC test was performed using two-fold broth dilution method in 96 well microtitre plates. Stock solution (1mg/mL) of each substrate and ciprofloxacin was prepared in DMSO under aseptic conditions. The first experimental well was filled with Mueller-Hinton broth (180 µL) and the other wells were filled with 100 µL of Mueller-Hinton broth. A volume of 20 µL of each substance stock solutions was added to the first well. Double-fold serial dilution was then carried out across the plate. Overnight batch culture of *Staphylococcus aureus* ATCC 6538P & 43300, *Escherichia coli* ATCC 8739, *Acinetobacter baumannii* F24 and clinical resistant strains of *Escherichia coli* 1122, 1058 & 990 (10 µL of each microorganism′s culture) was used to inoculate the wells. The final inoculum size obtained was about 1×10^6 cfu/mL (prepared *via* viable plate count method). The plate was incubated for 24 h at 37 ºC. In all assays, positive growth controls (wells without any testing agents) and negative controls (wells without inocula) with DMSO were performed to ensure that it is incapable of inhibiting the growth of bacteria. MICs were expressed as the average of two successive concentrations of the antimicrobial agent showing no growth and growth, respectively. The microorganism′s growth was detected as turbidity, visualized by naked eyes or using a microtitre plate reader (at 630 nm) relative to an uninoculated well. MIC determination was carried out in duplicate (in same 96 well plates) and repeated three times for each microorganism and each tested agent.

Antitumor testing

Cell lines and culture conditions: The human breast adenocarcinoma cell line MCF-7, human ductal breast epithelial tumor cell line T47D, human prostate adenocarcinoma PC-3, the human adenocarcinoma cell line Hela and human kidney carcinoma A498 cell line, were purchased from ATCC (American Type Culture Collection). Cell lines were cultured in high glucose

Dulbecco's modified eagle medium (DMEM) (Invitrogen, USA) containing 10 % heat inactivated fetal bovine serum (HI-FBS) (Invitrogen), 2 mmol L^{-1} of L-glutamine, 50 U mL^{-1} of penicillin and 50 µg mL^{-1} of streptomycin. Cell lines were maintained at 37 ºC in a 5 % CO_2 atmosphere of 95 % humidity.

Cell proliferation by MTT assay: Viable cell count was determined using 3-(4,5-dimethylthiazol-2yl)-2,5-diphenyl tetrazolium bromide (MTT) colorimetric assay as described earlier [16]. Breifly, yellow tetrazolium dye was reduced by active cells into purple formazan product. The quantity of formazan product is directly proportional to the number of living cells in the culture.

Antiproliferative activities: The examined fluoroquinolones were first dissolved in a volume of DMSO to provide a final 50 mg/mL stock solution, which was utilized to prepare various concentrations of each compound in treatment media. Final concentration of DMSO was maintained constant in all treatment groups within a given experiment and never exceeded 0.1 %. To ensure exponential growth and linear relationship between absorbance and cell number, cells were plated at a density of 1×10^4 cells per well in 96-well culture plates. Cells were maintained in DMEM media and allowed to adhere overnight. After 24 h, they were treated with various concentrations, in three triplicates for each concentration, of each compound and incubated at 37 ºC in a 5 % CO_2 incubator for 48h. At the end of the treatment period, MTT assay was carried out as previously described [16]. Absorbance at 490 nm was read on a plate reader (Tecan Group Ltd., Switzerland). Doxorubicin was employed as a positive control.

RESULTS AND DISCUSSION

Antibacterial activity: There is a continuous need to find new antibacterial candidates with broader and/or more potent antibacterial profile that battle the newly evolved resistant strains [6,17]. These new derivatives **10-23** might have potential against bacterial strains since the main active features, 6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid, of clinically active fluoroquinolones were kept on the main nucleus and modification were carried out by introducing lipophilic substituted anilines at position 7, hoping to furnish active compounds especially against pervasive Gram-positive resistant strains. Moreover, structural activity relationship studies (SARS) showed that C-7 substituent has the major role on the inhibitory effect of DNA gyrase and cell permeability and activity [18-23].

This work was designed as an extension to previously published work by our group that aimed to prepare new fluoroquinolone derivatives (**3-23**) carrying electron donating methyl or methoxy substitutions and to examine their biological activity against both standard and resistant bacterial strains [24]. Synthone **2** (**Scheme-I**) possess an electron withdrawing C-8 nitro group to facilitate the coupling of the substituted anilines at C-7. The antibacterial activity of nitro acids **10-16** and reduced acids **17-23** are shown in Table-1.

All compounds, acids (**10-16**) and reduced (**17-23**) have a good antibacterial activity against the standard Gram-positive and Gram-negative bacterial strains. Compounds **10**, **15** and **17** have shown a comparable antibacterial activity (MIC value of 0.683, 0.39 and 0.244 µg/ml, respectively) to the reference ciprofloxacin (MIC value of 0.439 µg/mL) against the standard *Staphylococcus aureus*.

Compound **17** has shown a comparable antibacterial activity (MIC value of 0.073 µg/mL) to the reference ciprofloxacin (MIC value of 0.043 µg/mL) against standard *Escherichia coli*. Although nitro acids (**10-15**) have shown good antibacterial activity against both standard Gram-positive and Gram-negative strains, the reduced fluoroquinolones derivatives (**17-22**) have shown excellent antibacterial activity against both standard strains mainly Gram positive strain. In particular, compounds **17**, **18**, **19**, **21** and **22** were even stronger than the reference ciprofloxacin, against standard Gram-positive strains. These data suggest that the activity was mainly pronounced in the electron donating reduced aniline derivatives **17**, **22** that carries lipophilic *meta* and *para*-methyl and methoxy. The lower activity exhibited by *ortho*-position (**20**, **23**) could be explained based on steric hind-

TABLE-1
MIC VALUES (µg/mL) FOR THE PREPARED COMPOUNDS (**10-23**) AGAINST TESTED BACTERIAL STRAINS*,***

Derivative type	Compound	*S. aureus* ATCC 6538 P	*S.aureus* ATCC 43300 (MRSA)	*A. baumannii* F24	*E. coli* ATCC 8739	C-log p****
Reference	Ciprofloxacin	0.439	ND	ND***	0.043	1.86
Nitro acid derivatives	**10**	0.683	4.688	18.75	0.879	2.69
	11	1.563	18.75	ND	1.367	4.51
	12	3.125	2.343	ND	3.91	4.50
	13	3.125	18.75	ND	3.91	4.50
	14	3.906	ND	37.5	2.734	3.92
	15	0.390	ND	37.5	6.25	3.93
	16	1.758	1.172	ND	0.732	3.93
Reduced acid derivatives	**17**	0.244	ND	37.5	0.073	4.00
	18	0.055	ND	ND	0.22	3.19
	19	0.055	ND	50	0.366	3.19
	20	3.910	ND	NT***	6.25	3.19
	21	0.055	ND	NT	0.25	2.61
	22	0.055	ND	NT	0.24	2.61
	23	3.900	ND	NT	3.91	2.61

**S. aureus* ATCC 6538P, MRSA 43300, *E. coli* ATCC 8739, *A. baumannii* F24 and clinical resistant strains of *E. coli* 1122, 1058 & 990.
**All compounds tested (14) against clinical resistant strains of *E. coli* 1122, 1058 & 990 have shown activity above 100 µg/mL.
***ND means antibacterial activity was above 100 µg/mL, whereas NT means antibacterial activity was not tested.
****C-log p was calculated by using Chem Draw ultra version 11.

rance effect of C-2 substitution. The C-8 amino group in these series seems to provide stronger or new enzymatic interaction through hydrogen bonding.

Again, these data agree with our previous assumption that lipophilicity provided mainly by alkyl or methoxy aniline can be preferred with compounds that work against gram positive strains. This phenomenon was clear in present data, since most of the compounds, in particular compounds **18**, **19**, **21** and **22** were more active against Gram-positive strains. Additional H-B network provided by C-8 amino group seems to play a major rule in optimizing the antibacterial activity. In general, acid derivatives (**10-16**) were more active against the resistant Gram-positive strains in comparison to the reduced system (**17-23**). In particular, nitro targets (**10**, **11**, **12**, **13** and **16**) have shown strong activities against the resistant Gram-positive strain (methicillin resistant *Staphylococcus aureus* ATCC 43300, MRSA) bearing in mind that the reference ciprofloxacin has not shown any detectable activity against both Gram-positive resistant strains. This is logic since that the more lipophilic quinolones have a better ability to penetrate the lipophilic cell membrane of Gram-positive bacteria, while less lipophilic compounds are more liable to penetrate the cell wall of Gram-negative bacteria [25]. In the same vein, present work reveals that most of the compounds have low activity against clinical isolate of Gram-negative resistant strains and this is probably due to mutations in the genes for the bacterial targets of fluoroquinolones (DNA gyrase [GyrA] and topoisomerase IV [ParC]) or to active efflux of the agents *via* antibiotic efflux pumps [26]. In fact, all compounds tested against clinical resistant strains of *E. coli* 1122, 1058 & 990 have shown activity above 100 µg/mL.

Anticancer activity: There is an urgent need to explore new promising antiproliferative activity [10]. Availability of five cancer cell lines fortified screening these fluoroquinolones using an *in vitro* cell culture system. On the other hand, the significant co-relation between bacterial infections and cancer might justify screening these compounds against different cancer cell lines [27]. Recent functional studies have characterized the role of the proposed water-metal ion bridge in mediating quinolone-topoisomerase IV enzyme interactions. Moreover, they demonstrate that the water-metal ion bridge is the primary interaction between quinolones and the bacterial topoisomerase II enzymes, which are mediated through C3/C4 keto acid of drug skeleton and this may explain the tolerance for structural diversity of substituents at positions N1, C7, and C8 of quinolones [28].

Biological screening of cytotoxic activity against five cancer cell lines (T47D, MCF-7, A498, HeLa and PC-3) using an *in vitro* cell culture system was revealed for acid derivatives (**10-15**) and reduced derivatives (**17-22**) in Table-2. Although most compounds tested, have shown weak activity relative to the positive control doxorubicin, nitro acids (**10-15**) were more active than reduced derivatives (**17-22**). For example, compound **15** has shown reasonable activity against four different cell lines. This could be explained through the lipophilic nature of nitro derivatives. The average C-log p of these compounds is higher than their corresponding reduced counterparts.

It is worth to mention that most nitro compounds displayed growth inhibition against more than one cell line. This could be explained through the lipophilic nature of nitro derivatives. Also, these fluoroquinolone derivatives have similar mechanism related to their core structure; 6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid. The fact that ester derivatives **3-9** showed no activity, due to loss the chelator free carboxylic acid group, support the assumption that 4-quinolon-3-carboxylic acid chelated core is very essential for anticancer activity. This is further fortified by the mechanism of known quinolone anticancer drug vasoroxin. It is well documented that it intercalates DNA and inhibits topoisomerase II which leads to replication dependant, site selective DNA damage, G2 arrest and apoptosis [29]. Yet, no clear SARS could be established from these data against cancer cells. However, more work will be carried out to study the chelation and lipophilic effect of these fluoroquinolones.

Conclusion

New fluoroquinolones (**17-23**) as potential antibacterial compounds were synthesized and characterized. Their activity was pronounced against mainly Gram-positive standard strain and simultaneously they exhibited good activity against *E. coli* standard strain. Further investigations will be carried out to establish SAR for anticancer activity and explore their mechanism.

TABLE-2
IC_{50} VALUES (µM) OF THE TESTED FLUOROQUINOLONES ON FIVE HUMAN CANCER CELL LINES

Compound	T47D	MCF7	A498	PC-3	HeLa
10	373 ± 11	297 ± 10	313 ± 15	370 ± 19	336 ± 17
11	296 ± 10	319 ± 14	334 ± 19	375 ± 18	241 ± 14
12	219 ± 17	234 ± 7	198 ± 9	260 ± 16	166 ± 11
13	380 ± 14	250 ± 12	203 ± 11	153 ± 7	332 ± 11
14	321 ± 18	259 ± 8	200 ± 12	210 ± 9	179 ± 10
15	162 ± 9	271 ± 7	179 ± 8	205 ± 13	237 ± 9
17	393 ± 21	410 ± 11	430 ± 26	289 ± 15	339 ± 11
18	422 ± 24	450 ± 18	471 ± 29	299 ± 16	294 ± 13
19	397 ± 16	389 ± 13	424 ± 26	307 ± 11	280 ± 16
20	485 ± 26	479 ± 21	444 ± 29	337 ± 26	307 ± 18
21	453 ± 28	409 ± 19	352 ± 23	180 ± 17	373 ± 13
22	432 ± 20	399 ± 21	362 ± 27	315 ± 23	255 ± 10
Doxorubicin	3 ± 0.8	1 ± 0.01	1 ± 0.01	1 ± 0.01	2 ± 0.1

*Values are expressed as mean ± SD of three experiments

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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