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Synthesis and Antibacterial Activity of Some Novel Quinolones

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Abstract

A series of novel quinolone-3-carboxylic acids have been synthesized and have been analyzed by physico-chemical techniques (elemental analysis, ^{1}H-NMR, ^{13}C-NMR, FT IR, thin layer chromatography). The new quinolones were evaluated for in vitro activity by determining minimum inhibitory concentration against a variety of bacteria.

Keywords: *fluoroquinolones, quinolones, antibacterial activity, antimicrobial agents*

Introduction

After the concept of selective toxicity in chemotherapy was introduced at the beginning of the 20th century, (Ehrlich, 1913), classes of substances with antibacterial properties, produced by microorganisms or created through synthesis were obtained. After the discovery of penicillin, the first antibiotic introduced in clinical use in man in 1940s, a large number of different types of antibiotics were produced. Antibiotics such as beta-lactams, macrolides, aminoglycozides and tetracyclines were discovered and introduced during an extremely short period. These were obtained either by isolation from fungi or by chemically modification of the naturally isolated substrates. These dominated the antimicrobial industry, while synthetically obtained substances only played a minor role.

In 1962, G. Y. Lesher and his collaborators introduced the first quinoline derivative, nalidixic acid **(**1-ethyl-1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine-3-carboxilyc acid), which had moderate activity against gram-negative organisms and was used for treating urinary tract infections [1,2].

In the following years [3], a large gamma of derivatives with common elements were synthesized, which could be grouped by: cinoline (cinoxacin**),** pyrido-pyrimidine (pipemidic acid; piromidic acid), naphthyridine (nalidixic acid) and quinolones (oxolinic acid, miloxacin, tioxacin, etc.). These derivatives, with differentiated structures, have 2 common pharmacological properties, which allowed them to be classified as first generation biologically active derivatives with quinolone structure. The two common characteristics for first generation quinolones are:

-a narrow antibacterial spectrum, designed especially for enterobacteriaceae;

-a pharmacokinetics which allows for rapid elimination and reduced tissue absorption, only allowing them to be used as urinary antiseptics.

The success of first generation quinolones spurred the research in this area, which led to the obtainment through synthesis, after 1980, of a new series of compounds with stronger antibacterial properties and a broader spectrum of antibacterial activity which included gram positive and gram negative organisms, and which where defined by their ability to be applied on all localized infections.

Koga and his collaborators introduced Norfloxacin into clinical use. in 1980, the first quinoline with a fluorine atom substituted at the C-6 position and a piperazine C-7 [4]. Norfloxacin was the first quinolone with increased antimicrobial activity, acting on a large spectrum of gram positive and gram negative microorganisms, including Pseudomonas aeruginosa.

Research in the field of derivatives with a quinolone structure have lead to new compounds obtained recently, which have been classified as third and fourth generation systemic quinolones, largely effective against Staphilococcus aureus. Their large antibacterial spectrum includes anaerobes, Chlamydia and Mycoplasma.

The four generations have the following common aspects:

-an identical mechanism of action by inhibition the A subunit of DNA-gyrasa;

-an exclusively chromosomal bacteria resistance;

-some similar bacteria effects: photo toxicity, neurotoxicity, cartilage toxicity.

Until now a large number of antibacterial substances belonging to the above mentioned class have been used in medicine. Derivatives of 4-oxo-1, 4-dihydro-quinoline-3-carboxylic acids are used when treating infections of the urinary tract, the respiratory tract, intestinal infections, ear/nose/throat infections, STD's, soft tissue and skin infections, meningitis caused by gram negative and Staphilococci bacteria, liver and bile infections, septicemia and endocarditis, prophylaxis and surgical infections and on patients with immune deficiencies.

Materials and Methods

1-Ethyl-6-halo-7-chloro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid ethyl ester (Method A)

A mixture of 6-halo-7-chloro-4-hidroxy-quinolin-3-carboxylic acid ethyl ester (3) [4] (0,03 mol), K_2CO_3 (19,234 g, 0,135 mol) and DMF (100 mL) was heated at 100^0C with stirring, The mixture was cooled at 80^0C, added diethyl sulphate (21,24 g, 0,135 mol) and heated at 100^0C with stirring. After one hour, the mixture was filtered. The filtrate was evaporated to dryness and extracted with $CHCl_3$. The $CHCl_3$ layer was washed with H_2O, dried and evaporated to dryness. The crude ester was recrystallized from isoPrOH-H_2O to yield (6: R_1 = ethyl).

1-Isopropyl-6-halo-7-chloro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid ethyl ester (Method B)

A mixture of 6-halo-7-chloro-4-hidroxy-quinolin-3-carboxylic acid ethyl ester (3) (0,02 mol), K_2CO_3 (13,82 g, 0,1 mol) and DMF (60 mL) was heated at 100^0C with stirring, The mixture was cooled at 40^0C, added 2-bromo-*iso*propane (12,3 g, 9,5 mL, 0,1 mol) and heated at 40-50^0C with stirring. After 18 hours, the mixture was filtered. The filtrate was evaporated to dryness and extracted with $CHCl_3$. The $CHCl_3$ layer was washed with H_2O, dried and evaporated to dryness. The crude ester was recrystallized from EtOH to yield (6: R_1 = *iso*propyl).

1-Alkyl-6-halo-7-chloro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid (7) (Method C)

A mixture of (4) (0,025 mol) in a solution of sodium hydroxide (2,08 g, 0,05 mol) in H_2O (21 mL) - EtOH (7 mL) was refluxed with stirring. After 1,5 ore, the mixture was acidified with AcOH, and the resulting precipitate was filtered off, washed with H_2O and dried The solid was recrystallized from DMF to yield (7).

1-Ethyl-6-halo-7-chloro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid (7) (Method D)

To a mixture of 6-halo-7-chloro-4-hidroxy-quinolin-3-carboxylic acid ethyl ester (3) (0,02 mol) and 108 g aqueous 40 % sodium hydroxide solution was added 4,54 g (0,03 mol) diethyl sulphate. The mixture was stirred at 20^0 C for 30 minutes and then at 100^0 for 30 minutes. A further 4,54 g (0,03 mol) diethyl sulphate was added and stirring was continued for 1 h. The mixture was cooled at 20^0 C, and was filtered and the solid residue was dissolved in 300 ml water. The solution was acidified with hydrochloric acid and filtered. The solid residue was washed with water. The solid was recrystallized from DMF to yield (7). (R_1=ethyl)

1-isoPropyl-6-halo-7-chloro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid (7) (Method E)

To a suspension of 0,28 mol sodium borohydride in 250 ml dichloretane was added during 5 minutes 48 ml de acetic acid, under stirring and cooling. After 30 minutes was added 0,1 mol de 3-cloro-4-halo-aniline and 0,1 moli acetone, and the mixture was stirred at 20^0C. After 24 h was added NaOH 1N. The DClE layer was washed with brine, dried over Na_2SO_4, and evaporated to dryness to give a crude oil. To the crude oil was added diethyl ethoxymethylene malonate (0,1 mol, 21,62 g), and the mixture was stirred at 150-160^0C for 1 h. The reaction mixture was then poured into 210 g polyphosphoric acid and the mixture was stirred at la 90-100^0C. After 1 h, the mixture was then poured into 400 mL H_2O. 1-alckyl-6-halo-7-chloro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid ethyl ester was extracted with $CHCl_3$. The $CHCl_3$ layer was washed with H_2O, dried over Na_2SO_4, and evaporated to dryness. A mixture of crude ester in a solution of sodium hydroxide (0,1 mol, 40 g) in H_2O (200 mL) – EtOH (20 mL) was refluxed with stirring. After 2,5 hours, the mixture was acidified with AcOH, and the resulting precipitate was filtered off, washed with H_2O and dried. The solid was recrystallized from DMF to yield (7).

1-Ethyl-6-halo-7-heterocyclil-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid (8) (Method F)

A mixture of (7) (0,02 mol), heterocycle (0,1 mol) and DMF/DMSO (44 mL) was stirred at 100-130^0C. After 3-8 h was added H_2O (22 mL) and acetic acid (pH=7) and the resulting precipitate was filtered off. The crude product was recrystallized from DMF to yield (8).

1-Ethyl-6-fluoro-7-(morpholin-1-yl)-8-chloro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid (9) (Method G)

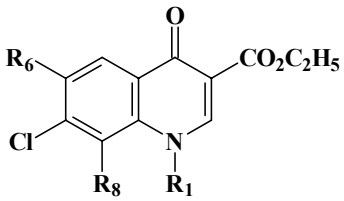
To a solution of 1-ethyl-6-fluoro-7-morpholinyl-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid (3,2g; 0,01 moli) in $CHCl_3$ (550 mL) was added 2,56 mL SO_2Cl_2, and the mixture was stirred at room temperature. After 5 minutes the mixture was washed with water. The $CHCl_3$ layer was dried over Na_2SO_4, and evaporated, to which 50 mL MeOH was added. The precipitate was collected and dried to give 1-ethyl-6-fluoro-7-(morpholin-1-yl)-8-chloro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid. mp 244,6-246^0C (dec.); yield – 40%.

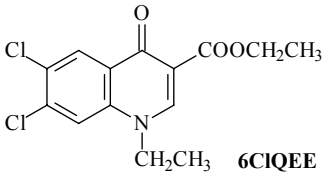
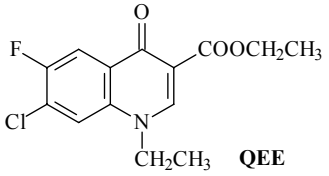
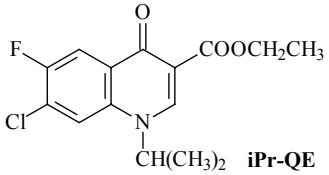
Results and Discussions

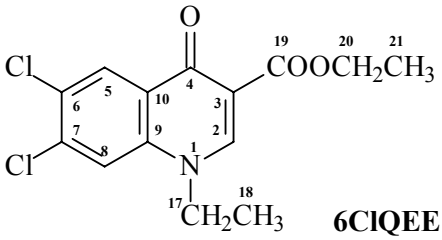
The synthesis of the novel quinolones followed a Gould-Jacobs cyclization process (Scheme 1). An appropriate unsubstituted aniline (1) is reacted with diethylethoxy methylene malonate (EMME) [4] to produce the resultant anilinomethylenemalonate (2).A subsequent thermal process induces Gould-Jacobs cyclization to afford the corresponding 4-hidroxy-quinoline-3-carboxylate ester (3)[5].

The following operation is the alkylation of the quinoline amine which is usually accomplished by reaction with a suitable alkyl halide or dialkyl sulphates to produce the quinolone 3-carboxylate ester (6) (Table 1).

Table 1. 4-Oxo-quinoline-3-carboxylic acids ethyl ester



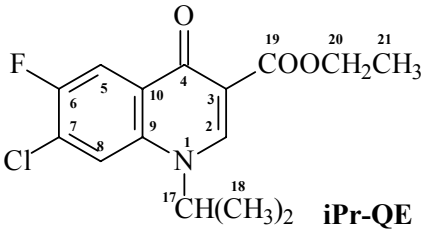
4-Oxo-quinoline-3-carboxylic acids ethyl ester		Method/ Recrystn. solvent	mp ^{0}C	Yield %
 **6ClQEE**	$C_{14}H_{13}Cl_2NO_3$ 314.16 313.027248 C 53.52% H 4.17% Cl 22.57% N 4.46% O 15.28%	A/ isoPrOH-H_2O	157-160	77,4
 **QEE**	$C_{14}H_{13}ClFNO_3$ 297.71 297.056799 C 56.48% H 4.40% Cl 11.91% F 6.38% N 4.70% O 16.12% [6]	A [6]/ isoPrOH-H_2O	145	57
 **iPr-QE**	$C_{15}H_{15}ClFNO_3$ 311.74 311.072449 C 57.79% H 4.85% Cl 11.37% F 6.09% N 4.49% O 15.40%	B/ EtOH	51,4-52,3	35



6ClQEE

^{1}H-NMR($CDCl_3$, δ ppm, *J* Hz): 8.52(s, 1H, H-2); 8.45(s, 1H, H-5); 7.56(s, 1H, H-8); 4.38(q, 2H, H-17, 7.1); 4.22(q, 2H, H-20, 7.3); 1.56(t, 3H, H-21, 7.3); 1.41(t, 3H, H-18, 7.1).

^{13}C-NMR($CDCl_3$, δ ppm): 172.54(C-4); 165.10(C-19); 148.98(C-2); 137.59(Cq); 137.49(Cq);130.04(Cq); 129.40(CH); 128.60(Cq); 117.71(CH); 111.74(Cq); 61.14(C-20); 49.19(C-17); 14.50(C-22); 14.46(C-18).
FT-IR(solid in ATR, ν cm^{-1}): 3071w; 2987w; 2936w; 1719vs; 1633m; 1610w; 1587s; 1532w; 1478m; 1447m; 1381w; 1328m; 1309m; 1258w; 1230m; 1211m; 1141w; 1123m; 1103m; 1024m; 961w; 936w; 912w; 884w; 865w; 850w; 802w; 748w; 678w; 647w; 625w; 591w; 535w; 492w; 474w; 428w.



iPr-QE

^{1}H-NMR($CDCl_3$, δ ppm, *J* Hz): 9.16(s, 1H, H-2); 8.15(d, 1H, H-8, $J(^{19}F-^{1}H)$=6.9 Hz); 7.98(d, 1H, H-5, $J(^{19}F-^{1}H)$=9.5 Hz); 4.73(spt, 1H, H-17, 6.1); 4.48(q, 2H, H-20, 7.1); 1.46(t, 3H, H-21, 7.1); 1.39(d, 6H, H-18, 6.1).
^{13}C-NMR($CDCl_3$, δ ppm): 165.01(C-4); 162.34(C-19); 156.29(d, C-6, $J(^{19}F-^{13}C)$=249.5 Hz); 152.71(C-2); 147.88(Cq); 131.10(C-8); 127.17(Cq); 127.28(d, C-7, $J(^{19}F-^{13}C)$=21.2 Hz); 124.67(d, C-10, $J(^{19}F-^{13}C)$=8.0 Hz); 115.33(Cq); 108.94(d, C-5, $J(^{19}F-^{13}C)$=23.5 Hz); 80.10(C-17); 61.80(C-20); 22.60(C-18); 14.33(C-21).
FT-IR(solid in ATR, ν cm^{-1}): 3078w; 3003w; 2975s; 2917m; 2869w; 1719vs; 1616m; 1579s; 1563s; 1477vs; 1386s; 1364s; 1336s; 1295m; 1257s; 1207s; 1156vs; 1091vs 1035s; 942s; 882s; 825s; 793m; 761m; 730m; 649w; 614w; 568w; 522w.

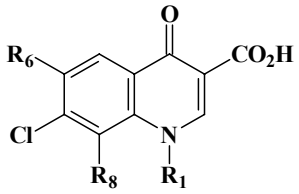
A modified approach resorts to the use of a monosubstitued aniline (5) as a starting material which avoids subsequent N-1-amine alkylation (R_1 = isopropyl).

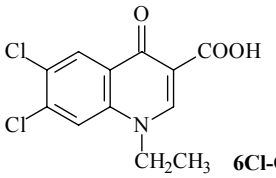
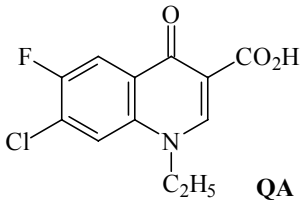
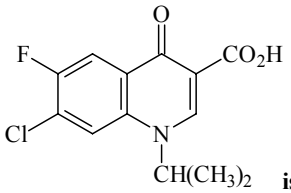
A strong acid (such as polyphosphoric acid) is often needed to induce cyclization directly resulting in the formation of N-isopropyl-4-oxo-quinolone-3-carboxylate ester (6) (R_1 = isopropyl).

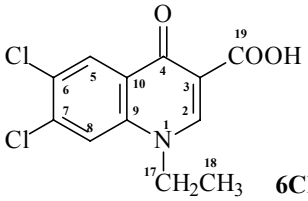
In either case, the final manipulation is acide or basic hydrolysis to cleave the ester generating the biologically active free carboxylic acid (7) (Table 2).

The biologically active free carboxylic acid (7) was also obtained from the corresponding 4-hidroxy-quinoline-3-carboxylate ester (3) by alkylation with dialkyl sulphates in presence of alkali, for exemple the reaction it can conveniently be carried out in aqueous 40 % sodium hydroxide solution [7].

Table 2 4-Oxo-quinoline-3-carboxylic acids



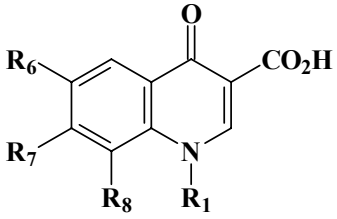
4-Oxo-quinoline-3-carboxylic acids		Method Recrystn. solvent	mp ^{0}C	Yield %
 **6Cl-QA**	$C_{12}H_9Cl_2NO_3$ 286.11 284.995948 C 50.38% H 3.17% Cl 24.78% N 4.90% O 16.78%	C/ DMF D/ DMF	294-297,2	62
 **QA**	$C_{12}H_9ClFNO_3$ 269,66 C 53,45 % H 3,36 % Cl 13,15 % F 7,05 % N 5,19 % O 17,8 % [6]	C [6]/ DMF D/ DMF	278,5 -281,9 277,2-281,3	85 60
 **isoPrQ**	$C_{13}H_{11}ClFNO_3$ 283,68 C 55,04 % H 3,91 % Cl 12,49 % F 6,7 % N 4,94 % O 16,92 % [6]	C/ DMF E/ DMF	243-244 242-244	45 27


6Cl-QA

^{1}H-NMR(dmso-d6, δ ppm, *J* Hz): 9.06(s, 1H, H-2); 8.42(s, 1H, H-5); 8.41(s, 1H, H-8); 4.59(q, 2H, H-17, 7.1); 1.39(t, 3H, H-18, 7.1).
^{13}C-NMR(dmso-d6, δ ppm): 176.31(C-19); 165.47(C-4); 150.33(C-2); 138.46(Cq); 137.51(Cq); 129.59(Cq); 127.11(CH); 125.57(Cq); 120.55(CH); 108.61(Cq); 49.36(C-17); 14.61(C-18).
FT-IR(solid in ATR, ν cm^{-1}): 3094w; 3038w; 2990w; 1715s; 1599vs; 1547m; 1526m; 1486m; 1456vs; 1437vs; 1382s; 1300m; 1258m; 1219s; 1147m; 1122m; 1090m; 973m; 936s; 909m; 864m; 805m; 771w; 752w; 688w; 666m; 541w.

The replacement of 7-chloro group with a heterocycle yielded compounds (8) (Table 3).

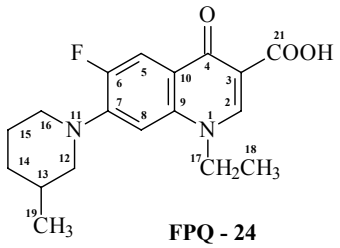
Table 3 Quinolones



Qunolone	R_1	R_6	R_7	R_8	Method	mp ^{0}C	Yield %
FPQ-24	ethyl	F	3-methyl-	H	F	188,1-	40

$C_{18}H_{21}FN_2O_3$ 332,37 332,153620 C 65,05% H 6,37% F 5,72% N 8,43% O 14,44%			piperidin-1-yl			189,4	
6ClPQ-24 $C_{18}H_{21}ClN_2O_3$ 348,82 348,124070 C 61,98% H 6,07% Cl 10,16% N 8,03% O 13,76%	ethyl	Cl	3-methyl-piperidin-1-yl	H	F	216,4-218,4	58
PQ-24 $C_{19}H_{23}FN_2O_3$ 346,40 346,169271 C 65,88% H 6,69% F 5,48% N 8,09% O 13,86%	isopropyl	F	3-methyl-piperidin-1-yl	H	F	209,1-211,7	41
PQ-22 $C_{18}H_{21}FN_3O_3$ 346,38 346,156694 C 62,42% H 6,11% F 5,48% N 12,13% O 13,86%	isopropyl	F	3-methyl-piperazin-1-yl	H	F	215-218	56
PQ-23 $C_{17}H_{19}FN_2O_4$ 334,34 334,132885 C 61,07% H 5,73% F 5,68% N 8,38% O 19,14%	isopropyl	F	morpholin-1-yl	H	F	266-268	64
FPQ-25 [8] $C_{16}H_{17}FN_2O_4$ 320,32 320,117235 C59,99 H5,35 F5,93 N8,75 O19,98	ethyl	F	morpholin-1-yl	H	F	257,4-258,7	76
6ClPQ-25 [8] $C_{16}H_{17}ClN_2O_4$ 336,77 336,087684 C 57,06% H 5,09% Cl 10,53% N 8,32% O 19,00%	ethyl	Cl	morpholin-1-yl	H	F	267,1-269,2	80
6ClPQ-27 $C_{17}H_{20}ClN_3O_3$ 349,81 349,119319 C 58,37% H 5,76% Cl 10,13% N 12,11% O 13,72%	ethyl	Cl	3-methyl-piperazin-1-yl	H	F	170,5-171,4	58
FPQ-28	ethyl	F	morpholin-1-yl	Cl	F	244,6-	40

$C_{16}H_{16}ClFN_2O_4$ 354,76 354,078263 C 54,17% H 4,55% Cl 9,99% F 5,36% N 7,90% O 18,04%						246	



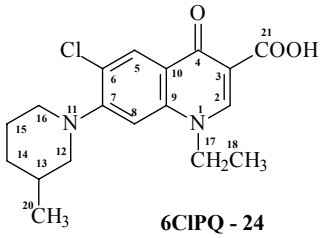
FPQ - 24

^{1}H-NMR (dmso-d6, δ ppm, *J* Hz): 8.90(s, 1H, H-2); 7.82(d, 1H, H-5, 13.4); 7.10(d, 1H, H-8, 7.4); 4.55(q, 2H, H-17, 6.9); 3.57(tl, 2H, sist. AB, H-12A, H-16A, 9.0); 2.50÷2.87 (m, 2H, sist. AB, H-12B, H-16B); 1.83÷1.56 (m, 4H, H-14, H-15); 1.40(t, 3H, H-18, 6.9); 1.11 (m, 1H, H-13); 0.93(d, 3H, H-19, 6.1).

^{13}C-NMR(dmso-d6, δ ppm): 176.01(C-4); 166.03(C-21); 152.79(d, C-6, $J(^{13}C-^{19}F)$=247.4 Hz); 148.23(C-2); 146.01(Cq); 145.87(Cq); 137.20(Cq); 119.51(d, Cq, $J(^{13}C-^{19}F)$=7.6 Hz); 111.00(d, C-5, $J(^{13}C-^{19}F)$=23.0 Hz); 107.03(d, C-10, $J(^{13}C-^{19}F)$=2.2 Hz); 105.46(d, C-8, $J(^{13}C-^{19}F)$=3.5 Hz); 57.21(d, C-12, $J(^{13}C-^{19}F)$=4.8 Hz); 50.09(d, C-16, $J(^{13}C-^{19}F)$=4.2); 48.92(C-17); 32.05(C-15); 30.55(C-13); 24.59(C-14); 18.93(C-19); 14.24(C-18);

FT-IR(solid in ATR, ν cm^{-1}): 3042; 2964; 2931; 2811; 1714; 1623; 1540; 1508; 1443; 1392; 1366; 1302; 1251; 1205; 1131; 1084; 1047; 972; 944; 892; 856; 807; 748; 701; 634; 550; 498; 458.

Remarkably, it was evidenced in this case a through space interlinkage between the fifth position fluor atom and the carbon atoms adjacent to the nitrogen from the piperdinic cycle. The presence of the long distance interlinkage with fluorine explains the unresolved multiplicity of near-by hydrogen atoms.

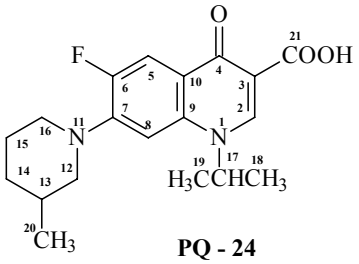


6ClPQ - 24

^{1}H-NMR(dmso-d6, δ ppm, *J* Hz): 9.00(s, 1H, H-2); 8.22(s, 1H, H-5); 7.30(s, 1H, H-8); 3.42(m, 4H, H-12-16); 2.83(m, 1H, H-15); 1.81(m, 3H, H-14-15); 1.47(t, 3H, H-18, 7.3); 1.17(q, 1H, H-13, 6.4); 1.00(d, 3H, H-20, 6.4).

^{13}C-NMR(dmso-d6, δ ppm, *J* Hz): 175.60(C-4); 166.11(C-21); 154.98(Cq); 149.31(C-2); 139.85(Cq); 127.79(C-5); 127.16(Cq); 121.20(Cq); 108.51(Cq); 108.40(C-8); 59.00(C-12); 51.98(C-17); 49.36(C-16); 32.58(C-15); 31.19(C-13); 25.25(C-14); 19.30(C-20); 14.61(C-18).

FT-IR(solid in ATR, ν cm^{-1}): 3037; 2958; 2927; 2849; 2807; 2722; 1715; 1609; 1535; 1512; 1449; 1385; 1359; 1301; 1269; 1243; 1203; 1117; 1086; 1022; 976; 924; 897; 852; 806; 753; 714; 680; 620; 553; 493; 436.



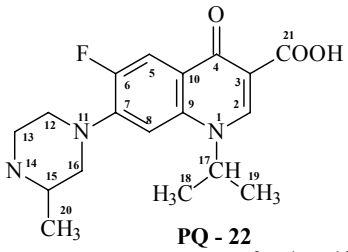
PQ - 24

^{1}H-NMR(dmso-d6, δ ppm, *J* Hz): 8.78(s, H-2); 7.92(d, $^{3}J(^{1}H\text{-}^{19}F)$=13.5, H-5); 7.31(d, $^{4}J(^{1}H\text{-}^{19}F)$= 7.3, H-8); 5.28(spt, 1H, H-17, 6.5); 3.60(m, 2H, sist. AB, H-12A, H-16B, 10.8); 2.92(m, 1H, sist. AB, H-12B or H-16B); 2.63(m, 1H, sist. AB, H-12B, 10.8); 1.58(t, 3H, H-18, 6.5); 1.44÷1.83(m, 4H, H-14-15); 1.17(m, 1H, H-13); 0.98(d, 3H, H-19, 6.5).

^{13}C-NMR(dmso-d6, δ ppm, *J* Hz): 178.85(C-4); 167.23(C-21); 152.24(d, C-6, $^{4}J(^{19}F\text{-}^{13}C)$=254.3 Hz); 147.01(Cq); 144.47(C-2); 138.77(Cq); 112.06(d, C-5, $^{2}J(^{19}F\text{-}^{13}C)$=23.7 Hz); 107.23(d, C-10, $J(^{13}C\text{-}^{19}F)$=2.1 Hz); 106.33(d, C-8, $^{1}J(^{19}F\text{-}^{13}C)$=3.4 Hz); 105.76(d, C-8, $J(^{13}C\text{-}^{19}F)$=3.4 Hz);58.24(d, C-16, $^{4}J(^{19}F\text{-}^{13}C)$=4.6 Hz); 53.59(C-17); 51.18(d, C-12, $^{4}J(^{19}F\text{-}^{13}C)$=4.8 Hz); 33.05(C-15); 31.58(C-13); 25.62(C-14); 22.40(C-18-19); 19.95(C-20).

Spectacularly it is evidenced the *through space coupling* between the ά position carbon atoms of the saturated heterocyclicl and the sixth position fluorine atom of the quinolone.

FT-IR(solid in ATR, ν cm^{-1}): 3058; 2927; 2848; 2809; 1707; 1625; 1604; 1497; 1444; 1390; 1369; 1343; 1301; 1249; 1192; 1132; 1112; 1021; 967; 928; 897; 858; 832; 809; 754; 707; 664; 636; 566; 534; 468; 437.

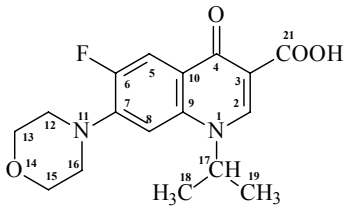


PQ - 22

^{1}H-NMR(dmso-d6, δ ppm, *J* Hz): 8.74(s, H-2); 7.76(d, $^{3}J(^{1}H\text{-}^{19}F)$=13.4, H-5); 7.85(d, 13.2, H-5); 7.25(d, $^{4}J(^{1}H\text{-}^{19}F)$=6.8, H-8); 5.26(spt, 5.7, H-17); 3.52÷3.34(m, 7H, H-12-13-15-16); 1.55(m, 3H, H-20); 1.03(d, 5.7, 6H, H-18-19).

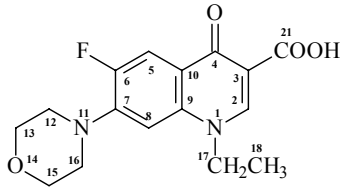
^{13}C-NMR(dmso-d6, δ ppm, *J* Hz): 175.68(C-4); 166.10(C-21); 152.80(d, $J(^{13}C\text{-}^{19}F)$=247.3, C-6); 145.78(d, $^{2}J(^{13}C\text{-}^{19}F)$=9.9, C-7); 143.53(C-9); 137.71(C-2); 119.15(d, $^{3}J(^{13}C\text{-}^{19}F)$=7.6, C-10); 111.11(d, $J(^{13}C\text{-}^{19}F)$=23.5, C-5); 107.10(C-3); 105.28(C-8); 56.85(C-16); 52.56(C-17); 52.48(C-15); 50.05(C-12); 45.03(C-13); 40.13(C-12); 21.39(C-18-19); 19.27(C-20).

FT-IR(solid in ATR, ν cm^{-1}): 3482; 2972; 2833; 1707; 1608; 1571; 1533; 1486; 1462; 1375; 1331; 1258; 1237; 1195; 1134; 1098; 1067; 1048; 1017; 989; 928; 895; 857; 833; 780; 735; 711; 663; 621; 590; 556; 526; 466.



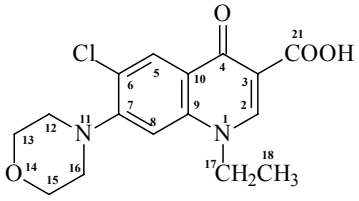
PQ - 23

^{1}H-NMR(dmso-d6, δ ppm, *J* Hz): 8.77(s, H-2); 7.93(d, $^{3}J(^{1}H\text{-}^{19}F)$=13.4, H-5); 7.32(d, $^{4}J(^{1}H\text{-}^{19}F)$= 7.1, H-8); 5.28(spt, 6.9, H-17); 3.80(m, 4H, H-13-15); 3.32(m, 4H, H-12-16); 1.55(d, 6.9, 6H, H-18-19).
^{13}C-NMR(dmso-d6, δ ppm, *J* Hz): 175.76(C-4); 166.04(C-21); 152.82(d, $J(^{13}C\text{-}^{19}F)$=248.1, C-6); 145.32(d, $J(^{13}C\text{-}^{19}F)$=9.9, C-7); 143.76(C-9); 137.66(C-2); 119.95(d, $^{3}J(^{13}C\text{-}^{19}F)$=7.4, C-10); 111.28(d, $^{3}J(^{13}C\text{-}^{19}F)$=22.0, C-5); 105.59(C-8); 105.58(C-3); 65.86(C-13-15); 52.56(C-17); 49.85(C-12-16); 21.41(C-18-19).
FT-IR(solid in ATR, ν cm^{-1}): 3075; 2985; 2875; 2852; 1704; 1628; 1607; 1546; 1501; 1466; 1447; 1373; 1343; 1298; 1244; 1214; 1191; 1169; 1123; 1106; 1072; 1039; 1017; 957; 937; 889; 872; 822; 804; 752; 703; 667; 638; 564; 490; 470.



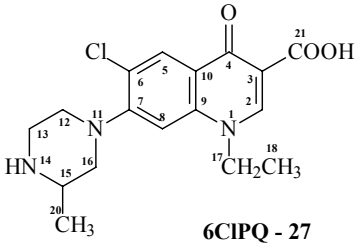
FPQ - 25

^{1}H-NMR(dmso-d6, δ ppm, *J* Hz): 8.93(s, H-2); 7.90(d, $^{3}J(^{1}H\text{-}^{19}F)$=13.4, H-5); 7.16(d, $^{4}J(^{1}H\text{-}^{19}F)$= 7.3, H-8); 4.57(q, 2H, H-17, 7.0); 3.80(m, 4H, sist. A_2B_2, H-13-15, 4.5); 3.30(m, 4H, sist. A_2B_2, H-12-16, 4.5); 1.41(t, 3H, H-18, 7.0).
^{13}C-NMR(dmso-d6, δ ppm, *J* Hz): 177.07(C-4); 166.98(C-21); 152.55(Cq); 149.51(C-2); 138.09(Cq); 120.54(Cq); 112.13(C-6); 112.09(C-5); 106.68(C-8); 110.42(C-3);66.82(C-13-15); 50.78(C-17); 49.98(C-12-16); 15.30(C-18).
FT-IR(solid in ATR, ν cm^{-1}): 3055; 2978; 2945; 2872; 2836; 1730; 1617; 1519; 1474; 1438; 1363; 1299; 1249; 1201; 1115; 1033; 956; 927; 883; 832; 804; 749; 705; 645; 493; 457.



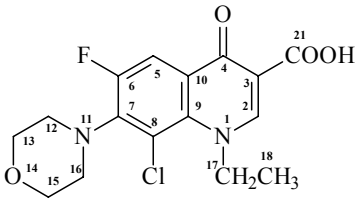
6ClPQ - 25

^{1}H-NMR(dmso-d6, δ ppm, *J* Hz): 9.02(s, 1H, H-2); 8.27(s, 1H, H-5); 7.36(s, 1H, H-8); 4.64(q, 2H, H-17, 7.1); 3.85(m, sist. A_2B_2, 4H, H-13-15); 3.28(m, sist. A_2B_2, 4H, H-12-16); 1.46(t, 3H, H-18, 7.1).
^{13}C-NMR(dmso-d6, δ ppm): 175.61(C-4); 165.34(C-21); 153.01(Cq); 148.89(CH-2); 138.72(Cq); 126.90(C-5); 125.91(Cq); 120.66(Cq); 107.86(C-8); 65.67(C-13-15); 50.53(C-12-16); 48.55(C-17); 13.89(C-18).
FT-IR(solid in ATR, ν cm^{-1}): 3035; 2971; 2947; 2904; 2865; 1724; 1609; 1514; 1466; 1438; 1384; 1337; 1294; 1237; 1191; 1111; 1062; 995; 950; 912; 865; 842; 805; 750; 713; 686; 625; 552; 490; 453; 426.



6ClPQ - 27

^{1}H-NMR(dmso-d6, δ ppm, *J* Hz): 8.99(s, 1H, H-2); 8.23(s, 1H, H-5); 7.28(s, 1H, H-8); 4.61(q, 2H, H-17, 7.3); 3.46(m, 1H, H-15); 3.10÷2.80(m, 6H, H-12-13-16); 1.45(t, 3H, H-18, 7.3); 1.07(d, 3H, 6.2).
^{13}C-NMR(dmso-d6, δ ppm): 175.67(C-4); 165.22(C-21); 153.63(Cq); 148.45(C-2); 138.93(Cq); 126.97(C-5); 126.03(Cq); 120.39(Cq); 107.45(C-8); 57.74(C-16); 50.90(C-12); 49.64(C-15); 48.45(C-17); 44.67(C-13); 18.72(C-20); 13.69(C-18).
FT-IR(solid in ATR, ν cm^{-1}): 3398; 3043; 2982; 2878; 2837; 1667; 1623; 1607; 1573; 1519; 1469; 1447; 1359; 1330; 1284; 1251; 1207; 1140; 1123; 1090; 1053; 1024; 994; 913; 863; 836; 822; 787; 752; 723; 682; 660; 626; 599; 547; 516; 498; 450.



FPQ - 28

^{1}H-NMR(dmso-d6, δ ppm, *J* Hz): 8.97(s, 1H, H-2); 8.07(d, 1H, H-5, 11.8); 4.89(q, 2H, H-17, 7.2); 3.82(m, 4H, sist. A_2B_2, H-13-15); 3.37(m, 4H, sist. A_2B_2, H-12-16); 1.46(t, 3H, H-18, 7.2).
^{13}C-NMR(dmso-d6, δ ppm, *J* Hz): 175.56(C-4); 166.12(C-21); 154.95(d, J(^{13}C-^{19}F)=254.8, C-6);158.37(Cq); 153.04(C-2); 125.94(Cq); 124.76(Cq); 116.86(Cq); 111.57(d, J(^{13}C-^{19}F)=23.5, C-5); 98.35(C-3); 67.23(C-13-15); 53.64(C-12-16); 51.58(C-17); 16.14(C-18).
FT-IR(solid in ATR, ν cm^{-1}): 3056; 2957; 2895; 2849; 1717; 1615; 1558; 1532; 1492; 1435; 1376; 1300; 1253; 1207; 1102; 1033; 980; 920; 890; 846; 803; 740; 651; 528; 464.

The new compounds were evaluated for „in vitro" activity by determining minimum inhibitory concentration against a variety of bacteria: *E. Coli* ATCC25922, *S.aureus ATCC29213* and *P.aeruginosa ATCC 27813,* (Table 4), by agar dilution method [9,10]. FPQ-25 and FPQ-28 showed excellent "in vitro" activity against *E. Coli* ATCC 25922 (MIC 0,125 μg/mL), and *S.aureus ATCC29213(*MIC 0,06 μg/mL)

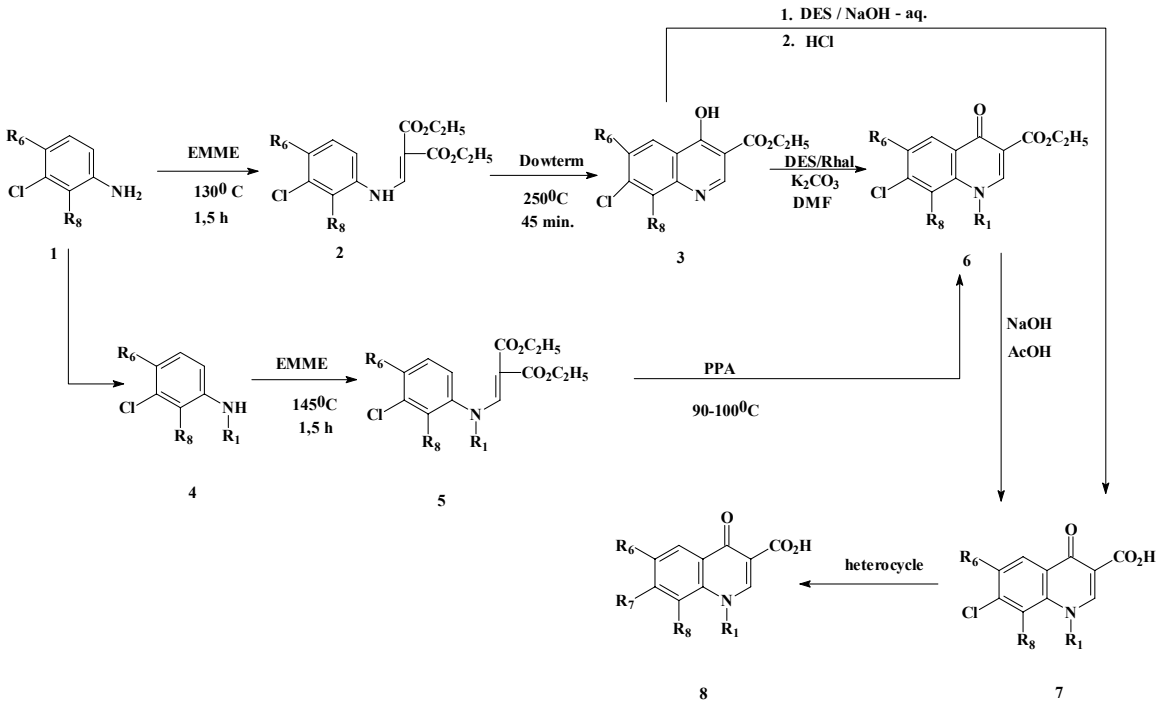
Table 4 *"In vitro"Antibacterial Activity*

Comp.	**Minimum inhibitory concentration μg/ml**		
	***E.coli* 25992**	***S.aureus* ATCC29213**	***P.aeruginosa* ATCC 27813**
FPQ-24	2	0,5	32
6ClPQ-24	8	2	>128
PQ-24	8,0	2	64
PQ-22	0,5	4	8
6ClPQ-25	4	2	128
FPQ-25	0,125	0,06	8
FPQ-28	0,125	0,06	8

Conclusions

In conclusion, we have synthesized new quinolones and we have investigated their antibacterial activity. The results of the present study indicate that combination of substituents in the fluoroquinolone ring, could produce powerful antibacterial agents such as compound FPQ-25: 1-ethyl-6-fluoro-7-morpholinyl-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid, and FPQ-28: 1-ethyl-6-fluoro-7-morpholinyl-8-chloro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid, in concordance with the QSARs studies [11]

Scheme 1



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