Dedicated to the memory of
acad. Ecaterina Cioranescu-Nenitzescu

Synthesis and Antibacterial Activity of Some Novel Desfluoroquinolones

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This paper presents experimental data regarding the synthesis of several 1,4-dihydro-4-oxo-quinolin-3-carboxylic acids, without a fluorine atom in 6-position by Gould-Jacobs cyclization. These novel desfluoroquinolones have been analised by physico-chemical technics (elemental analisys, ^{1}H-NMR, ^{13}C-NMR,FT IR, thin layer chromatography). The new desfluoroquinolones were evaluated for in vitro activity by determinating minimum inhibitory concentration against a variety of bacteria.

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

Worldwide, Gram-positive organisms have re-emerged as the major hospital pathogens [1]. Fluoroquinolones are among the most attractive agents in the treatment of bacterial infections since the discovery of Norfloxacin [2-4]. After the discovery of Norfloxacin, structure-activity relationships(SAR) analysis of the quinolonic nucleus led to the development of new derivatives with beter solubility, higher antimicrobial activity prolonged serum high-life, fewer adverse side effects, and both oral and parental routes of administration [5]

At the conference of „Inter-Science", which is one of the world's largest society for chemotherapeutic drugs, from September 28 to October 1, 1997, in Toronto,Canada (under the auspices of the US Microbiologycal Society) was presented a new type of quinolone synthetic antibacterial agent without a fluorine atom in 6-position, "T-3811" by Toyama Chemical Co., Ltd. (*USAN* : GARENOXACIN MESYLATE) [6,7].

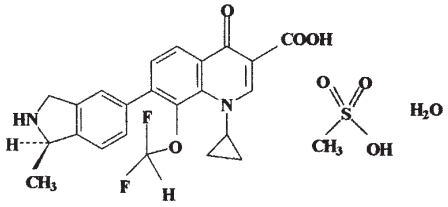

Fig. 1. T-3811
1-Ccyclopropyl-8-(difluoromethoxy)-7-[(1R)-2,3-dihydro-1-methyil-1-H-isoindol-5-yl]-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid monomethanesulphonate, monohydrate

T-3811 has a wide anti-bacterial spectrum, demonstrating effective antibacterial activity against Gram-positive strains, Gram-negative strains, as well as tubercle bacillus, Mycoplasma and Chlamidia. In particular, T-3811 shows potent activity against Gram-positive strains including MRSA (Methicillin Resistant Sthaphylococcus Aureus), PRSP (Penicillin Resistant Pneumoniae), and VRE (Vancomycin Resistant Enterococcus). Compared with conventionally quinolones, T-3811 has much less phototoxicity and articular toxicity in experimental animals.

Another quinolone synthetic antibacterial agent without a fluorine atom in 6-position, is „T-3912"[8].

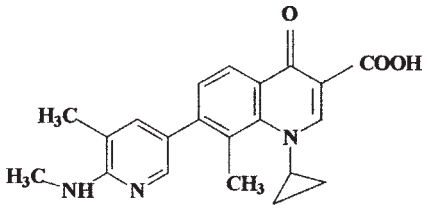

Fig. 2. T-3912 1-Cyclopropyl-8-methyl-7[5-methyl-6-(methylamino)-3-pyridinyl]-1,4-dihydro- 4-oxo-quinoline-3-carboxylic acid

"T-3912" has a strong antibacterial activity against the types of bacteria that cause infection in the fields of dermatology, otorhinolaryngology and opthalmology.

"T-3912" has a stronger antibacterial activity than currently available drugs for superficial infections caused by Staphylococcus Aureus and Staphylococcus Epidermidis, and pimples caused by Propionibacterium Acne as well as against drug resistant bacteria such as MRSA (Methicillin Resistant Staphylococcus Aureus).

In this paper, we furnish the experimental details of the synthesis of quinolones without a fluorine atom in 6-position (fig.3).

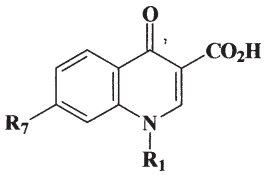

Fig. 3. Structure of the new compounds
R_1 = ethyl, isopropyl, R_7 = morpholinyl, 4-methyl-piperazinyl, 3-methyl-piperidinyl, 4-methyl-piperidinyl

Experimental part

Melting points were determined in open capillary on Melting point apparatus OptiMelt and are uncorrected.

Progress of the reaction was followed by TLG on Merck silica gel 60F_{254} plates eluted with the solvent system : chloroform: methanol: ammoniac (43:43:14) (v:v:v).

^{1}H- and ^{13}C-NMR spectra were recorded in $CDCl_3$, DMSO-d_6 and trifluoroacetic acid, on two instruments Varian, Varian

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Gemini 300 BB (operating at 300 MHz for proton and 75 MHz for carbon) and UNITY 400 Plus(operating at 400 MHz for proton and 100 MHz for carbon).Tetramerthylsilane as internal standard was the reference for the chemical shifts. All chemical shifts are given in the delta scale (ppm *vs* internal TMS). FT IR were recorded on an instrument Bruker Vertex 70 with diamond optic.

Synthesis of 7-chloro-4-hydroxy-quinoline—3-carboxylic acid ethyl ester (HQE)

A mixture of 3-chloro-aniline (64.43 g 0.5 mol) and diethyl ethoxymethylenemalonate (EMME) (110.32 g, 0.5 mol) was heated at 130^{0}C, with stirring and distillating the resulting EtOH. After 1.5 h, the crude diethyl [(3-chloro-anilino)-methylene]-malonate was added to poly-phosphoric acid (PPA) (600 g) and heated at 90^{0}C. After one hour the mixture was then poured into 1.2 L H_2O, and the resulting precipitate was filtered off, washed with water and dried. The solid was recrystallized from DMF to yield 7-chloro-4-hydroxy-quinoline—3-carboxylic acid ethyl ester (mp >300^{0}C, yield 64%) The structural characterization was previously reported [11].

Synthesis of 1-ethyl-7-chloro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid ethyl ester (HQEE)

A mixture of 6-halo-7-chloro-4-hidroxy-quinolin-3-carboxylic acid ethyl ester (QEE) [4] (7.55 g, 0.03 mol), K_2CO_3 (19.234 g, 0,135 mol) and DMF (100 mL) was heated at 100^{0}C with stirring, The mixture was cooled at 80^{0}C , added diethyl sulphate (21,24 g, 0,135 mol) and heated at 100^{0}C 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 1-ethyl-7-chloro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid ethyl ester (mp 145^0 C; yeld 70 %). The structural characterization was previously reported [11].

Synthesis of 1-isopropyl-7-chloro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid ethyl ester (iPr-HQE)

A mixture of 7-chloro-4-hidroxy-quinolin-3-carboxylic acid ethyl ester (3) (6.93 g, 0.24 mol), K_2CO_3 (16.58 g, 0.12 mol) and DMF (100 mL) was heated at 100^{0}C with stirring, The mixture was cooled at 40^{0}C, added 2-bromo-isopropane (14.76 g, 11.4 mL, 0.12 mol) and heated at 40-50^{0}C with stirring. After 18 h, 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 DMF- H_2O-isopropanol to yield 1-isopropyl—7-chloro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid ethyl ester (6 : R_1 = isopropyl) (mp = 58.3-59.3^{0}C, yield 54%)

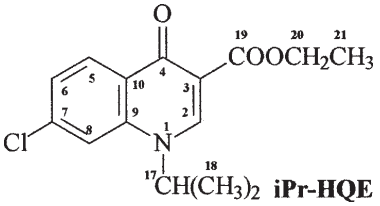


Fig. 4 iPr-HQ

^{1}H-NMR($CDCl_3$, δ ppm, *J* Hz): 9.24(s, 1H, H-2); 8.27(d, 1H, H-5, 8.8); 8.10(d, 1H, H-8, 1.9); 7.55(dd, 1H, H-6, 1.9, 8.8); 4.75(spt, 1H, H-17, 6.1); 4.50(q, 2H, H-20, 7.1); 1.48(t, 3H, H-21, 7.1); 1.41(d, 6H, H-18, 6.1).

^{13}C-NMR($CDCl_3$, δ ppm): 165.32(C-4); 162.85(C-19); 153.59(d, C-2); 137.94(Cq); 128.40(CH); 127.85(CH); 125.63(CH); 123.71(Cq); 108.13(Cq); 80.10(C-17); 61.72(C-20); 22.68(C-18); 14.42(C-18).

FT-IR(solid in ATR, ν cm^{-1}): 2980s; 2917m,; 2869w; 1719vs; 1607m; 1585 s; 1475s; 1384m; 1359s; 1300w; 1266s; 1209s; 1159s; 1093vs; 1064m; 943m; 922m; 893m; 877m; 831m; 809m; 756w; 632w; 553w.

Synthesis of 1-ethyl-7-chloro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid (HQA)

a) 1-Ethyl-7-chloro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid was obtained from 1-ethyl-7-chloro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid ethyl ester – the synthesis and structural characterization was previously reported [11].

b) 1-Ethyl-7-chloro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid was also obtained from 7-chloro-4-hydroxy-quinoline—3-carboxylic acid ethyl ester (3). To a mixture of 7-chloro-4-hidroxy-quinolin-3-carboxylic acid ethyl ester (3) (5.03 g, 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 min and then at 100^{0}C for 30 min. A further 4.54 g (0.03 mol) diethylsulphate 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 was filtered . The solid residue was washed with water. The solid was recrystallized from DMF to yield 1-ethyl-7-chloro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid.

Synthesis 1-isopropyl -7-chloro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid (iPr-HQA)

a) 1-isopropyl -7-chloro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid was also obtained from 1-isopropyl—7-chloro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid ethyl ester. A mixture of 1-isopropyl-7-chloro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid ethyl ester (3.44 g, 0.0115 mol) in a solution of sodium hydroxide (1.44 g, 0.036 mol) in H_2O (30 mL) - EtOH (10 mL) was refluxed with stirring. After 1.5 h, 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 the 4-oxo-quinoline-3-carboxylic acid. The structural characterization was previously reported [11].

b)To a suspension of 0.28 mol sodium borohydride in 250 mL dichloretane was added during 5 min 48 mL de acetic acid, under stirring and cooling. After 30 min was added 0.1 mol de 3-cloro--aniline and 0,1 moli acetone and the mixture was stirred at 20^{0}C. 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^{0}C for 1 hour. The reaction mixture was then poured into 210 g polyphosphoric acid and the mixture was stirred at la 90-100^{0}C. After 1 hour, the mixture was then poured into 400 mL H_2O. 1-isopropyl-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 h, 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 1-isopropyl -7-chloro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid.(yeld 30%) The structural characterization was previously reported [11]

Using this procedure we synthesized also the compounds :1-(2-butyl) -7-chloro-1,4-dihydro-4-oxo-

quinoline-3-carboxylic acid (Acid B) (mp = 179.5-180.3^{0}C; yield 43%) and 1-(2-pentyl) -7-chloro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid (Acid C) (mp = 158.5-159.6^{0}C; yield 18%).

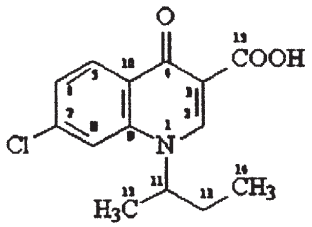


Fig. 5. Acid B

^{1}H-NMR(dmso-d6, δ ppm, *J* Hz): 8.78(s, 1H, H-2); 8.33(d, 1.4, 1H, H-8); 8.31(d, 8.7, 1H, H-5); 7.62(dd, 8.7, 1.4, 1H, H-6); 5.10(sx, 6.6, 1H, H-11); 1.91(qv, 6.6, 2H, H-13); 1.51(d, 6.6, 3H, H-12); 0.83(t, 7.5, 3H, H-14).

^{13}C-NMR(dmso-d6, δ ppm, *J* Hz): 177.00(C-4); 165.95(C-15); 145.29(C-2); 141.06(C-9); 139.92(Cq); 128.29(CH); 126.82(CH); 124.39(C-10); 117.40(CH); 108.55(C-3); 57.78(C-11); 28.45(C-13); 19.71(C-12); 10.20(C-14).

FT-IR(solid in ATR, ν cm^{-1}): 3532; 3114; 3086; 2976; 2885; 1710; 1605; 1550; 1529; 1501; 1445; 1387; 1360; 1346; 1321; 1298; 1196; 1160; 1122; 1092; 1010; 953; 922; 893; 867; 851; 832; 801; 765; 685; 626; 615.

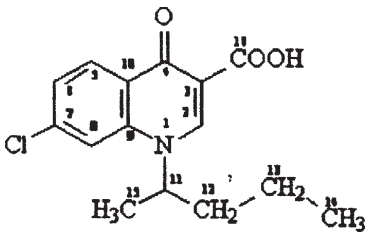


Fig. 6. Acid C

^{1}H-NMR(dmso-d6, δ ppm, *J* Hz): 8.80(s, 1H, H-2); 8.37(d, 8.6, 1H, H-5); 8.36(d, 1.7, 1H, H-8); 7.78(dd, 1.7, 8.6, 1H, H-6); 5.18(sx, 6.6, 1H, H-11); 1.89(m, 2H, H-12); 1.50(d, 6.6, 3H, H-15); 1.25(m, 2H, H-13); 0.84(t, 7.4, 3H, H-14).

^{13}C-NMR(dmso-d6, δ ppm): 177.03(C-4); 165.95(C-16); 145.30(C-2); 141.05(C-9); 139.93(C-10); 128.32(CH); 126.90(CH); 124.45(Cq); 117.36(C-8); 117.36(C-8); 108.59(C-3); 56.31(C-11); 37.49(C-12); 20.13(C-13); 18.73(C-15); 13.82(C-14).

FT-IR(solid in ATR, ν cm^{-1}): 3107; 2964; 2939; 2875; 1718; 1607; 1556; 1537; 1508; 1463; 1405; 1379; 1349; 1305; 1254; 1196; 1158; 1091; 1037; 962; 919; 871; 834; 794; 740; 685; 621; 599; 571; 481; 429.

Synthesis of 1-isopropyl-7-(4-methyl-piperazin-1-yl)-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid (HPQ-21)

A mixture of iPr-HQA (5,31 g, 0.02 mol), 4-methyl-piperazine (20 g, 0,2 mol) and DMF (44 mL) was stirred at 110-120^{0}C. After 6 h was added H_2O (22 mL) and acetic acid (*p*H=7) and the resulting precipitate was filtered off. The crude product was recrystallized from DMF to yield HPQ-21 (mp 239-240^{0}C; yield 37 %)

^{1}H-NMR(dmso-d6, δ ppm, *J* Hz): 8.64(s, H-2); 8.08(d, 9.2, H-5); 7.26(dd, 9.2, 2.1, H-6); 7.03(d, 2.1, H-8); 5.18(hp, 6.5, H-17); 3.42(tl, 4.6, H-12-16); 2.41(tl, 4.6, H-13-15); 2.18(s, H-2); 1.47(d, 6.5, H-18-19).

^{13}C-NMR(dmso-d6, δ ppm): 177.16(C-4); 167.87(C-20); 155.73(C-9); 144.58(C-2); 142.78(C-7); 128.29(C-5);

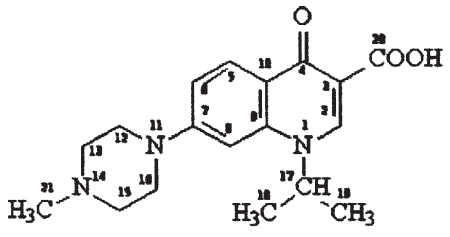


Fig. 7. HPQ-21

117.44(C-3); 115.75(C-6); 107.81(C-10); 98.96(C-8); 55.32(C-12-16); 47.71(C-13-15); 46.76(C-21); 22.60(C-18-19).

FT-IR(solid in ATR, ν cm^{-1}): 3071; 2989; 2969; 2934; 2843; 2804; 1705; 1612; 1546; 1510; 1444; 1369; 1345; 1295; 1246; 1211; 1186; 1155; 1137; 1112; 1075; 1057; 1017; 1002; 969; 816; 786; 679; 651; 574; 472; 418.

Synthesis of 1-Ethyl-7-(3-methyl-piperidin-1-yl)-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid (HPQ-24)

A mixture of HQA (5.03 g, 0.02 mol), 3-methyl-piperidine (9.92 g, 0,1 mol) and DMF (44 mL) was stirred at 100-110^{0}C. After 8 h was added H_2O (22 mL) and acetic acid (*p*H=7) and the resulting precipitate was filtered off. The crude product was recrystallized from DMF to yield HPQ-24 (mp 190.1-192.1^{0}C; yield 43 %)

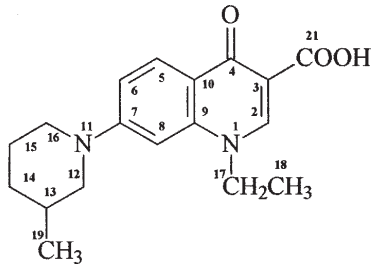


Fig. 8. HPQ-24

^{1}H-NMR(dmso-d6, δ ppm, *J* Hz): 8.81(s, 1H, H-2); 8.08(d, 1H, H-5, 9.1); 7.28(dd, 1H, H-6, 2.2, 9.1); 6.87(1H, H-8, 2.2); 4.50(q, 2H, H-17, 6.9); 3.98(tl, 2H, sist. AB, H-12A, H-16B, 10.9); 2.92(m, 1H, sist. AB, H-12B or H-16B); 2.62(dd, 1H, sist. AB, H-12B, 10.9, 12.6); 1.42÷1.82(m, 4H, H-14-15); 1.37(t, 3H, H-18, 6.9); 1.16(m, 1H, H-13); 0.92(d, 3H, H-19, 5.6).

The H - 16 protons form an unsuficiently resolved AB system, so it apears as an enlarged triplet with a higher constant than expected.

^{13}C-NMR(dmso-d6, δ ppm): 176.20(C-4); 166.51(C-21); 154.17(Cq); 148.22(C-2); 141.28(Cq); 127.13(C-5); 115.70(Cq); 114.53(C-8); 106.53(Cq); 97.59(C-6); 54.45(C-12); 48.39(C-17); 47.36(C-16); 32.43(C-15); 30.17(C-13); 24.19(C-14); 18.94(C-19); 14.17(C-18).

FT-IR(solid in ATR, ν cm^{-1}): 3090; 2916; 2841; 1705; 1608; 1546; 1508; 1440; 1400; 1301; 1240; 1181; 1120; 1080; 1040; 963; 836; 786; 748; 705; 648; 507; 469.

Synthesis of 1-Ethyl-7-morpholinyl-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid (HPQ-25)

A mixture of iPr-HQA (5.03g, 0.02 mol), morpholine (8.7 g, 0,1 mol) and DMSO (44 mL) was stirred at 110-120^{0}C. After 6 h was added H_2O (22 mL) and acetic acid (*p*H=7) and the resulting precipitate was filtered off. The crude product was recrystallized from DMF to yield HPQ-25 (mp 267.3-269^{0}C; yield 35%)

^{1}H-NMR(dmso-d6, δ ppm, *J* Hz): 8.86(s, H-2); 8.18(d, 1H, H-5, 9.1); 7.00(dd, 1H, H-6, 1.8, 9.1); 6.98(d, 1H, H-8, 1.8); 4.54(q, 2H, H-17, 7.0); 3.81(m, 4H, sist. A_2B_2, H-13-15,

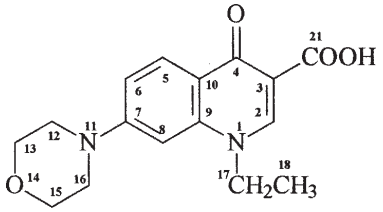


Fig. 9. HPQ-25

4.5); 3.40(m, 4H, sist. A_2B_2, H-12-16, 4.5); 1.43(t, 3H, H-18, 7.0).

^{13}C-NMR(dmso-d6, δ ppm, *J* Hz): 177.58(C-4); 167.32(C-21); 155.69(Cq); 149.20(C-2); 142.24(Cq); 128.18(C-5); 117.95(Cq); 115.33(C-6); 109.25(C-3); 99.30(C-8); 66.80(C-13-15); 49.53(C-17); 48.09(C-12-16); 15.17(C-18).

FT-IR(solid in ATR, ν cm^{-1}): 3051; 2972; 2893; 2840; 1696; 1612; 1521; 1454; 1370; 1342; 1285; 1244; 1122; 1033; 998; 967; 911; 876; 815; 788; 658; 610; 523; 477; 433.

Synthesis of 1-Ethyl-7-(3-methyl-piperazin-1-yl)-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid (HPQ-27)

A mixture of HQA (5.03 g, 0.02 mol), 3-methyl-piperazine (10 g, 0,1 mol) and DMSO (44 mL) was stirred at 110^{0}C. After 5.5 h was added H_2O (22 mL) and acetic acid (*p*H=7) and the resulting precipitate was filtered off. The crude product was recrystallized from DMF to yield HPQ-27 (mp 191.3-192.6^{0}C; yield 32%).

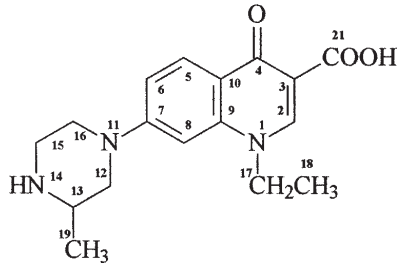


Fig. 10. HPQ-27

^{1}H-NMR(dmso-d6, δ ppm, *J* Hz): 8.82(s, 1H, H-2); 8.10(d, 1H, H-5, 9.1); 7.29(dd, 1H, H-6, 2.1, 9.1); 6.89(d, 1H, H-8, 2.1); 4.50(q, 2H, H-17, 7.1); 3.90÷2.40(m, 7H, 2H-12, H-13, 2H-15, 2H-16); 1.38(t, 3H, H-18, 7.1); 1.05(d, 3H, H-19, 6.3).

^{13}C-NMR(dmso-d6, δ ppm): 176.28(C-4); 166.51(C-21); 154.55(Cq); 148.27(C-2); 141.15(Cq); 127.03(C-5); 116.09(Cq); 114.45(C-8); 106.82(Cq); 97.80(C-6); 54.00(C-12); 50.00(C-13); 48.42(C-17); 47.03(C-16); 44.95(C-15); 19.26(C-19); 14.21(C-18).

FT-IR(solid in ATR, ν cm^{-1}): 3464; 2990; 2834; 2766; 1616; 1573; 1517; 1470; 1384; 1344; 1319; 1277; 1230; 1156; 1112; 1083; 1050; 1005; 949; 919; 814; 748; 672; 541.

Synthesis of 1-(2-butyl)-7-(4-methyl-piperdin-1-yl)-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid (HPQ-31)

A mixture of Acid B (5.60 g, 0.02 mol), 4-methyl-piperidine (19.84 g, 0.2 mol) and DMF (44 mL) was stirred at 100-120^{0}C. After 5 h was added H_2O (22 mL) and acetic acid (*p*H=7) and the resulting precipitate was filtered off. The crude product was recrystallized from DMF to yield HPQ-31 (mp 181.4-183^{0}C; yield 30%).

H-NMR($CDCl_3$, δ ppm, *J* Hz): 8.66(s, 1H, H-2); 8.29(d, 9.2, 1H, H-5); 7.11(dd, 9.2, 2.0, 1H, H-6); 6.79(d, 2.0, 1H, H-8); 4.66(sxt, 6.7, 1H, H-16); 3.93(dl, 12.9, 2H, H-11, H-15); 2.99(td, 12.9, 2.5, 2H, H-11', H-15'); 1.98(hp, 7.0, 1H, H-13); 1.81(dl, 12.0, 2H, H-12, H-14); 1.60(d, 7.0, 3H, H-17); 1.32(ddd, 14.0, 12.2, 4.0, 2H, H-12', H-14'); 0.99(d, 6.5, 3H, H-21); 0.99(t, 7.5, 3H, H-19);

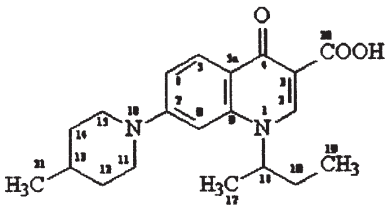


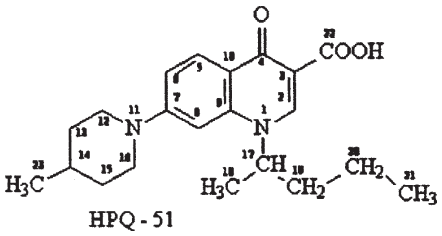
Fig. 11. HPQ-31

The grafic marks ['] designate the ecuatorial or axial position of the protons towards the substituent.

^{13}C-NMR($CDCl_3$, δ ppm): 176.81(C-4); 167.96(C-20); 154.90(C-9); 143.18(C-2); 142.46(C-7); 128.23(C-5); 114.77(C-6); 117.17(C-5a); 107.99(C-3); 96.92(C-8); 57.11(C-16); 48.15(C-11-15); 34.49(C-12); 30.70(C-13); 29.06(C-18); 21.69(C-21); 20.16(C-17); 15.58(C-19).

Synthesis of 1-(2-pentyl)-7-(4-methyl-piperdin-1-yl)-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid (HPQ-51)

A mixture of Acid C (5.87 g, 0,02 mol), 4-methyl-piperidine (9.92 g, 0.1 mol) and DMF (44 mL) was stirred at 110^{0}C. After 7 h was added H_2O (22 mL) and acetic acid (*p*H=7) and the resulting precipitate was filtered off. The crude product was recrystallized from DMF to yield HPQ-31 (mp 1138.5-140.5^{0}C; yield 30%)



HPQ - 51

Fig. 12. HPQ-51

^{1}H-NMR(dmso-d6, δ ppm, *J* Hz): 8.58(s, H-2); 8.05(d, 9.3, H-5); 7.21(dd, 2.0, 9.3, H-6); 7.02(d, 2.0, H-8); 5.08(m, H-17); 4.04(m, 2H); 4.00(m, 2H); 2.89(tl, 2H); 1.80-1.62(m, 6H); 1.45(d, 6.5, H-23); 1.18(m, 3H); 0.86(d, 6.3, H-18); 0.80(t, 7.4, H-21).

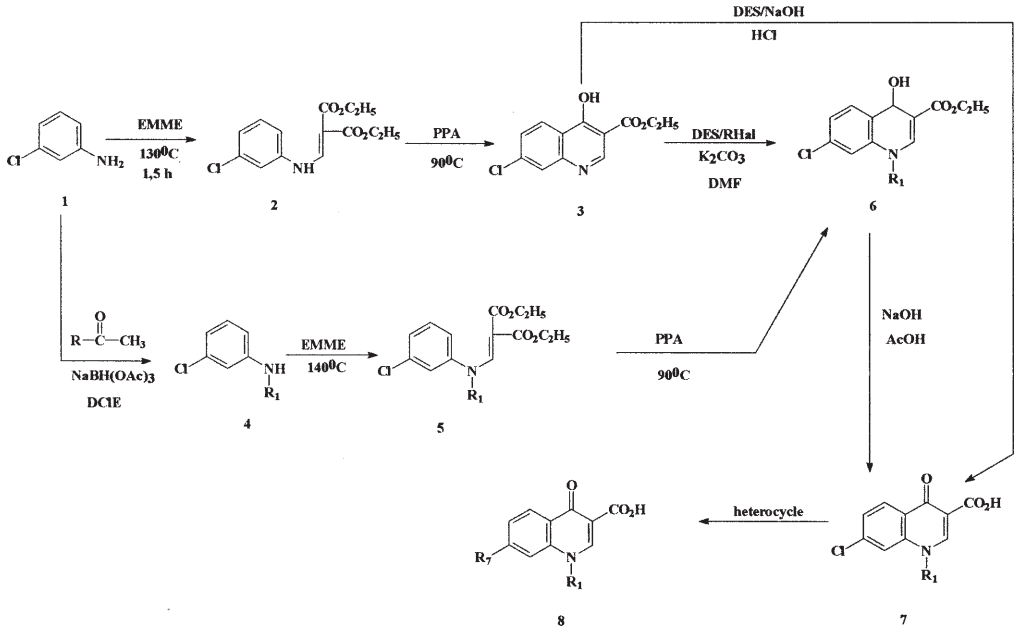
^{13}C-NMR(dmso-d6, δ ppm): 176.97(C-4); 167.92(C-22); 155.54(C-9); 144.61(C-2); 143.50(C-7); 128.41(C-5); 116.74(C-3); 115.84(C-6); 107.82(C-10); 98.40(C-8); 55.85(C-17); 48.43(C-12-16); 38.57(C-13-15); 34.19(C-14); 31.34(C-19-20); 22.76(C-23); 21.17(C-18); 14.77(C-21).

FT-IR(solid in ATR,ν cm^{-1}): 3066; 2919; 2865; 1710; 1611; 1544; 1508; 1450; 1377; 1358; 1329; 1304; 1237; 1157; 1131; 1111; 1009; 946; 813; 794; 747; 653; 577; 541; 511; 474; 430.

Results and disscusions

The synthesis of the novel quinolones followed a Gould-Jacobs cyclization process (scheme 1). An appropiate unsubstituted aniline (3-chloro-aniline) (1) is reacted with diethylethoxy methylene malonate (EMME) [9] 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)[10].

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



Scheme 1

Table 1
"IN VITRO" ANTIBACTERIAL ACTIVITY

Compound	Minimum inhibitory concentration µg/ml		
	E.coli 25992	S.aureus ATCC29213	P.aeruginosa ATCC 27813
HPQ-21	8	64	>128
HPQ-25	16	16	>128
HPQ-27	>128	32	>128

qinolone 3-carboxylate ester (4). 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, 2-butyl, 2-pentyl). 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 (4) (R_1 = isopropyl, 2-butyl, 2-pentyl). In either case, the final manipulation is acide or basic hydrolysis to cleave the ester generating the biologically active free carboxylic acid (7). 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 can conveniently be carried out in aqueous 40 % sodium hydroxide solution [11]. The displacement of 7-chloro group with a heterocycle yielded compounds (8) .

Some of 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* si *P.aeruginosa ATCC 27813,* (table 1), by agar dilution method [13,14]. HPQ-21 showed „in vitro" activity against *E. Coli* ATCC 25922 (MIC 8 µg/mL).

Conclusions

In conclusion, we have synthesized new quinolones and we have investigated their antibacterial activity. The results of the present study indicate that substituent combination in the quinolone ring might produce antibacterial agents such as compound HPQ-21:1-*iso*propyl-7-(4-methyl-piperazin-1-yl)-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid in concordance with the QSARs studies [15]

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Manuscript received: 22.08.2008