# Synthesis, Antimicrobial Activity and Docking Studies of Novel 8-Chloro-quinolones

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*This paper presents experimental data regarding the synthesis of several quinolone derivatives. These compounds have been analyzed through physico-chemical techniques (elemental analysis, $^{1}$H-NMR, $^{13}$C-NMR, FT IR). The quinolone compounds were evaluated for "in vitro" activity by determination minimum inhibitory concentration against a varia of microorganisms. Molecular, topological, conformational characteristics on 3D quinolones optimized structure were calculated using Spartan 14 Software. Molecular docking approach, using CLC Drug Discovery Workbench Software was conducted in order to achieve accurate predictions on optimized conformation for both, the quinolone (as ligand) and their target receptor protein to form a stable complex, which is potentially able to improve quinolone biological activity.*

*Keywords: quinolones, fluoroquinolones, antimicrobial activity, molecular docking*

Drugs belonging to the quinolone compounds are characterized by a quicker biological activity and a broad antibacterial spectrum [1-6]. They are active on both gram positive and gram negative bacteria, as well as on recently discovered bacteria with intercellular development (Legionella, Mycoplasma, etc), or even on acid-resistant bacteria (M. tuberculosis and M. leprae). The area of use of quinolones has expanded from urinary infections to systemic acute and chronic infections (lung and bronchus infections, osteitis, septicemia and endocarditis, chronic infections (chronic bronchitis, purulent osteoarthritis**,** chronic prostatite, cystitis and chronic sinusitis). Compared to beta-lactamic antibiotics (penicillin, cephalosporin) they are easily absorbed by the digestive system, allowing for oral intake and avoiding parental administration. They also have an excellent tissue distribution and concentration, which justifies their area of applicability. Antimicrobial agents belonging to the class of quinolones have a clear advantage over beta-lactamic antibiotics because the risk of resistance by plasmid replication is extremely low. Resistance to bacteria is a threat to virtually all antibacterial agents and quinolones are no exception. However, 4-oxo-1,4-dihydro-quinolones have proven to be less affected by this phenomenon, compared to other antibacterial agents. Because 4-oxo-1,4-dihydro-quinolones are relatively new chemotherapy agents, the existence of new resistance mechanisms could be just a matter of time. Still, the existence of pathogenous bacteria puts constant pressure on researchers to develop new compounds that are less affected by resistant bacteria [7-16].

## Experimental part

Melting points were determined in opened capillary on Melting point apparatus OptiMelt and are uncorrected. Progress of the reaction was followed by TLG on Merck silica gel 60$F_{254}$ plates eluted with the solvent system: tetrahydrofuran : dioxan: ammoniac (60:20:30) (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 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 was recorded on an instrument Bruker Vertex 70 with diamond optic

*Synthesis of 1-ethyl-6-fluoro-7-(pyrrolidin-1-yl)-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid(FPQ35)* [18,19] A mixture of 1-ethyl-6-fluoro-7-chloro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid (QA)[17] (4:$R_6$=F) (scheme 1) (2.69 g, 0.01 mol), pyrrolidine (3.556 g, 0.05 mol) and DMF (30 mL) was stirred 5 hours at 70-80$^0$C. The resulting precipitate was filtered off. The crude product was recrystallized from DMF to yield FPQ35 (5:$R_6$=F) (mp: 336.6-337.9$^0$C; yield 50 %). $^{1}$H-NMR: table 3; $^{13}$C-NMR: table 5; FT-IR(solid in ATR, ν cm$^{-1}$): 3044m; 2976m; 2902m; 2852m; 1702s; 1629vs; 1561m; 1515vs; 1492vs; 1462vs; 1409s; 1387s; 1358vs; 1327s; 1287m; 1241s; 1195s; 1142m; 1103m; 1050m; 1005s; 947m; 892m; 868m; 805s; 747m. Elemental Analyses: Calculated for: $C_{16}H_{17}FN_2O_3$: C, 63.15%; H, 5.63%; N, 9.21%; Found: C, 63.28%; H, 5.97%; N, 9.28%.

In the same way, was synthesized the compound *1-ethyl-6-chloro-7-(pyrrolidin-1-yl)-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid* (*6ClPQ35*) [20] (5:$R_6$=Cl)(mp: 312.2-315.5$^0$C; yield 75 %).$^{1}$H-NMR: table 3; FT-IR(solid in ATR,ícm$^{-1}$):3057m; 2929s; 2846m; 1708s; 1614vs; 1558m; 1530m; 1510s; 1467vs; 1442s; 1402s; 344sm; 1273m; 1252m; 1217m; 1177m; 1111m; 1095m; 1027m; 995m; 933w; 873w; 809m; 748w; 649m.Elemental Analyses: Calculated for: $C_{16}H_{17}ClN_2O_3$: C, 59.90%; H, 5.34%; N, 8.73%. Found: C, 59.71%; H, 5.23%; N, 8.74%.

*Synthesis of 1-ethyl-6-fluoro-7-(pyrrolidin-1-yl)-8-chloro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid (FPQ-36)* To a solution of FPQ-35 (6:$R_6$=F) (3.04 g; 0.01 mol) in $CHCl_3$ (50 mL) was added 2.56 mL $SO_2Cl_2$, and the mixture was stirred at room temperature. After 30 min the mixture was washed with water. The $CHCl_3$ layer was dried over $Na_2SO_4$, and evaporated to dryness. The crude quinolone was recrystallized from DMF to yield FPQ-36 (6: $R_6$ = F) (mp 214.5-217.8$^0$C, yield 65%).$^{1}$H-NMR: table 3; $^{13}$C-NMR: table 5; FT-IR-table 6. Elemental Analyses: Calculated for: $C_{16}H_{16}FClN_2O_3$: C, 56.73%; H, 4.76%; N, 8.27%. Found: C, 56.69%; H, 4.80%; N, 8.20%.

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In the same way, was synthesized the compound *1-ethyl-6,8-dichloro-7-(pyrrolidin-1-yl)-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid(6ClPQ-36)* (6:$R_6$=Cl) (mp 200-203.3$^0$C, yield 67%).$^1$H-NMR: table 3; FT-IR-table 6;$^{13}$C-NMR ($CDCl_3$+TFA, δ ppm): 175.94(C-4); 169.81(C-19); 153.64(C-2); 144.21(Cq); 137.98(C-7); 136.09(C-9); 127.29(C-5); 126.96(C-3); 108.08(C-10); 95.22(C-8); 55.82(C-20, C-23); 48.13(C-17); 42.76(C-21, C-22); 16.37(C-18). Elemental Analyses: Calculated for: $C_{16}H_{16}Cl_2N_2O_3$: C, 54.10%; H, 4.54%; N, 7.89%. Found: C, 54.01%; H, 4.60%; N, 7.88%.

*Synthesis of 1-ethyl-6-fluoro-7-(piperazin-1-yl)-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid(NF)*[18] A mixture of 1-ethyl-6-fluoro-7-chloro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid (QA) (4:$R_6$=F) [17] (2.7 g, 0.01 mol) and piperazine x 6 $6H_2O$ (10.75 g, 0.05 mol) and DMSO (30 mL) was stirred at 120-130$^0$C for 2.5 h. The mixture was concentrated to give crude quinolone. The crude product was dissolved sodium hydroxide 2N and then was precipitated to *p*H 7.2 with acetic acid 10 %. The resulting precipitate was filtered off and was dissolved in acetic acid 10 % and then was precipitated to *p*H 7.2 with sodium hydroxide 2N. The resulting precipitate was filtered off. And then was recrystallized from DMF to yield NF (Norfloxacine) (7:$R_6$=F) (mp 218.3-220.6$^0$C; yield 65%). $^1$H-NMR: Table 4; $^{13}$C-NMR: Table 5; FT-IR(solid in ATR, ν cm$^{-1}$): 3272w; 3050w; 2947w; 2831w; 1710m; 1616vs; 1583m; 1519m; 1477vs; 1374s; 1353m; 1330s; 1252s; 1198m; 1176w; 1124w; 1103w; 1039w; 921w; 867w; 847w; 822w; 807w; 750w; 735w. Elemental Analyses: Calculated for: $C_{16}H_{18}FN_3O_3$: C, 60.18%; H, 5.68%; N, 13.16%. Found: C, 60.11%; H, 5.70%; N,13.15%.

In the same way, was synthesized the compound *1-ethyl-6-chloro-7-(piperazin-1-yl)-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid (NClX)*[18](7:$R_6$=Cl) (mp 226.8-228.5$^0$C; yield 66%), $^1$H-NMR:table 4; $^{13}$C-NMR(dmso-d6, ä ppm, T=333K): 176.02(C-4); 165.72(C-19); 154.19(C-9); 148.95(C-2); 139.19(C-7); 127.21(C-5); 126.41(C-10); 120.56(C-3); 107.80(C-8); 51.95(C-12, C-16); 48.88(C-17); 45.45(C-13, C-15); 14.15(C-18). FT-IR(solid in ATR, ν cm$^{-1}$): 2979m; 2913m; 1620vs; 1605vs; 1578s; 1547m; 1471s; 1448s; 1416m; 1397m; 1378s; 1361m; 1348m; 1322s; 1281m; 1258s; 1234m; 1203m; 1161m; 1148m; 1123m; 1003w; 926m; 841w; 822w; 741w;708m. Elemental Analyses: Calculated for: $C_{16}H_{18}ClN_3O_3$: C, 57.23%; H, 5.40%; N: 12.51%. Found: C, 57.18%; H, 5.60%; N, 12.49%.

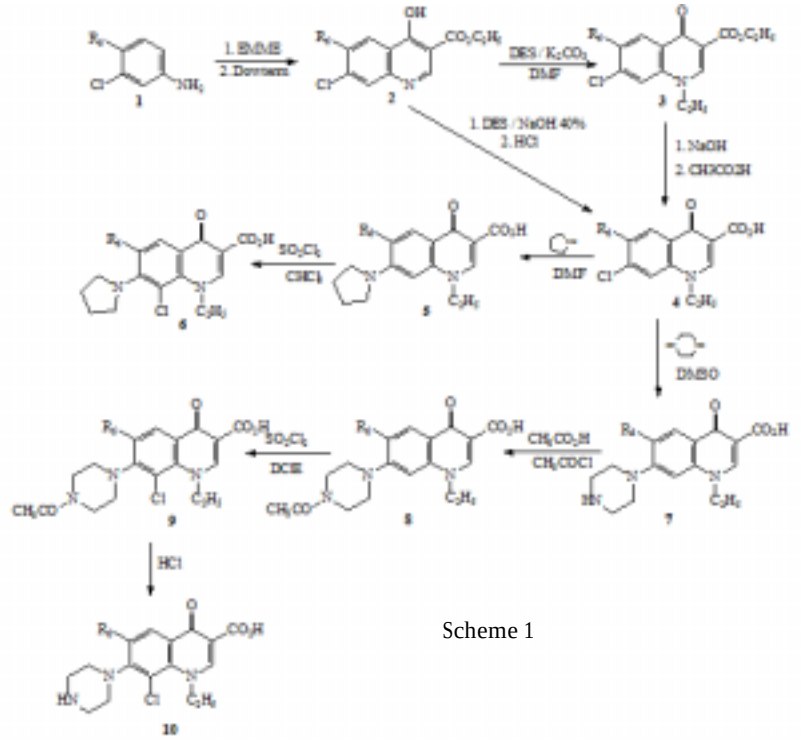
*Synthesis of 1-ethyl-6-fluoro-7-(4-acetyl-piperazin-1-yl)-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid (AcNF)* [18,21] Acetyl chloride (30 mL) was added to a solution of NF (7:$R_6$=F) (3.19 g; 0.01 mol) in acetic acid(30 mL) and then the mixture was stirred 4 hours at reflux temperature. At the end of the reaction, the mixture was cooled and was poured onto 200 mL of water. The precipitate formed was filtered off, washed with water, and after drying, was recrystallized from DMF to yield AcNF (8:$R_6$=F). (mp 297.8-299.9$^0$C, yield 59%). $^1$H-NMR(dmso-d6, δ ppm, *J* Hz, T=333 K): 8.92(s, 1H, H-2); 7.94(d, 1H, H-5, $^3J$(F-H$^5$)=13.5 Hz); 7.19(d, 1H, H-8, $^4J$(F-H$^8$)= 7.4 Hz); 4.58(q, 2H, H-17, 7.1); 3.66(m, 4H, H-12, H-16, syst. $A_2B_2$); 3.32(bs, 4H,H-13,H-15, syst. $A_2B_2$);1.43(t, 3H, H-18, 7.1). FT-IR(solid in ATR, ν cm$^{-1}$): 3037w; 2978w; 2952w; 2870w; 2842w; 1718m; 1626vs; 1505m; 1474s; 1433vs; 1378s; 1358s; 1297m; 1264m; 1245vs; 1212m; 1193s; 1139m; 1103m; 1032m; 974m; 917m; 891m; 848w; 826m; 804m; 748m. Elemental Analyses: Calculated for: $C_{18}H_{20}FN_3O_4$: C, 59.83%; H, 5.58%; N, 11.63%. Found: C, 59.94%; H, 5.85%; N, 11.69%.

In the same way, was synthesized the compound *1-ethyl-6-chloro-7-(4-acetyl-piperazin-1-yl)-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid (AcNClX)* (8:$R_6$=Cl). (mp 306-310$^0$C, yield 54%.) $^1$H-NMR(dmso-d6, δ ppm, *J* Hz, T=333K): 14.99(bs, 1H, HOOC, deuterable); 8.97(s, 1H, H-2); 8.29(s, 1H, H-5); 7.35(s, 1H, H-8); 4.58(q, 2H, H-17,7.1); 3.67(m, 4H, H-13, H-15, syst. $A_2B_2$); 3.19((m, 4H, H-12, H-16, syst. $A_2B_2$); 2.07(s, 3H, acetyl); 1.44(t, 3H, H-18, 7.1). FT-IR(solid in ATR, ν cm$^{-1}$): 3062w; 2982w; 2927w; 2845w; 1721vs; 1652vs; 1610vs; 1541m; 1526m; 1508m; 1462vs; 1444vs; 1381m; 1346m; 1301m; 1283m; 1241s; 1198s; 1142m; 1119m; 1090w; 1050w; 994m; 976m; 916m; 901m; 852m; 806m; 685m. Elemental Analyses: Calculated for: $C_{18}H_{20}ClN_3O_4$: C, 57.22%; H, 5.34%; N, 11.12%. Found: C, 57.34%; H, 5.66%; N, 11.16%.

*Synthesis of 1-ethyl-6-fluoro-7-(4-acetyl-piperazin-1-yl)-8-chloro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid (AcFPQ50)* 2.56 mL $SO_2Cl_2$ was added to a solution of AcNF (8:$R_6$=F) (3.61g; 0.01 mol) in DClE (150 mL), and the mixture was stirred at 40-50$^0$C. After 2 h the mixture was washed with water. The organic layer was dried over $Na_2SO_4$, and evaporated to dryness. The crude quinolone was recrystallized from DMF to yield AcFPQ50 (9:$R_6$=F), mp 255.7-258.2$^0$C, yield 65%).$^1$H-NMR(dmso-d6, δ ppm, *J* Hz, T=333 K):14.80(bs,1H,H-19,deuterable);.89(s,1H,H-2);8.03(d,1H, H-5,$^3J$(F-H$^5$)=11.9 Hz); 4.85(q, 2H,H-17,7.1);3.32(bs, 2H,H-12,H-16); 3.26(bs,2H, H-13,H-15); 2.07(s, 3H,H-acetyl); 1.42(t,3H,H-18,7.1).$^{13}$C-NMR(dmso-d6,äppm,T=333K): 175.93(C-4); 168.62(C-19); 165.20(C-CO acetyl); 155.90(d,C-6,$J$(F-C$^6$)=249.5Hz); 152.80(C-2); 143.36(d,C-7,$^2J$(F-C$^7$)=14.2Hz); 136.29(C-9); 123.87(C-10); 119.72(C-8); 111.06(d,C-5,$^2J$(F-C$^5$)=22.8Hz); 107.66(C-3); 53.19(C-17); 50.93(d,C-12 or C-16,$^4J$(F-C$^{12(16)}$)=4.8Hz); 50.70 (d,C-16 or C-12,$^4J$(F-C$^{16(12)}$)=4.8 Hz); 46.49(C-13 or C-15); 41.53(C-15 or C-13);21.38(C-$CH_3$ acetyl); 15.88(C-11).FT-IR(solid in ATR, ν cm$^{-1}$): 3034w; 2848w; 1723m;1640s; 1616s; 1502m; 1483m; 1431vs; 1384m; 1354m; 1298m; 1283w; 1250s; 1203m; 1262w; 1114w; 1089w;1043w;992m;946m;884m 835w; 802m; 732w. Elemental Analyses: Calculated for: $C_{18}H_{19}ClFN_3O_4$: C, 54.62%; H, 4.84%; N, 10.62%. Found: C, 54.73%; H, 4.79%; N, 10.64%.

In the same way, was synthesized the compound *1-ethyl-6,8-dichloro-7(4-acetyl-piperazin-1-yl)-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid(Ac6ClPQ50)* (9: $R_6$=Cl) (mp 260.1-263.7$^0$C, yield 65%). $^1$H-NMR(dmso-d6, δ ppm, *J* Hz,T=333K):14.48(bs, 1H, H-19); 8.93(s,1H,H-2); 8.20(s,1H, H-5); 8.25(s, 1H, H-8); 4.80(q, 2H, H-17,7.1); 3.90÷3.45(m, 4H, H-13, H-15); 3.25(m, 4H, H-12, H-16); 2.07(s, 3H, $CH_3$ acetyl); 1.40(t, 3H, H-18,7.1).$^{13}$C-NMR(dmso-d6, ä ppm, T=333K): 175.71(C-4); 168.50(C-CO acetyl); 164.99(C-19); 153.06(C-2); 150.62(C-9); 138.48(C-7); 130.86(C-8); 125.79(C-5); 124.83(C-10); 121.85(C-3); 108.63(C-8); 3.08(C-13 or C-15); 50.18(C-12 or C-16); 49.80(C-17); 46.54(C-12, C-16); 41.56(C-13 or C-15); 21.28(C-15); 15.53(C-18). FT-IR(solid in ATR, ν cm$^{-1}$): 2979m; 2913m; 1620vs; 1605vs; 1578s; 1547m; 1471s; 1448s; 1416m; 1397m; 1378s; 1361m; 1348m; 1322s; 1281m; 1258s; 1234m; 1203m; 1161m; 1148m; 1123m; 1003w; 926m; 841w; 822w; 741w; 708m. Elemental Analyses: Calculated for: $C_{18}H_{19}Cl_2N_3O_4$: C, 52.44%; H, 4.65%; N, 10.19%. Found: C, 52.48%; H, 4.59%; N, 10.24%.

*Synthesis of 1-ethyl-6-fluoro-7-(piperazin-1-yl)-8-chloro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid (FPQ50)* A solution of AcFPQ50 (9:$R_6$=F) (1.6 g, 0.003 mol) with NaOH 35% (30 g) was heated under reflux temperature, 6 h. At the end of the reaction, the compound was precipitated to *p*H 7.0 with acetic acid 30%. The resulting precipitate was filtered off and then was recrystallized from DMF to yield



Scheme 1

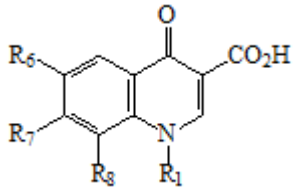


Fig. 1 The structure of the new compounds

FPQ50 (10:$R_6$=F) (mp 227-230$^0$C; yield 63%). $^1$H-NMR: table 4; $^{13}$C-NMR: table 5; FT-IR-table 6. Elemental Analyses: Calculated for: $C_{16}H_{17}ClFN_3O_3$: C, 54.32%; H, 4.84%; N, 11.88%. Found: C, 54.38%; H, 4.86%; N, 11.90%.

In the same way, was synthesized the compound *1-ethyl-6,8-dichloro-7-(piperazin-1-yl)-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid(6ClPQ50)* (10:$R_6$=Cl) (mp 228.2-230.4$^0$C; yield 58.6%). $^1$H-NMR: table 4; FT-IR-table 6. Elemental Analyses: Calculated for: $C_{16}H_{17}Cl_2N_3O_3$: C, 51.91%; H, 4.63%; N, 11.35%. Found: C, 51.88%; H, 4.65%; N, 11.39%.

Biological Assays: The quinolone derivatives were evaluated for „*in vitro*" activity by determining minimum inhibitory concentration against a variety of bacteria: *E. coli* ATCC8739, *S. aureus* ATCC6538 and *P. aeruginosa* ATCC 9027, by agar dilution method [22].

Molecular mechanics calculations: Molecular, topological, conformational characteristics on 3D quinolones optimized structure were calculated using Spartan 14 Software

Docking studies: Molecular docking approach**,** using CLC Drug Discovery Workbench Software was conducted in order to achieve accurate predictions on optimized conformation for both, the quinolone (as ligand) and their target receptor protein to form a stable complex.

**Results and discussions**

The synthesis of the quinolone derivatives (fig.1) followed a Gould-Jacobs cyclization process (Scheme1). Appropriate unsubstituted aniline (1) is reacted with diethylethoxymethylene malonate (EMME) to produce the resultant anilinomethylenemalonate. A subsequent thermal process induces Gould-Jacobs cyclization to afford the corresponding 4-hidroxy-quinoline-3-carboxylate ester (2). The following operation is the alkylation of the quinolone which is usually accomplished by reaction with diethyl sulphates to produce the qinolone-3-carboxylate ester (3). The final manipulation is basic hydrolysis to cleave the ester generating the biologically active free carboxylic acid (4). The biologically active free carboxylic acid (4) was also obtained from the corresponding 4-hidroxy-quinoline-3-carboxylate ester (2) by alkylation with diethyl sulphates in presence of alkali, for example the reaction can conveniently be carried out in aqueous 40 % sodium hydroxide solution. The displacement of 7-chloro group with heterocyclic yielded compound (5) and compound (7). 8-Chloro-quinoline-3-carboxylic acid (6) was synthesized from 8-unsubstituted quinoline-3-carboxylic acid (5) by chlorination with sulfuryl chloride. When, $R_7$ = piperazine, is necessary to protect the nitrogen atom from piperazine group. After chlorination and hydrolysis is obtained the final compound (10).

These novel quinolone derivatives have been analysed by physico-chemical techniques (elemental analysis, $^1$H-NMR, $^{13}$C-NMR, FT IR).

Quninolone derivatives have been evaluated for "*in vitro*" activity by determining minimum inhibitory concentration against of bacteria *Escherichia coli, Staphylococcus aureus and Pseudomonas aeruginosa,* by agar dilution method (Table 1). After analyzing chemical structure-biological activity relationships, it was observed that the presence of chlorine in 8 position of the quinolones core, leads to increased antimicrobial activity against *Staphylococcus aureus* for the compounds having pyrrolidinyl moiety in 7-position:FPQ 36 and 6ClPQ36. The presence of the chlorine atom in 8 positions of the 7-piperazinyl quinolones (FPQ 50 and 6ClPQ50) leads to decrease the activity against all the tested strains.

In addition, a study of the molecular and structural characteristics and properties has been achieved using Spartan 14 software. For each structure of the analyzed class, the 3D structure used for calculations was generated and its geometry has been optimized by energy minimization, in order to obtain the most stable conformer (fig. 2 and fig. 3). For these conformers, the most important topological, conformational characteristics and QSAR properties has been calculated: weight, no. of conformers and tautomers, area, volume, ovality, polarizability, log P, energy of solvation, dipole moment, energy of the HOMO and LUMO orbitals, angles and distances, dihedral angles (table 2). These properties were discussed in order to assess the flexibility and the binding ability of studied conformers to bind to the receptor protein. NMR and IR spectra of the quinolone compounds have been calculated with Spartan 14 software. After analyzing the experimental and calculated spectra (H-NMR, C-NMR, IR) the correlation

| Compound | Minimum inhibitory concentration (MIC) ( µg/ml) | | |
|---|---|---|---|
| | *Escherichia coli* ATCC 8739 | *Staphylococcus aureus* ATCC 6538 | *Pseudomonas aeruginosa* ATCC 9027 |
| NF | > 0.08 | 0.32 | 0.32 |
| FPQ 50 | 2.00 | 4.00 | 16 |
| NCIX | 0.32 | 1.28 | 5.12 |
| 6ClPQ50 | 2 | 8 | 32 |
| FPQ 35 | 31.25 | 2.00 | > 128 |
| FPQ 36 | 16 | 0.25 | 16 |
| 6ClPQ 35 | >128 | 32.00 | >128 |
| 6ClPQ36 | >128 | 8.00 | >128 |

**Table 1**
ANTIBACTERIAL ACTIVITY *IN VITRO*

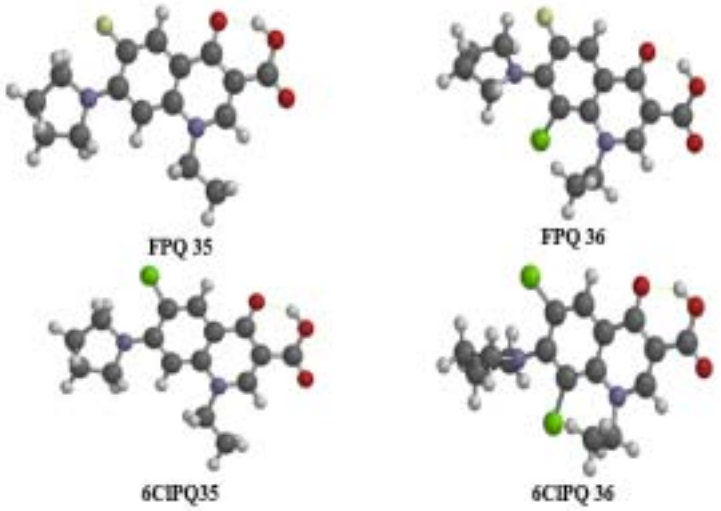



Fig. 2. Optimized geometry of 7-pyrrolidinyl-quinolones

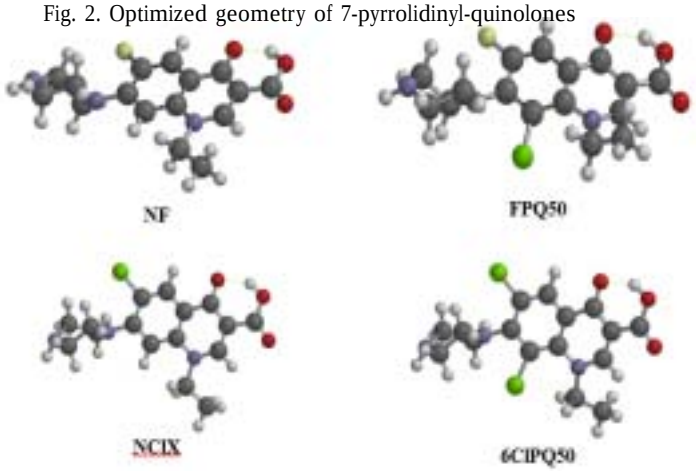



Fig. 3. Optimized geometry of 7-piperazinyl-quinolones

between experimental and calculated data has been observed (table 3-6, fig. 4- 6).

The docking studies have been carried out using CLC Drug Discovery Workbench Software. The score and hydrogen bonds formed (table 7) with the amino acids from group interaction are used to predict the binding modes, the binding affinities and the orientation of the docked quinolones at the active site of the protein. The protein-ligand complex (fig. 7-10) have been realized based on the 2.1A Crystal Structure of *S. AUREUS* GYRASE Complex with GSK299423 and DNA who *was* available through the Protein Data Bank (PDB entry 2XCS). The result of molecular docking study, as shown in figure 7 and figure 8, for quinolone FPQ 36, compound with the better activity *in vitro* against *Staphylococcus aureus* ATCC 6538 (MIC= 0.25 µg/ml) reveals docking score -33.20 (table 7) and shows the occurance of three hydrogen bonds with ARG 1122 (3.109 Å) and ASP 1083 (2.688 and 3.200 Å). The better score docking have been obtained from quinolone FPQ 50 (-37.80) (MIC= 0.32µg/mL against *Staphylococcus*

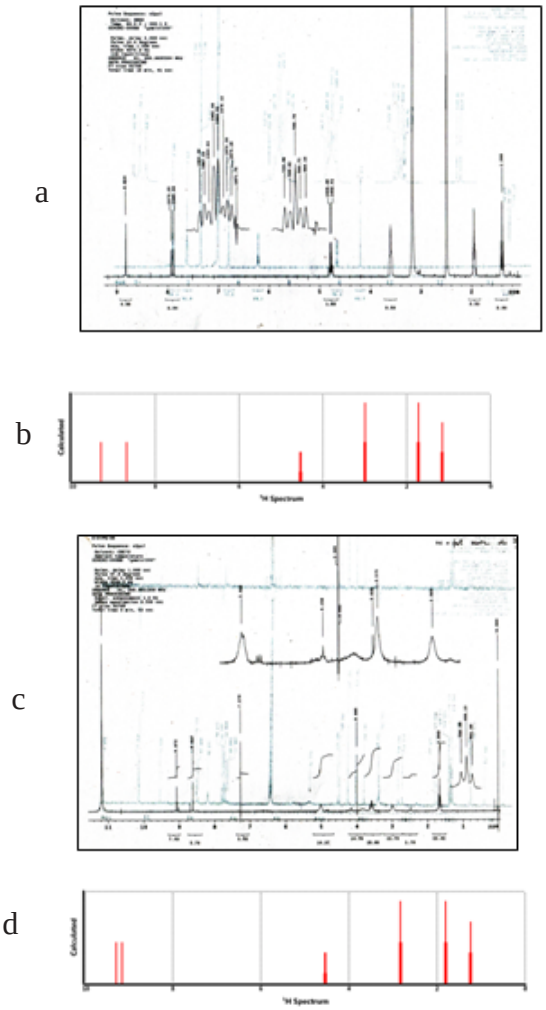



Fig. 4 Calculated and measured H-NMR spectra of FPQ36 and 6ClPQ36 (a) FPQ36 experimental spectra; (b) FPQ36 calculated spectra (c) 6ClPQ36 experimental spectra; (d) 6ClPQ36 calculated spectra

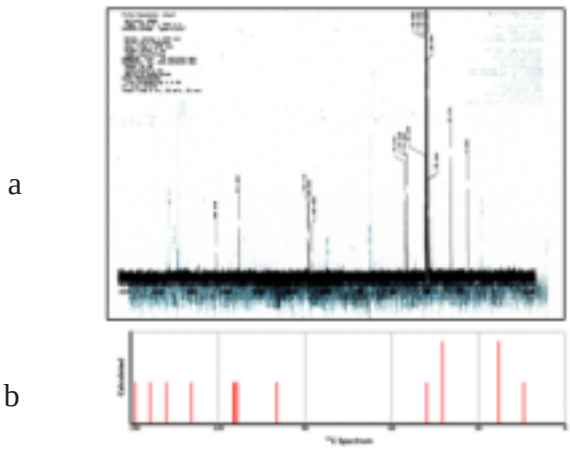



Fig. 5 Calculated and measured C-NMR spectra of FPQ36 and 6ClPQ36 (a) FPQ36 experimental spectra; (b) FPQ36 calculated spectra

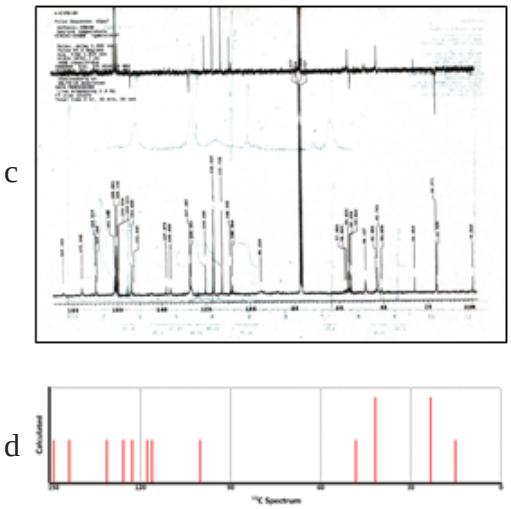


Fig. 5 Calculated and measured C-NMR spectra of FPQ36 and 6ClPQ36 (c) 6ClPQ36 experimental spectra; (d) 6ClPQ36 calculated spectra

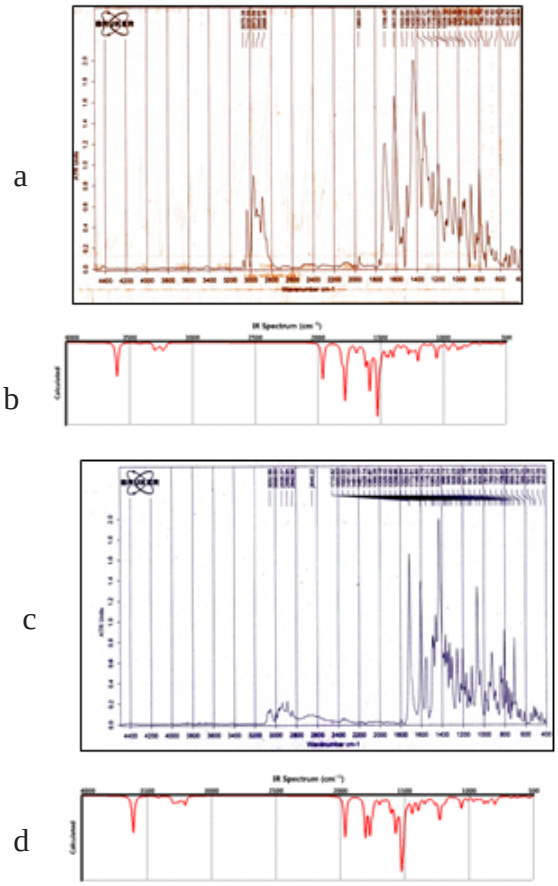


Fig. 6 Calculated and measured C-NMR spectra of FPQ36 and 6ClPQ36
(a) FPQ36 experimental spectra; (b) FPQ36 calculated spectra
(c) 6ClPQ36 experimental spectra; (d) 6ClPQ36 calculated spectra

**Table 2**
SELECTED BOND LENGTHS AND ANGLES

| FPQ36 | 6ClPQ36 | FPQ50 | 6ClPQ50 |
|---|---|---|---|
| Distance (O18H17) = 1.761 Å<br>The distance between the hydrogen atom 17 and oxygen atom 18 (1.761 Å) is typical of an intramolecular hydrogen bonds involving atoms 18, 17 and 16.<br>Dihedral(H17O16C15C3) = 0.58°<br>Dihedral(C4O18H17O16) = -1.13°<br>value close to zero, indicates that the atoms C4, C3,C15,O16,H17 and O18 are placed in the same plane<br>Dihedral (C26N22C7C8) = 71.97 °<br>Dihedral (C23N22C7C6) = 50.20°<br>shows that the pyrrolidine ring is rotated around the link C7-N22.<br>Dihedral (C2N1C11C12) = 103.94 °<br>Distance C6-F20 = 1.358 Å<br>Distance C8-Cl21= 1.745 Å<br>Distance N1-C11 = 1.501 Å<br>Distance Cl21 – C11 = 3.207 Å<br>Dihedral (Cl21C8C9N1) = 171.07°<br>Dihedral (C8C9N1C11) = -20.80°<br>Dihedral (H19C5C10C4) = -2.66 °<br>Dihedral (C5C10C4O18) = 0.96°<br>Distance C24-N22 = 2.349 Å<br>Distance C25-N22 = 2.368 Å<br>Distance Bond C24C25 -N22= 2.229 | Distance (O18H17) = 1.765 Å<br>The distance between the hydrogen atom 17and oxygen atom 18 (1.761 Å) is typical of an intramolecular hydrogen bonds involving atoms 18, 17 and 16.<br>Dihedral(H17O16C15C3) = 0.55 °<br>Dihedral(C4O18H17O16) = -1.00°<br>value close to zero, indicates that the atoms C4, C3,C15,O16,H17 and O18 are placed in the same plane<br>Dihedral (C26N22C7C8) = -96.17 °<br>Dihedral (C23N22C7C6) = -79.94 °<br>shows that the pyrrolidine ring is rotated around the link C7-N22.<br>Dihedral (C2N1C11C12) = 101.06°<br>Distance C6-Cl20 = 1.740 Å<br>Distance C8-Cl21 = 1.747 Å<br>Distance N1-C11 = 1.501Å Å<br>Distance Cl21 – C11 = 3.038 Å<br>Dihedral (Cl21C8C9N1) = -6.25 °<br>Dihedral (C8C9N1C11) = -17.55 °<br>Dihedral (H19C5C10C4) = -1.86 °<br>Dihedral (C5C10C4O18) = 1.011 °<br>Distance C24-N22 =2.360 Å<br>Distance C25-N22 = 2.344 Å<br>Distance Bond C24C25 -N22 = 2.221 | Distance (O18H17) = 1.7664 Å<br>The distance between the hydrogen atom 17 and oxygen atom 18 (1.764 Å) is typical of an intramolecular hydrogen bonds involving atoms 18, 17 and 16.<br>Dihedral (H17O16C15C3) = 0.96°<br>Dihedral (C4O18H17O16) = -1.42°<br>value close to zero, indicates that the atoms C4, C3,C15,O16,H17 and O18 are placed in the same plane<br>Dihedral (C27N22C7C8) = 79.88 °<br>Dihedral (C23N22C7C6) = 49.05 °<br>shows that the piperazine ring is rotated around the link C7-N22.<br>Dihedral (C2N1C11C12) = 27.94°<br>Distance C6-F20 = 1.360 Å<br>Distance C8-Cl21= 1.745 Å<br>Distance N1-C11 (Bond45) = 1.505 Å<br>Distance Cl21 – C11 = 2.995 Å<br>Dihedral (Cl21C8C9N1) = -13.20°<br>Dihedral (C8C9N1C11) = - 24.66 °<br>Dihedral (H19C5C10C4) = - 4.32°<br>Dihedral (C5C10C4O18) = 2.55°<br>Distance N25-N22= 2.897 Å<br>is typical of the piperazine ring in configuration "chair". | Distance (O18H17) = 1.767 Å<br>The distance between the hydrogen atom 17 and oxygen atom 18(1.767Å) is typical of an intramolecular hydrogen bonds involving atoms 18, 17 and 16.<br>Dihedral(H17O16C15C3) = -1.02°<br>Dihedral(C4O18H17O16) = 1.61°<br>value close to zero, indicates that the atoms C4, C3,C15,O16,H17 and O18 are placed in the same plane<br>Dihedral (C27N22C7C8) = 98.84°<br>Dihedral (C23N22C7C6) = -110.69°<br>shows that the piperazine ring is rotated around the link C7-N22.<br>Dihedral (C2N1C11C12) = - 26.29°<br>Distance C6-Cl20 = 1.740 Å<br>Distance C8-Cl21 = 1.747 Å<br>Distance N1-C11(Bond45) =1.505 Å<br>Distance Cl21 – C11 = 2.988 Å<br>Dihedral (Cl21C8C9N1) = 11.62°<br>Dihedral (C8C9N1C11) = 24.13 °<br>Dihedral (H19C5C10C4) = 3.92°<br>Dihedral (C5C10C4O18) = - 2.53°<br>Distance N25-N22 = 2.861 Å<br>is typical of the piperazine ring in configuration "chair". |

**Table 3**

CALCULATED AND MEASURED $^1$H-NMR SPECTRA OF 7- PYRROLIDINYL-QUINOLONES

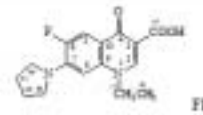
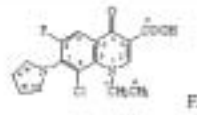
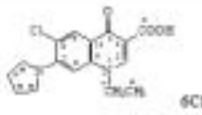
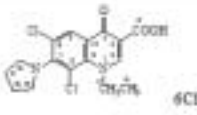
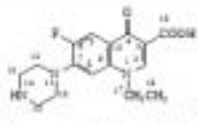
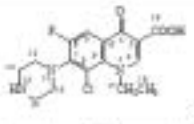
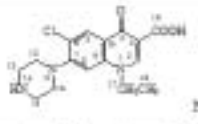
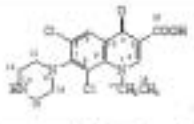
|  FPQ 35 | |  FPQ-36 | |  6ClPQ 35 | |  6ClPQ 36 | |
|---|---|---|---|---|---|---|---|
| Experimental data $^1$H-NMR (dmso-d6, δ ppm, J Hz) | Calculated data | Experimental data $^1$H-NMR (dmso-d6, δ ppm, J Hz) | Calculated data | Experimental data $^1$H-NMR (dmso-d6, δ ppm, J Hz) | Calculated data | Experimental data $^1$H-NMR ($CDCl_3$+TFA δ ppm, J Hz) | Calculated data |
| 8.96 (s, H-2) | 9.46 (s, H-2) | 8.83(s, 1H, H-2) | 9.30(s, 1H, H-2) | 8.89(s, 1H, H-2) | 9.44(s, 1H, H-2) | 9.07(s, 1H, H-2) | 9.29 (s, 1H, H-2) |
| 7.95(d, 1H, H-5, $^3J$(F-H$^5$)=13.5 Hz) | 8.60(d,1H, H-5) | 7.91(d, 1H, H-5, $^3J$(F-H$^5$)=13.4Hz | 8.69(d, 1H, H-5) | 8.14(s, 1H, H-5) | 9.02(s, 1H, H-5) | 8.62(s, 1H, H-5) | 9.16(s, 1H, H-5) |
| 6.60(d, 1H, H-8, $^3J$(F-H$^8$)= 12.3 Hz 6.9) | 5.67(d,1H, H-8) | - | - | 6.83(s, 1H, H-8) | 5.70(s, 1H, H-8) | - | - |
| 4.57(q, 2H, H-17, 7.1) | 3.59(q,2H,H-17) | 4.79(q, 2H, H-17, 7.1) | 4.54(q, 2H, H-17) | 4.52(q, 2H, H-17, 7.1) | 3.51(q, 2H, H-17) | 5.02(q, 2H, H-17, 7.1) | 4.53(q, 2H, H-17) |
| 3.76(m, 4H, H-20, H-23) | 3.14(m, 4H, H-20, H-23) | 3.60(m, 2H, H-23, H-20, syst. $A_2B_2$) | 3.00(m, 2H, H-23, H-20) | 3.66(m, 4H, H-20, H-23) | 3.17(m, 4H, H-20, H-23) | 3.58(m, 4H, H-20, H-23) | 2.83(m, 4H, H-20, H-23) |
| 2.13(m, 4H, H-21, H-22) | 1.68(m, 4H, H-21, H-22) | 1.96(m, 4H, H-21, H-22, syst. $A_2B_2$) | 1.72(m, 4H, H-21, H-22) | 1.97(m, 4H, H-21, H-22) | 1.70(m, 4H, H-21, H-22) | 2.99(m, 4H, H-21, H-22) | 1.80(m, 4H, H-21, H-22) |
| 1.65(t, 3H, H-18, 7.1) | 1.71(t,3H,H-18) | 1.40(t, 3H, H-18, 7.1) | 1.14(t, 3H, H-18) | 1.42(t, 3H, H-18, 7.1) | 1.68(t, 3H, H-18) | 1.68(t, 3H, H-18, 7.1) | 1.22 (t, 3H, H-18) |

**Table 4**

CALCULATED AND MEASURED $^1$H-NMR SPECTRA OF 7-PIPERAZINYL-QUINOLONES

|  NF | |  FPQ-50 | |  NC1X | |  6ClPQ 50 | |
|---|---|---|---|---|---|---|---|
| Experimental data $^1$H-NMR(dmso-d6, δ ppm, J Hz) | Calculated data | Experimental data $^1$H-NMR(dmso-d6, δ ppm, J Hz) | Calculated data | Experimental data $^1$H-NMR(dmso-d6, δ ppm, J Hz) | Calculated data | Experimental data $^1$H-NMR($CDCl_3$+TFA δ ppm, J Hz) | Calculated data |
| 8.92(s, 1H, H-2) | 9.56 (s,1H, H-2) | 8.89(s, 1H, H-2) | 9.56(s, 1H, H-2) | 8.95(s, 1H, H-2) | 9.53(s, 1H, H-2) | 8.92(s, 1H, H-2) | 9.53(s, 1H, H-2) |
| 7.85(d,1H,H-5,$^3J$(F-H$^5$)=13.5Hz) | 8.63 (d,1H, H-5) | 8.00(d, 1H, H-5, $^3J$(F-H$^5$)=11.8 Hz) | 8.63(d, 1H, H-5) | 8.20(s, 1H, H-5) | 9.14(s, 1H, H-5) | 8.26(s, 1H, H-5) | 9.05(s, 1H, H-5), |
| 7.12(d,1H,H-8, $^4J$(F-H$^8$)= 2.5Hz) | 7.13(d, 1H, H-8) | - | - | 7.26(s, 1H, H-8) | 7.17(s, 1H, H-8) | - | - |
| 4.58(q, 2H, H-17, 7.2) | 3.70(q, 2H, H-17) | 4.84(q, 2H, H-17, 7.1) | 4.18(q, 2H, H-17) | 4.57(q, 2H, H-17, 7.1) | 3.63(q, 2H, H-17) | 4.79(q, 2H, H-17, 7.1) | 4.17(q, 2H, H-17) |
| 3.23(m, 4H, H-12, H-16, syst. $A_2B_2$) | 2.78(m,4H, H-12,H-16) | 3.26(m, 4H, H-12, H-16) | 2.83(m, 4H, H-12, H-16) | 3.16(m, 4H, H-12, H-16, syst. $A_2B_2$) | 2.63(m, 4H, H-12, H-16) | 3.34(m, 4H, H-12, H-14, syst. $A_2B_2$) | 2.62(m, 4H, H-12, H-14) |
| 2.89(m, 4H, H-13, H-15, syst. $A_2B_2$) | 2.78(m,4H, H-13,H-15) | 2.89(m, 4H, H-15, H-13) | 2.81(m, 4H, H-15, H-13) | 2.92((m, 4H, H-13, H-15, syst. $A_2B_2$) | 2.82((m, 4H, H-13, H-15) | 2.88((m, 4H, H-13, H-15, syst. $A_2B_2$) | 2.87((m, 4H, H-13, H-15) |
| 1.42(t, 3H, H-18, 7.2) | 1.76(t,3H,H-18) | 1.40(t, 3H, H-18, 7.1) | 1.44(t, 3H, H-18) | 1.44(t, 3H, H-18, 7.1) | 1.72(t, 3H, H-18) | 1.38(t, 3H, H-18, 7.1) | 1.45(t, 3H, H-18) |

| FPQ35 | | FPQ-36 | | NF | | FPQ-50 | |
|---|---|---|---|---|---|---|---|
| Experimental data $^{13}$C-NMR (dmso-d6, δ ppm) | Calculated data | Experimental data $^{13}$C-NMR (dmso-d6, δ ppm) | Calculated data | Experimental data $^{13}$C-NMR (dmso-d6, δ ppm) | Calculated data | Experimental data $^{13}$C-NMR (dmso-d6, δ ppm) | Calculated data |
| 169.57 (C-4) | | 174.72(d, C-4, $^4J$(F-C$^4$) =2.5 Hz) | | 176.02(C-4) | | 175.85(d, C-4,$^4J$(F-C$^4$)=2.4 Hz) | |
| 168.74(C-19) | | 164.97(C-19) | | 166.03(C-19) | | 165.08(C-19) | |
| 152.05(dC-6, $J$(F-C$^6$)=255.3Hz) | 133.17 (C-6) | 154.92(d,C-6,$J$(F-C$^6$) =253.1 Hz) | 143.6(C-6) | 152.80(d, C-6, $J$(F-C$^6$)=250.2 Hz) | 143.3(C6) | 155.81(d, C-6, $J$(F-C$^6$) =251.4 Hz) | 143.2 (C6) |
| 147.45(C-2) | 140.7 (C-2) | 151.63(C-2) | 148.8(C-2) | 148.27(s,C-2) | 141.4 (C2) | 152.36(C-2) | 145.6 (C2) |
| 145.45(d,C-7,$^2J$(F-C$^7$) =12.0Hz) | 138.27 (C-7) | 143.57(d,C-7,$^2J$(F-C$^7$) =15.4 Hz) | 137.99(C-7) | 145.93(d, C-7, $^2J$(F-C$^7$)=10.1 Hz) | 140.4 (C7) | 143.71(d, C-7, $^2J$(F-C$^7$) =16.9 Hz) | 140.1 (C7) |
| 139.65(C-9) | 132.70 (C-9) | 137.02(C-9) | 129.59(C-9) | 137.13(C-9) | 130.1 (C9) | 138.34(C-9) | 132.4(C9) |
| 120.43(C-3) | 99.61 (C-3) | 123.74(d,C-10, $^2J$(F-C$^{10}$) =7.5Hz) | 114.78(C-10) | 118.90(d, C-10, $^2J$(F-C$^{10}$)=7.7 Hz) | | 123.26(d, C-10, $^2J$(F-C$^{10}$) =7.1 Hz) | 114.60(C 10) |
| 111.06(d,C-5,$^2J$(F-C$^5$) =24.9Hz) | 114.81(C-5) | 119.34(C-8); | 114.26(C-8) | 110.99(d, C-5, $^2J$(F-C$^5$)=23.2 Hz) | 113.2(C5) | 118.93(C-8) | 114.95 (C8) |
| 103.09(C-10) | 104.37(C-10) | 110.09(d,C-5,$^2J$(F-C$^5$) =23.7 Hz) | 113.40(C-5) | 106.95(C-3) | 99.4 (C3) | 110.79(d, C-5, $^2J$(F-C$^5$)=23.2 Hz) | 112.79 (C5) |
| 97.91(d, C-8, $J$(F-C$^8$) =6.5 Hz) | 88.60 (C-8) | 107.81(C-3) | 99.92(C-3) | 105.38(d, C-8, $^2J$(F-C$^8$)=3.1 Hz) | 108.8 (C8) | 107.76(C-3) | 100.1 (C3) |
| 51.97(C-17) | 38.33 (C-17) | 52.61(C-17) | 47.89(C-17) | 50.75(d,C-12,C-16,$^4J$(F-C$^{12,16}$)=4.6 Hz) | 42.0 (C12, C16) | 52.95(C-17) | 44.4(C17) |
| 51.18(d, C-20, C-23, $^4J$(F-C$^{23}$) =6.5 Hz) | 42.70(C-20) | 50.27(d,C-20,C-23, $^4J$(F-C$^{12,16}$) =6.9 Hz) | 42.42(C-20) | 48.92(C-17) | 38.8 (C17) | 51.71(d, C-16, C-12 $^4J$(F-C$^{16}$)=4.4 Hz) | 40.3(C12 si C16) |
| 25.42(C-21, C-22) | 22.11(C21,C 22) | 25.24(C-21, C-22) | 23.01(C-21,C-22) | 45.30(C-13, C-15) | 34.6 (C13, C15) | 45.68(C-13, C-15) | 34.7 (C13 si C15) |
| 13.79(C-18) | 11.28(C-18) | 14.89(C-18) | 14.24(C-18) | 14.23(C-18) | 11.2(C18) | 15.52(C-18) | 14.6 (C18) |

**Table 5**

CALCULATED AND MEASURED $^{13}$C-NMR SPECTRA

**Table 6**

CALCULATED AND MEASURED IR SPECTRA

| | FPQ 36 | | 6ClPQ36 | | FPQ50 | | 6ClPQ50 | |
|---|---|---|---|---|---|---|---|---|
| Group | Experimental ($\nu$ cm$^{-1}$) | Calculated ($\nu$ cm$^{-1}$) | Experimental ($\nu$ cm$^{-1}$) | Calculated ($\nu$ cm$^{-1}$) | Experimental ($\nu$ cm$^{-1}$) | Calculated ($\nu$ cm$^{-1}$) | Experimental ($\nu$ cm$^{-1}$) | Calculated ($\nu$ cm$^{-1}$) |
| =CH in aromatic | 3056w | 3427 | 3046w | 3418 | 3052m | 3426 | 3042 m | 3416 |
| Ethyl group | 2957w;2895w 2849w; | 3280;3272 3214 | 2981m;2948w 2913w;2834m | 3302;3280 3271 | 2875m | 3293 3285 | 2854m | 3293 3215 |
| Acid group | 1718s | 1962 | 1716vs | 1962 | 1632vs | 1960 | 1619vs | 1960 |
| C=O strech (COOH) | 1615s | 1785 | 1610vs | 1804 | 1608vs | 1784 | 1560vs | 1805 |
| Skeletal vibration of quinolone ring | 1532m | 1619 | 1491vs | 1770 | 1527m | 1593 | 1429m | 1765 |
| O-C-O group of acid | 1434s | 1524 | 1430vs | 1571 | 1436vs | 1522 | 1343vs | 1573 |
| Hydroxyl group | 1253s | 1438 | 1236m | 1525 | 1337s | 1417 | 1239m | 1515 |
| C-F strech | 1102m | 956 | - | - | 1236m | 1145- | - | - |
| C-Cl strech | 846m | 856 | 835m | 797 | 889 m | 963 | 820 m;740m | 890;824 |

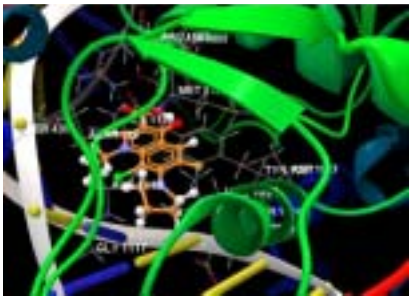


Fig. 7 The docked FPQ 36

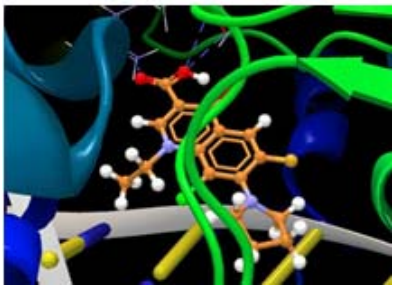


Fig. 8 Hydrogen bonds between the residues of the ARG 1122, ASP 1083 and FPQ 36 were displayed in dashed lines

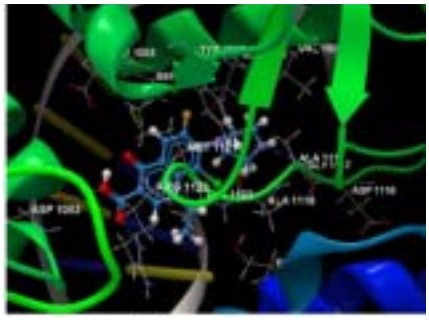


Fig. 9 The docked FPQ50

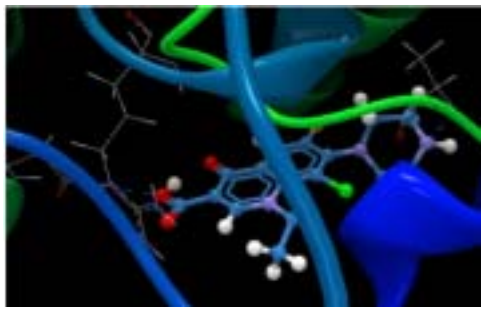


Fig.10 Hydrogen bonds between the residues of the ASP 1083, ARG 1122, ALA 1118 and the FPQ 50 were displayed in dashed lines

**Table 7**

THE LIST OF INTERMOLECULAR INTERACTIONS BETWEEN THE LIGAND MOLECULES DOCKED WITH 2XCS

| Comp. | Score | Group interaction | Hydrogen bond | Bond length |
|---|---|---|---|---|
| NF | -35.94 | ALA 1120, TYR 1087, SER 1084, MET 1121, ASP 1083, ARG 1122, SER 1067, VAL 1071, ALA 1068, MET 1075, ARG 1069, GLY 1072 | - N $sp^3$from piperazine – N $sp^2$ from GLY 1072<br>-O $sp^2$ from CO-N $sp^2$ ARG 1122<br>- O $sp^2$ from COOH-N $sp^2$ from ARG 1122 | 3.251 Å<br>2.651 Å<br>2.702 Å |
| FPQ50 | -37.80 | SER 438, ASP 1083, ASP 1116, GLY 1117, ALA 1118, ALA 1119, ALA 1120, ARG 1122, MET 1121, SER 1084, ASP 1083, TYR 1087, GLU 1088, VAL 1091 | -O $sp^2$ from COOH(CO) -N $sp^2$ from ARG 1122<br>-O $sp^2$ from COOH (OH)- O $sp^2$ from ASP 1083<br>- N $sp^3$ from piperazine- N $sp^2$ from ALA 1118 | 3.067 Å<br>2.921 Å<br>2.872 Å |
| NClX | -34.94 | GLY 1082, ASP, 1083, SER 1084, ARG 1122, ALA 1120, ALQA 1119, SER 438, ALA 1118, GLY 1117, MET 1121, ASP 437, TYR 1087, SER 1084 | -N $sp^3$ from piperazine - O $sp^2$ from ASP 1083<br>-N $sp^3$ from piperazine – N s $p^2$ from ARG 1122<br>-O $sp^2$ from COOH(OH) -N $sp^2$ from ALA 1118<br>-O $sp^2$ from COOH (OH)- O $sp^2$ from ALA1118 | 2.863 Å<br>2.809 Å<br>2.906 Å<br>2.740 Å |
| 6ClPQ50 | -34.08 | ASP 1083, VAL 1071, GLY 1072, ASP 1073, MET 1121, ALA 1088, ARG 1069, ALA 1063, SER 1076, ALA 1120, ARG 1122, ASP 1083, SER 1084, GLY 1082, HIS 1081, ILE 1070, VAL 1071, ALA 1068 | - N $sp^3$from piperazine - Nsp$^2$ from GLY 1072<br>- N $sp^3$from piperazine - Osp$^2$ from ALA 1168 | 3.043 Å<br>2.549 Å |

| | | | | |
|---|---|---|---|---|
| FPQ35 | -36.87 | ASP 1083, MET 1121, ALA 1068, VAL 1071, ARG 1069, MET 1075, ASP 1083 GLY 1072, VAL 1071, ALA 1120, ARG 1122. | -O $sp^2$ from COOH (CO) - N $sp^2$ of ARG 1122<br>-O $sp^2$ from COOH - N $sp^2$ of ARG 1122 | 2.667 Å<br>2.711 Å |
| FPQ36 | -33.20 | GLY 1117, ALA 1118, ALA 1119, ALA 1120, SER 438, MET 1121, ARG 1122, ASP 1083, TYR 1087, VAL 1091, SER 1084. | -O $sp^2$ from COOH(CO) -N $sp^2$ from ARG 1122<br>-O $sp^2$ from COOH (OH)- O $sp^2$ from ASP 1083<br>-O $sp^2$ from COOH (OH)- O $sp^2$ from ASP 1083 | 3.109 Å<br>3.200 Å<br>2.688 Å |
| 6ClPQ35 | -34.50 | ASP 1083, SER 1084, TYR 1087, ARG 1122, MET 1121, ALA 1120, GLU 1088, VAL 1091, ALLA 1119, ALA 1118, GLY 1117. | -O $sp^2$ from COOH(CO) -N $sp^2$ from ARG 1122<br>-O $sp^2$ from COOH(OH)- O $sp^2$ from ASP 1083<br>- O $sp^2$ from COOH(OH)- O $sp^2$ from ASP 1083 | 3.016 Å<br>3.076 Å<br>2.957 Å |
| 6ClPQ36 | -32.23 | GLU 1088, VAL 1091, TYR 1087, ASP 1083, SER 1084, MET 1121, ARG 1122, ALA 1119, ALA 1120, ALA 1118, SER 438, GLY 1117 | -O $sp^2$ from COOH(CO) -N $sp^2$ from ARG 1122<br>-O $sp^2$ from COOH (OH)- O $sp^2$ from ASP 1083<br>-O $sp^2$ from COOH (OH)- O $sp^2$ from ASP 1083 | 3.071 Å<br>3.243 Å<br>2.907 Å |

**Table 7**
(continued)

*aureus* ATCC 6538). The result of molecular docking study, as shown in figure 9 and figure 10, for FPQ 50, shows three hydrogen bonds with ASP 1083 (2.921 Å), ARG 1122 (3.067 Å) and ALA 1118 (2.872 Å).

## Conclusions

In the present study, we have synthesized new quinolones and we have investigated their antibacterial activity. Their structure has been determined and confirmed by the following physico-chemical methods: elemental analysis, IR spectral analysis, H-NMR, C-NMR, thin layer chromatography. For the synthesized quinolone derivatives, a study of the characteristics and molecular properties has been conducted using Spartan 14 software. In the first stage of the study, the 2D and 3D structures has been generated. The most stable conformer for each structure was obtained by geometry optimization and energy minimization. The docking studies have been carried out using CLC Drug Discovery Workbench Software in order to predict the binding modes, the binding affinities and the orientation of the docked quinolones in the preferred binding site of the protein receptor.

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