Article

Molecular Docking Studies of Some Novel Fluoroquinolone Derivatives

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Abstract: An important parameter in the development of a new drug is the drug's affinity to the identified target (protein/enzyme). Predicting the ligand binding to the protein assembly by molecular simulations would allow the synthesis to be restricted to the most promising drug candidates. A restricted hybrid HF-DFT calculation was performed in order to obtain the most stable conformer of studied ligands and a series of DFT calculations using the B3LYP levels with 6-31G* basis set has been conducted on their optimized structures. The docking studies of the quinolone compounds have been carried out with CLC Drug Discovery Workbench software to identify and visualize the ligand-receptor interaction mode.

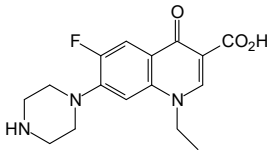
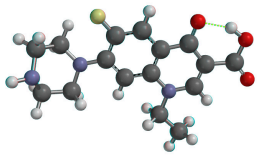
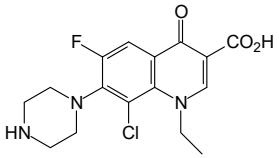
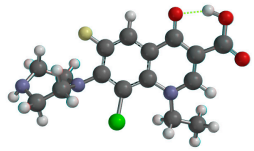
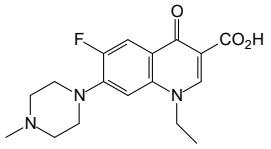
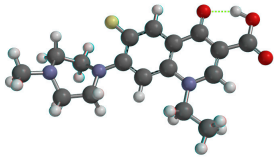
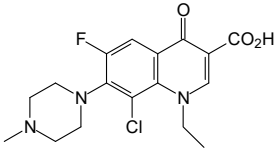
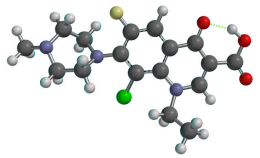
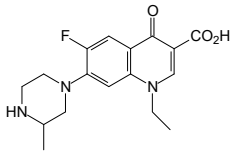
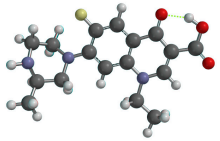
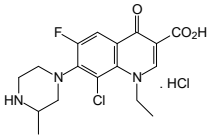
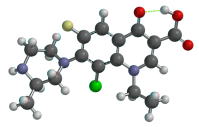
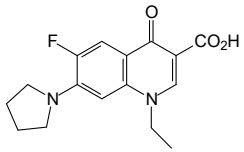
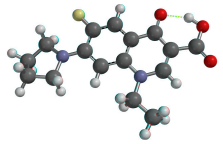
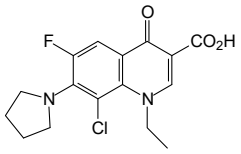
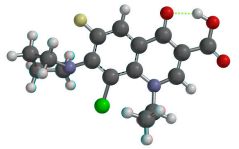
Keywords: molecular docking; fluoroquinolones; antimicrobial activity

1. Introduction

Infectious diseases are the second important cause of death global [1]. Treatment of infectious diseases becomes more difficult when common pathogens, such as *Staphylococcus aureus* and *Mycobacterium tuberculosis* develop drug resistance to drugs that were considered at one time, effective. Antibiotic drugs are a special class of therapeutic agents whose misuse have affected not only the individual patient, they have affected also the entire community. This is why, at some point after the widespread introduction and use of new antibiotics, antibiotic-resistant bacteria occurring in significant waves appear almost inevitable. In medical practice, many fluoroquinolones with antimicrobial activity are used, some of them are considered by pharmacists as the primary drugs in anti-infective therapy. Fluoroquinolones have a broad spectrum and a strong antibacterial activity [2-8]. They are characterized by pharmacokinetics that allows their use in all localized infections. In the development of a new antimicrobial agent, an important parameter is the affinity of a drug to the identified target (protein/enzyme). Predicting the binding of the ligand with the target (protein/enzyme) by molecular simulation would allow to restrict the synthesis to the most promising compounds [9-20]. Molecular docking can be accomplished by two interdependent steps [17-20]. The first step consists in sampling the ligand conformations in the active site of the protein receptor. The second step involves the classification of these conformations by a scoring function.

The objective of these paper is to evaluate *in silico* anti-pneumococcal activity of some fluoroquinolone derivatives (Table 1) by using CLC Drug Discovery Workbench Software. Docking studies have been conducted for all ligands and the docking scores were compared with the scores

Table 1. The structure of the fluoroquinolone compounds.

2D Structure	3D Structure	2D Structure	3D Structure
			
NF: 1-Ethyl-6-fluoro-7-(piperazin-1-yl)-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid $C_{16}H_{18}FN_3O_3$: M = 319.336 g/mol; m.p. = 218.3-220.6˚C [25]		**FPQ50:**1-Ethyl-6-fluoro-7-(piperazin-1-yl)-8-chloro-1,4-dihydro-4-oxo -quinoline-3-carboxylic acid $C_{16}H_{17}ClFN_3O_3$: M = 353.781 g/mol; m.p. = 227-230˚C [25]	
			
PF:1-Ethyl-6-fluoro-7-(4-methyl-piperazin-1-yl)-1,4-dihydro-4-oxo -quinoline-3-carboxylic acid; $C_{17}H_{20}FN_3O_3$: M = 333.363 g/mol; m.p. = 269.2-271.8˚C [26]		**FPQ51:**1-Ethyl-6-fluoro-7-(4-methyl-piperazin-1-yl)-8-chloro-1,4-dihydro -4-oxo-quinoline-3-carboxylic acid; $C_{17}H_{20}ClFN_3O_3$: M = 367.808 g/mol; m.p. = 219.6-221.5˚C [26]	
			
FPQ27: 1-Ethyl-6-fluoro-7-(3-methyl-piperazin-1-yl)-1,4-dihydro-4-oxo -quinoline-3-carboxylic acid; $C_{17}H_{20}FN_3O_3$: M = 353.781 g/mol; m.p. = 177.6-180.6˚C [24]		**FPQ29.HCl:** 1-Ethyl-6-fluoro-7-(3-methyl-piperazin-1-yl)-8-chloro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid. HCl $C_{17}H_{19}ClFN_2O_3$. HCl: M = 353.781 g/mol; m.p. = 227-230˚C [26]	
			
FPQ35: 1-Ethyl-6-fluoro-7-(pyrrolidin-1-yl)-1,4-dihydro-4-oxo-quinoline -3-carboxylic acid; $C_{16}H_{17}FN_2O_3$: M = 304.321 g/mol; m.p.= 336.6-337.9˚C [25]		**FPQ36:** 1-Ethyl-6-fluoro-7-(pyrrolidin-1-yl)-8-chloro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid; $C_{16}H_{16}ClFN_2O_3$: M = 338.766 g/mol; m.p. = 214.5-217.8˚C [25]	

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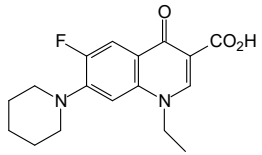
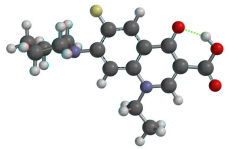
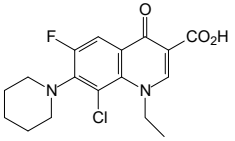
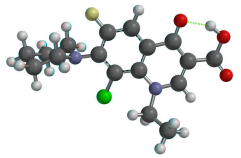
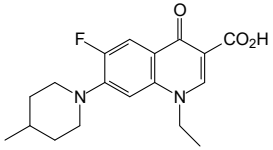
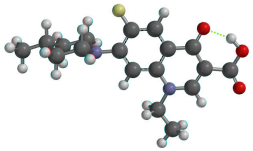
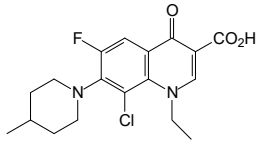
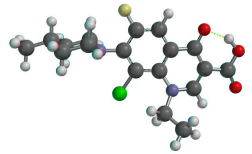
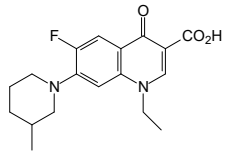
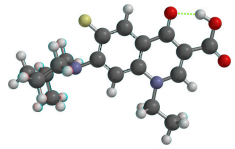
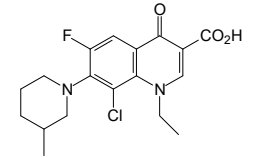
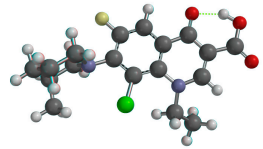
	
FPQ32: 1-Ethyl-6-fluoro-7-(piperidin-1-yl)-1,4-dihydro-4-oxo-quinoline -3-carboxylic acid; $C_{17}H_{19}FN_2O_3$: M = 318.348 g/mol; m.p. = 202.4-204.4˚C [26]	
	
FPQ33: 1-Ethyl-6-fluoro-7-(piperidin-1-yl)-8-chloro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid $C_{17}H_{18}ClFN_2O_3$: M = 352.793 g/mol; m.p. = 187-190˚C [26]	
	
Q83: 1-Ethyl-6-fluoro-7-(4-methyl-piperidin-1-yl)-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid; $C_{18}H_{21}FN_2O_3$: M = 332.37 g/mol; m.p. = 234.7-237.1˚C [22]	
	
Q85: 1-Ethyl-6-fluoro-7-(4-methyl-piperidin-1-yl)-8-chloro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid; $C_{18}H_{20}ClFN_2O_3$: M = 366.815 g/mol; m.p. = 201-202.5˚C [22]	
	
FPQ24: 1-Ethyl-6-fluoro-7-(3-methyl-piperidin-1-yl)-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid; $C_{18}H_{21}FN_2O_3$: M = 332.37 g/mol; m.p. = 188.1-189.4˚C [23]	
	
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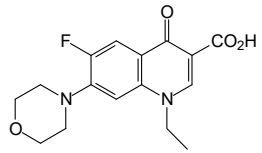
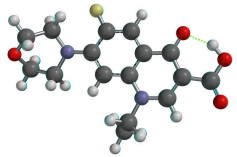
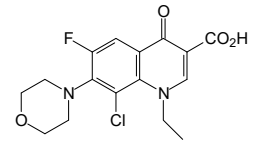
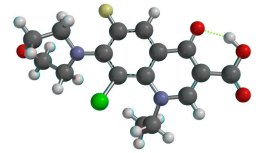
	
FPQ25: 1-Ethyl-6-fluoro-7-(morpholin-1-yl)-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid; $C_{16}H_{17}FN_2O_4$: M = 320.32 g/mol; m.p. = 257.4-258.7˚C [23]	
	
FPQ28: 1-Ethyl-6-fluoro-7-(morpholin-1-yl)-8-chloro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid: $C_{16}H_{17}ClFN_2O_4$: M = 354.76 g/mol ; m.p. = 244.6-246˚C [23]	

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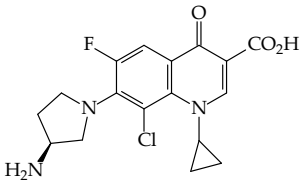

Figure 1. Clinafloxacin.

of standard drugs: Clinafloxacin (7-[(3R)-3-aminopyrrolidin-1-yl]-8-chloro-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid) (Figure 1).

2. Computational details

Molecular Docking studies have been realized with CLC Drug Discovery Workbench Software to obtain accurate predictions on optimized conformations for both, the ligand (fluoroquinolone compound) and their target receptor protein to form a stable complex. The fluoroquinolone compounds have been synthesized in our laboratory [21-26] and their 2D structure is shown in Table 1. The protein-ligand complex has been realized based structure of Clinafloxacin (Figure 1) with *Streptococcus pneumoniae* serotype 4 (strain ATCC BAA-334/TIGR4) which was available through the Protein Data Bank (PDB entry 3FOE) [28]. The score and hydrogen bonds formed with the amino acids from group interaction atoms are used to predict the binding modes, the binding affinities and the orientation of the docked ligands derivatives in the active site of the protein-receptor.

2.1. Ligand preparation

The ligands, fluoroquinolone derivatives, have been prepared using SPARTAN'14 software package [29]. Their molecular structures have been determined using DFT/B3LYP/6-31 G* level of basis set. In Table 2 are shown the electronic properties such as: HOMO (Highest Occupied Molecular Orbital) and LUMO (Lowest Unoccupied Molecular Orbital) energy values, HOMO and LUMO orbital coefficients distribution, molecular dipole moment, polar surface area (PSA), ovality, polarizability, octanol water partition coefficient (log P), volume, area, number of hydrogen-bond donors (HBDs) and acceptors (HBAs). The DFT calculations were performed according to the protocol described in our previous paper [30].

2.2. Molecular docking studies

Molecular docking studies have been performed with CLC Drug Discovery Workbench Software to obtain accurate predictions on optimized conformation for both, ligands and their target receptor protein, as well to their resulted complexes. The protein-ligand complex has been realized based on the structure of Clinafloxacin with *Streptococcus pneumoniae* serotype 4 (strain ATCC BAA-334/TIGR4) assembly available from Protein Data Bank (PDB entry 3FOE). The docking simulations were performed according to the docking protocol described in a previous paper [30], and involve the next steps: setup the binding site and setup binding pocket in a Molecule Project, dock ligands imported to a Molecule Table, inspect the docking results. To ensure that the ligand orientations and positions obtained by the molecular docking studies are valid, the used docking methods and parameters have been validated by redocking. The docking score and hydrogen bonds formed with the amino acids from group interaction atoms are used to predict the binding modes, the binding affinities and the orientation of the docked quinolone derivatives in the active site of the protein-receptor. Using the Calculate Molecular Properties tool it has been calculated commonly used properties of small

79 **Table 2.** Molecular properties for CPK Model computations for quinolone compounds using Spartan'14 V1.1.4 software.

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Compound	Molecular properties												
	Energy [au]	Dipole moment [Debye]	E HOMO [eV]	E LUMO [eV]	HOMO-LUMO GAP	Polarizability [10^{-30} m^3]	PSA[Å^2]	Ovality	Log P	Aria [Å^2]	Volume [Å^3]	HBA count	HBD count
NF	-1110.31833	12.76	-5.76	-1.41	4.35	65.09	56.587	1.45	1.37	317.19	305.05	5	1
FPQ50	-1569.88534	8.71	-6.00	-2.02	3.98	66.33	57.344	1.46	1.92	329.98	319.25	5	1
PF	-1149.63032	12.36	-5.77	-1.43	4.34	66.65	46.369	1.48	1.74	336.83	324.22	5	1
FPQ51	-1609.19720	8.91	-5.79	-1.97	3.82	67.92	46.808	1.49	2.30	349.36	338.39	5	1
FPQ27	-1149.63593	12.86	-5.76	-1.40	4.36	66.57	56.053	1.48	1.68	336.69	323.35	5	1
FPQ29	-1609.20487	9.10	-6.01	-1.96	4.05	67.80	56.717	1.49	2.24	349.71	337.57	5	1
FPQ35	-1054.99047	12.50	-5.77	-1.39	4.38	64.18	44.034	1.43	2.30	305.75	293.94	4	1
FPQ36	-1514.55632	8.83	-6.14	-1.97	4.17	65.44	44.405	1.45	2.86	319.72	308.85	4	1
FPQ32	-1094.30033	9.49	-6.63	-1.82	4.81	65.58	45.402	1.46	2.72	323.90	311.68	4	1
FPQ33	-1553.87373	8.28	-6.33	-2.05	4.28	66.75	44.781	1.47	3.28	336.69	325.36	4	1
Q83	-1133.61569	9.49	-6.36	-1.82	4.54	67.06	45.389	1.49	3.05	343.24	329.85	4	1
Q85	-1593.18913	8.29	-6.33	-2.05	4.58	68.23	44.785	1.50	3.61	356.00	343.54	4	1
FPQ24	-1133.61279	9.48	-6.34	-1.82	4.52	67.07	45.295	1.48	3.12	342.68	329.92	4	1
FPQ30	-1593.18622	8.23	-6.33	-2.06	4.27	68.24	44.768	1.50	3.68	355.38	343.58	4	1
FPQ25	-1130.18716	10.15	-6.02	-1.58	4.44	64.87	51.758	1.44	1.59	314.60	302.53	5	1
FPQ28	-1589.75575	8.26	-6.24	-1.97	4.97	66.00	51.859	1.45	2.15	325.74	316.05	5	1

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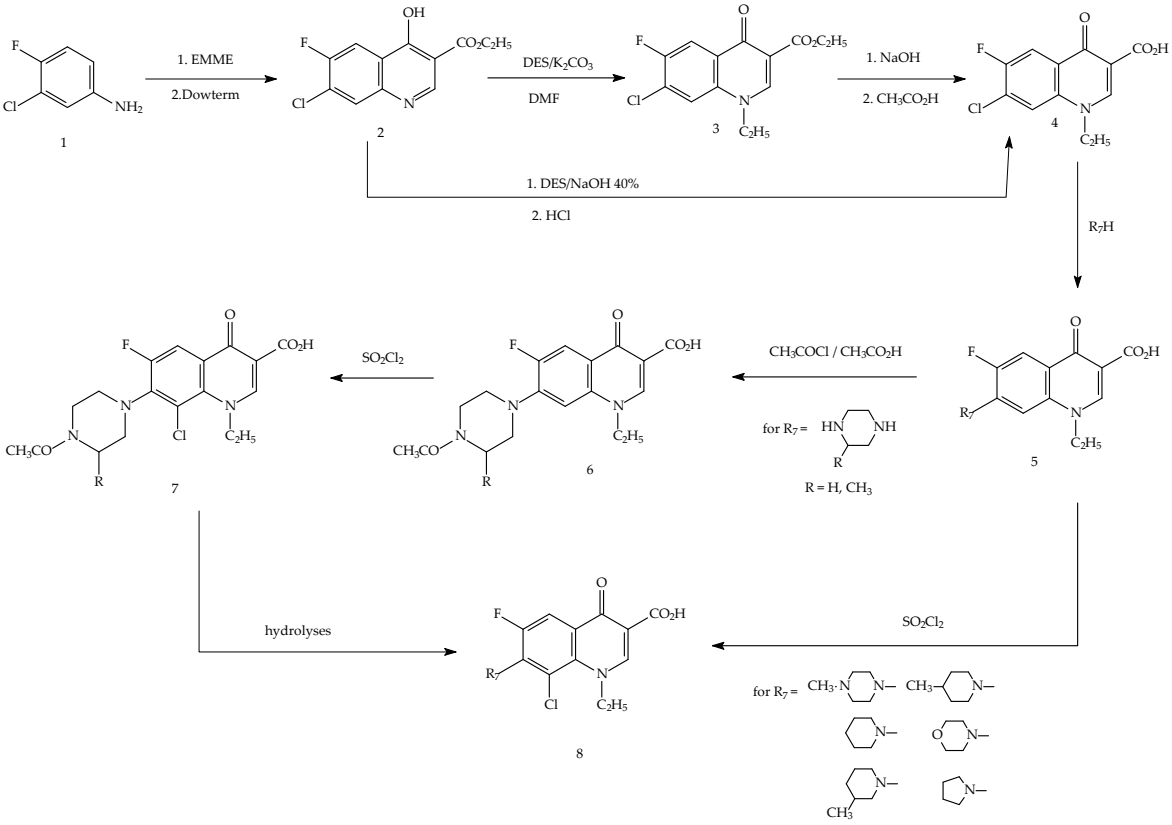
molecules, such as Lipinski's rule of five: the molecular weight, number of hydrogen bond donors, number of hydrogen bond and Log P (octanol-water partition coefficient).

3. Results and Discussion

The carried-out work was aimed to *in silico* assessment of biological activity of some fluoroquinolones using the CLC Drug Discovery Workbench Software. The library of compounds used for this study is shown in Table 1. These molecules were obtained by synthesis according to Scheme 1 [21-26].



Scheme 1. Preparation of fluoroquionolone compounds.

Appropriate unsubstituted aniline (1) is reacted with diethylethoxymethylenemalonate (EMME) [21] to produce the intermediate anilinomethylenemalonate, intermediate, which is subjected to a thermal process, for performing the Gould-Jacobs cyclization. The following operation is the alkylation of the quinolone (2) which is usually accomplished by reaction with a suitable alkyl halide or dialkyl sulphates to produce the qinolone-3-carboxylate ester (3). The final manipulation is acid or 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 dialkyl sulphates in presence of alkali. The displacement of 7-chloro group with a heterocyclic: substituted or unsubstituted piperidine,

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pyrrolidine, morpholine, 4-methyl-piperazine, yielded fluoroquinolone compounds (5). 8-Chloro-quinoline-3-carboxylic acid (8) have been synthesized from 8-unsubstituted quinoline-3-carboxylic acid (5) by chlorination with sulfuryl chloride. When, R_7 = 3-methyl-piperazine, or piperazine, is necessary to protect the nitrogen atom from piperazine group. After chlorination and hydrolysis, the final fluoroquinolones, (8) (R_7 = 3-methyl-piperazine, or piperazine), have been obtained [22-26].

The antimicrobial activity of fluoroquinolones from studied compound library was evaluated against the Gram-positive and Gram-negative microorganisms [26].

Based of the results of the antimicrobial evaluation, the compound FPQ-30 (1-Ethyl-6-fluoro-7-(3-methyl-piperidin-1-yl)-8-chloro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid) seems to be a promising compound. For this reason, studies of biological activity prediction have been extended to *Staphylococcus aureus MRSA* isolated from hospital infections [24] and to wild-type strains of *Staphylococcus aureus MRSA*, *Streptococcus spp. β-hemolytic*, *Streptococcus spp. γ-hemolytic* and *Escherichia coli* [29]. The fluoroquinolone FPQ30 demonstrated an increased antimicrobial activity against *Staphylococcus aureus MRSA* and against *Streptococcus spp. γ-hemolytic*, a moderate effect against *Streptococcus spp. β-hemolytic* and a limited action against *Escherichia coli* strains.

The promising *in vitro* results on some bacterial strains, correlated with the previous *in silico* molecular docking study against protein receptor *S. Aureus* DNA GYRASE sustain a potential therapeutic effect of the FPQ30 fluoroquinolone [26,29].

Starting from these results we have extending the *in silico* molecular docking study for the prediction of biological activity against other targets. Molecular docking studies have been conducted to achieve precise predictions on optimized conformation for both, the fluoroquinolone derivatives (as ligand) and their targets, receptor protein, to form a stable complex. The protein-ligand complex has been realized based of the structure of Clinafloxacin with Streptococcus pneumoniae serotype 4 (strain ATCC BAA-334/TIGR4) imported from Protein Data Bank (PDB ID: 3FOE) [28]. After the import of the protein receptor file from Protein Data Bank and after its preparation, the next step was the search of the binding site and the binding pockets. The NFX have been considered as reference ligand to compare the docking results of fluoroquinolone compounds. The ligand binding mode search was carried out inside the binding site volume. Binding pockets were used to guide the molecular docking of the ligands.

The binding site and docking pose of the co-crystallized NFX (clinafloxacin) interacting with amino acids residues are shown in Figure 2a and in Figure 2b the binding pocket is represented.

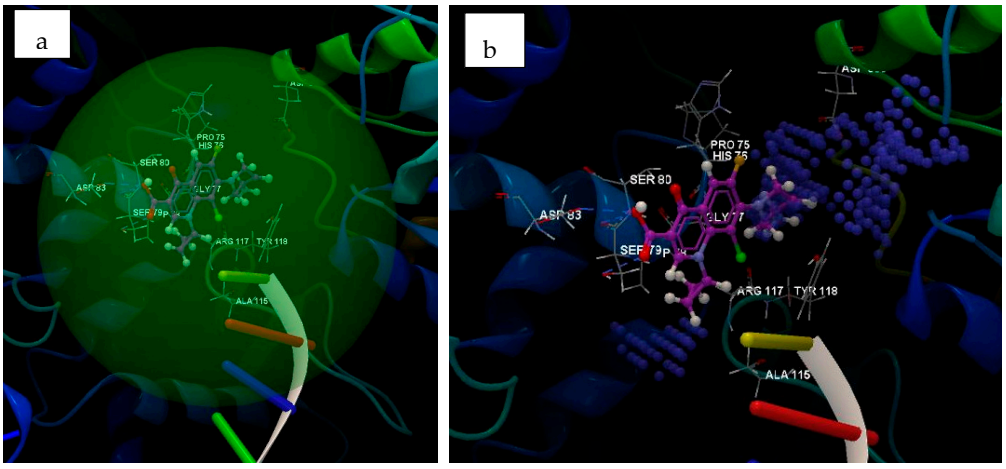

Figure 2. (a) Binding pocket and docking pose of the co-crystallized NFX; (b) Binding site and docking pose of the co-crystallized NFX.

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The docking score, the interacting group (Figure 3c) and hydrogen bonds (Figure 3a) formed with the amino acids from group interaction atoms are shown in Table 2. Clinafloxacin (Score 49.78; RMSD 0.10) forms three hydrogen bonds, two with SER 79: A (bond length: 3.182 and 3.103) and one with Asp 83: A (bond length 3.048 Å). In Figure 3b, docking validation of co-crystallized clinafloxacin is shown. The score and hydrogen bonds formed with the amino acids from group interaction atoms are used to predict the binding modes, the binding affinities and the orientation of the docked ligands derivatives in the active site of the protein-receptor.

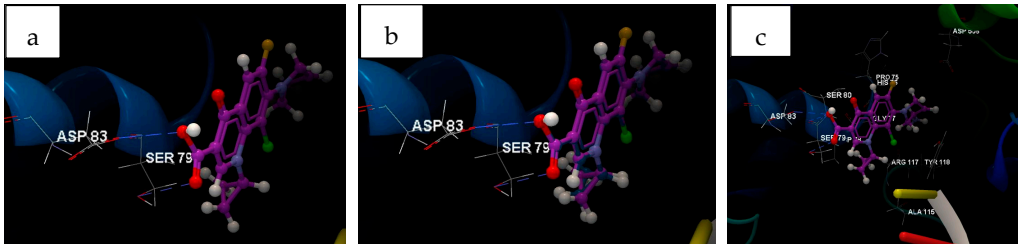

Figure 3. (a) Hydrogen bonds between amino acids residues and co-crystallized NFX; (b) Docking validation of the co-crystallized; (c) Docking pose of the co-crystallized NFX interacting with amino acids residues.

Also, molecular docking studies have been performed relating to some quinolone compounds known in medical therapeutics: norfloxacin (Score -50.50; RMSD 0.02) and pefloxacin (Score -51.90; RMSD 0.08). Norfloxacin (NF) and pefloxacin (PF) reveal a better docking score than docking score of the co-crystallized NFX (clinafloxacin). Norfloxacin forms two hydrogen bonds with HIS 76:A (bond length: 3.065 Å and 3.096 Å) and one with Asp 83:A (bond length 3.048 Å) (Figure 4a). Pefloxacin forms one hydrogen bond with HIS 76:A (bond length: 2.972 Å)(Figure 4b). Acording to the score docking evaluation, it was observed that, all the fluoroquinolone derivatives reveal docking score greater than -40. Only two compounds: FPQ 35 (Score -44.17; RMSD 0.09) and FPQ 36 (Score -45.99; RMSD 0.77) reveal docking scores less than docking score of the co-crystallized NFX.

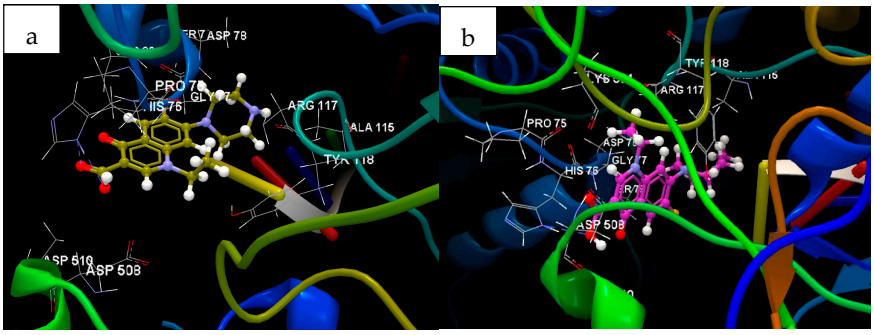

Figure 4. (a) Docking pose of the NF ligand interacting with amino acids residues; (b) Docking pose of the PF ligand interacting with amino acids residues.

The results of evaluation of the docking score for fluoroquinolones FPQ 33, FPQ 28, FPQ 51 and Q85, compounds with a good activity *in vitro* against *Staphylococcus Aureus* ATCC 6538 [26] (MIC=0.32 µg/ml) and with a good activity against MRSA for compound FPQ 28 [24] reveals better docking score than co-crystallized NFX, norfloxacin (NF) and pefloxacin (PF). Interactions of fluoroquinolone

Table 2. List of intermolecular interactions between the ligand molecules docked with 3FOE.

Comp.	Score	RMSD	Group interaction	Hydrogen bond	Bond length
NFX (Clinafloxacin)	-49.78	0.10	ASP 508: C, HIS 76: A, PRO 75: A, SER 80: A, ASP 83: A, SER 79: A, GLY 77: A, ASP 78: A, ARG 117: B, ALA 115: A, TYR 118: B	- O sp^2 from COOH(CO) - O sp^3 from SER 79: A	3.182 Å
				- O $sp^3$from COOH (OH)- O sp^2 from SER 79: A	3.103 Å
				- O $sp^3$from COOH (OH)- O sp^2 from ASP 83: A	3.048 Å
NF (Norfloxacin)	-50.50	0.02	ASP 510: C, ASP 508: C, HIS 76: A, GLY 77: A, PRO 75: A, ASP 78: A, SER 79: A, SER 80: A, TYR 118: B, ARG 117: B, ALA 115: B	- O $sp^2$from COOH(CO) - N sp^2 from HIS 76: A	3.065 Å
				- O $sp^3$from COOH (OH)- N sp^2 from HIS 76: A	3.096 Å
FPQ50	-50.15	0.0094	ASP 510: C, ASP 508: C, LYS 581: C, HIS 74: A, HIS 76: A, PRO 75: A, GLY 77: A, ASP 78: A, SER 79: A, SER 80: A, TYR:118: B, ARG 117: B	- O $sp^2$from COOH(CO) - N sp^2 from HIS 76: A	2.957 Å
				- O $sp^3$from COOH (OH)- O sp^2 from ASP 508: C	3.056 Å
				- O $sp^3$from COOH (OH)- O sp^2 from ASP 508: C	2.990 Å
PF (Pefloxacin)	-51.90	0.08	ASP 510: C, ASP 508: C, LYS 581: C, HIS 76: A, PRO 75: A, GLY 77: A, ASP 78: A, SER 79: A, TYR:118: B, ARG 117: B, ALA 115: B	- O $sp^3$from COOH (OH)- N sp^2 from HIS 76: A	2.978 Å
FPQ 51	-51.92	0.08	ASP 510: C, ASP 508: C, HIS 76: A, GLY 77: A, PRO 75: A, ASP 78: A, SER 79: A, SER 80: A, TYR 118: B, ARG 117: B, ALA 115: B	- O $sp^2$from COOH(CO) - N sp^2 from HIS 76: A	3.064 Å
				- O $sp^3$from COOH (OH)- N sp^2 from HIS 76: A	3.102 Å
FPQ 27	-50.15	0.02	ASP 510: C, ASP 508: C, GLY 111: C, HIS 76: A, PRO 75: A, GLY 77: A, ASP 78: A, SER 79: A, TYR:118: B, ARG 117: B, MET 116: B, ALA 115: B	- O $sp^3$from COOH (OH)- N sp^2 from HIS 76: A	2.972 Å
FPQ 29	-51.70	0.86	ASP 510: C, ASP 508: C, HIS 76: A, SER 80: A, GLY 77: A, ASP 78: A, SER 79: A, TYR:118: B, ARG 117: B, ALA 115: B	- O $sp^3$from COOH (OH)- N sp^2 from HIS 76: A	2.967 Å
FPQ24	-51.52	0.15	ASP 510: C, ASP 508: C, HIS 76: A, GLY 77: A, ASP 78: A, SER 79: A, TYR 118: B, ARG 117: B, MET 116: B, ALA 115: B	- O $sp^3$from COOH (OH)- N sp^2 from HIS 76: A	2.989 Å
FPQ 30	-50.15	0.02	ASP 510: C, ASP 508: C, LYS 581: C, HIS 74: A, HIS 76: A, GLY 77: A, ASP 78: A, SER 79: A, SER 80: A, TYR:118: B, ARG 117: B	- O $sp^2$from COOH(CO) - N sp^2 from HIS 76: A	2.938 Å
				- O $sp^3$from COOH (OH)- O sp^2 from ASP 508: C	2.826 Å
				- O $sp^3$from COOH (OH)- O sp^2 from ASP 508: C	2.965 Å

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FPQ 32	-53.11	0.02	ASP 510:C, ASP 508:C, GLY 511: C, HIS 76: A, PRO 75: A, GLY 77: A, ASP 78: A, SER 79: A, TYR:118: B, ARG 117: B, MET 116: B, ALA 115: B, LYS 581: C	- O $sp^3$from COOH (OH)- N sp^2 from HIS 76: A	2.997 Å
FPQ 33	-54.47	0.005	ASP 510: C, ASP 508: C, LYS 581: C, HIS 74: A, HIS 76: A, PRO 75: A, GLY 77: A, ASP 78: A, SER 79: A, SER 80: A, TYR:118: B, ARG 117: B	- O $sp^2$from COOH(CO) - N sp^2 from HIS 76: A - O $sp^3$from COOH (OH)- O sp^2 from ASP 508: C - O $sp^3$from COOH (OH)- O sp^2 from ASP 508: C	2.984 Å 3.046 Å 2.906 Å
Q 83	-51.53	0.51	ASP 510: C, ASP 508: C, LYS 581: C, HIS 74: A, HIS 76: A, PRO 75: A, GLY 77: A, ASP 78: A, SER 79: A, SER 80: A, TYR:118: B, ARG 117: B	- O $sp^2$from COOH(CO) - N sp^2 from HIS 76: A - O $sp^3$from COOH (OH)- O sp^2 from ASP 508: C - O $sp^3$from COOH (OH)- O sp^2 from ASP 508: C	2.998 Å 3.063 Å 2.965 Å
Q 85	-51.85	0.02	ASP 510: C, ASP 508: C, LYS 581: C, HIS 74: A, HIS 76: A, PRO 75: A, GLY 77: A, ASP 78: A, SER 79: A, SER 80: A, TYR:118: B, ARG 117: B	- O $sp^2$from COOH(CO) - N sp^2 from HIS 76: A - O $sp^3$from COOH (OH)- O sp^2 from ASP 508: C - O $sp^3$from COOH (OH)- O sp^2 from ASP 508: C	2.977 Å 3.022 Å 2.847 Å
FPQ 25	-51.73	0.03	ASP 508: C, ASP 510: C, HIS 76: A, PRO 75: A, GLY 77: A, ASP 78: A, SER 79: A, TYR:118: B, ARG 117: B, ALA 115: B	- O $sp^3$from COOH (OH)- N sp^2 from HIS 76: A	2.964 Å
FPQ 28	-52.81	0.23	ASP 510: C, ASP 508: C, HIS 76: A, GLY 77: A, ASP 78: A, SER 79: A, SER 80: A, TYR 118: B, ARG 117: B, ALA 115: B	- O $sp^2$from COOH(CO) - N sp^2 from HIS 76: A - O $sp^3$from COOH (OH)- N sp^2 from HIS 76: A	3.141 Å 3.110 Å
FPQ35	-44.17	0.09	ASP 508: C, ASP 510: C, HIS 76: A, PRO 75: A, SER 80: A, ASP 83: A, SER 79: A, GLY 77: A, ASP 78: A, ARG 117: B, TYR 118: B	- O sp^2 from COOH(CO) - O sp^3 from SER 79: A - O $sp^3$from COOH (OH)- O sp^2 from ASP 83: A	3.215 Å 3.081 Å
FPQ36	-45.99	0.77	ASP 510: C, HIS 76: A, PRO 75: A, GLY 77: A, ASP 78: A, SER 79: A, SER 80: A, TYR:118: B, ARG 117: B, MET 116: B, ALA 115: B,	- O $sp^3$from COOH (OH)- N sp^2 from HIS 76: A	3.057 Å

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derivatives: FPQ 33 (score: -54.47; RMSD: 0.005), FPQ 28 (score: -52.81; RMSD: 0.23), FPQ 51(score: -51.92; RMSD: 0.08), and Q 85 (score: -51.85; RMSD: 0.02) are shown in Figure 5. The most active compound, FPQ 33 has been predicted to have a significant docking score (-54.47; RMSD 0.005); FPQ 33 shows the occurrence of two hydrogen bonds, one bond with HIS 76:A (bond length: 2.984 Å) and two bonds with ASP 508:C (bond length: 3.046 Å and 2.906 Å).

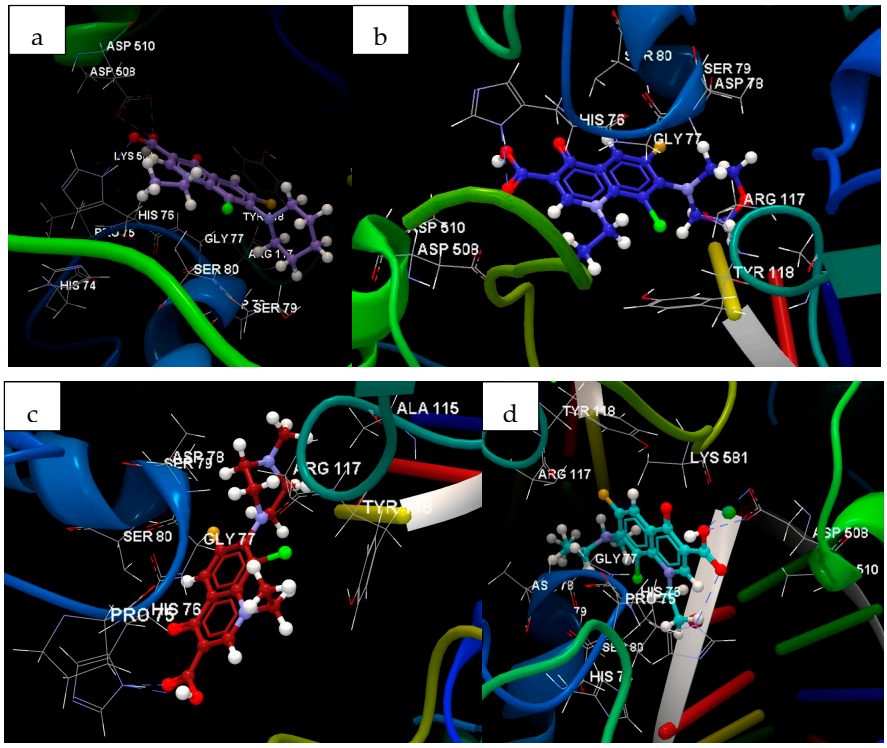

Figure 5. (a) Docking pose of the FPQ 33 ligand interacting with amino acids residues; (b) Docking pose of the FPQ 28 ligand interacting with amino acids residues; (c) Docking pose of the FPQ 51 ligand interacting with amino acids residues; (d) Docking pose of the Q 85 ligand interacting with amino acids residues.

In the Figure 6 is shown the docking pose of the all quinolone derivatives in the binding site of 3FOE. Results of the docking studies showed that fluoroquinolones have adopted various orientations. The same orientation with the co-crystallized ligand NFX (clinafloxacin) shows the compound FPQ 35 (Figure 7a). Fluoroquinolones FPQ 51, FPQ 27, FPQ 29, FPQ 24, FPQ 32, FPQ 25, FPQ 28 and FPQ 36 have adopted the same orientation with the norfloxacine (NF) and pefloxacine (PF) (Figure 7b). The compounds FPQ 50, FPQ 30, Q 83, Q 85 have adopted the same orientation with the compound FPQ 33, compound with the better predicted activity against *Streptococcus pneumoniae* (Figure 7c).

Important molecular properties: molecular weight, flexible bonds, the number of hydrogen bond donors, the number of hydrogen bond acceptors and log P have been calculated (Table 3). These parameters can predict if a molecule possesses properties that might turn it into an oral active drug, according to the Lipinski's rule of five [30]. The number of violations of the Lipinski rules allows to evaluate drug likeness for a molecule. According to the data presented in Table 3, two fluoroquinolones (Q 85 and FPQ 30) failed to respect one parameter (Log P >5) of the Lipinski Rules (Lipinski violation is 1).

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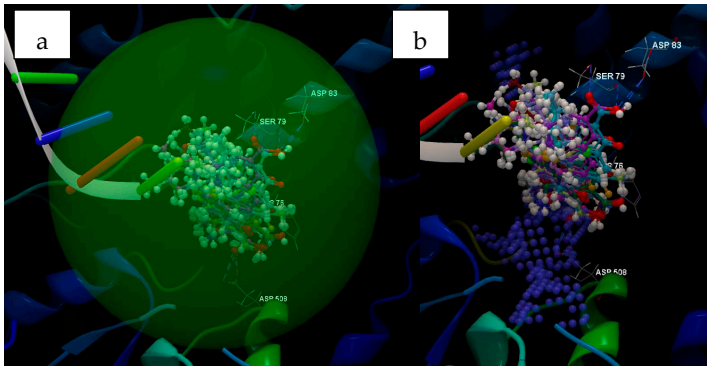

Figure 6. (a) Docking pose of the all compounds in the binding site of 3FOE; (b) Binding pocket and docking pose of the all compounds.

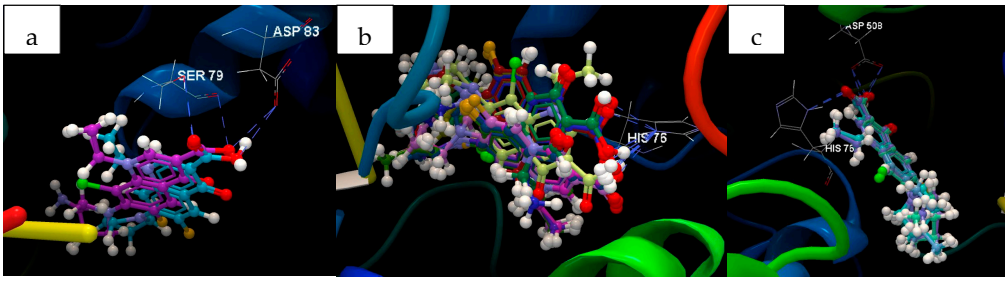

Figure 7. (a)Docking pose of the compound with the same orientation of the co-crystallized NF; (b)Docking pose of the compounds with the same orientation of the NF and PF; (c) Docking pose of the compounds with the same orientation of the FPQ 33.

Table 3. Calculated properties of ligands.

Compound	Atoms	Weight [Daltons]	Flexible bonds	Lipinski violations	Hydrogen donors	Hydrogen acceptors	Log P
NFX	42	365.79	3	0	3	6	0.82
NF	41	319.33	3	0	2	6	0.48
FPQ50	41	353.78	3	0	2	6	1.11
PF	44	333.36	3	0	1	6	0.95
FPQ51	44	367.80	3	0	1	6	1.57
FPQ27	44	333.36	3	0	2	6	0.91
FPQ29	44	367.80	3	0	2	6	1.54
FPQ35	39	304.32	3	0	1	5	3.90
FPQ36	39	338.76	3	1	1	5	4.53
FPQ32	42	318.34	3	0	1	5	4.26
FPQ33	42	352.79	3	1	1	5	4.89
Q83	45	332.37	3	1	1	5	4.70
Q85	45	366.81	3	1	1	5	5.32
FPQ24	45	332.37	3	1	1	5	4.70
FPQ30	45	366.81	3	1	1	5	5.32
FPQ25	40	320.32	3	0	1	6	3.04
FPQ28	40	354.76	3	0	1	6	3.67

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4. Conclusions

In silico molecular docking simulations have been performed to position all fluoroquinolone compounds into the preferred binding site of the protein receptor *Streptococcus pneumoniae*, to predict the binding modes, the binding affinities and the orientation of all ligands, corelating with the co-crystallized NFX. Molecular docking studies have been carried out relating also to some quinolone compounds known in medical therapeutics, norfloxacin and pefloxacin. The docking studies revealed that all compounds showed good docking score (Figure 8). The docking score is a measure of the antimicrobial activity of the studied compounds.

The studies presented in this paper show the importance of molecular docking approaches in the design and development of new compounds with biological activity. The prediction of the binding affinity of a new compound (ligand) to an identified target (protein/enzyme) is a significant parameter in the development of a new drug. The prediction of the binding mode of a ligand (a new compound) to the target (protein/enzyme) by molecular simulation would allow restricted the synthesis to the most promising compounds.

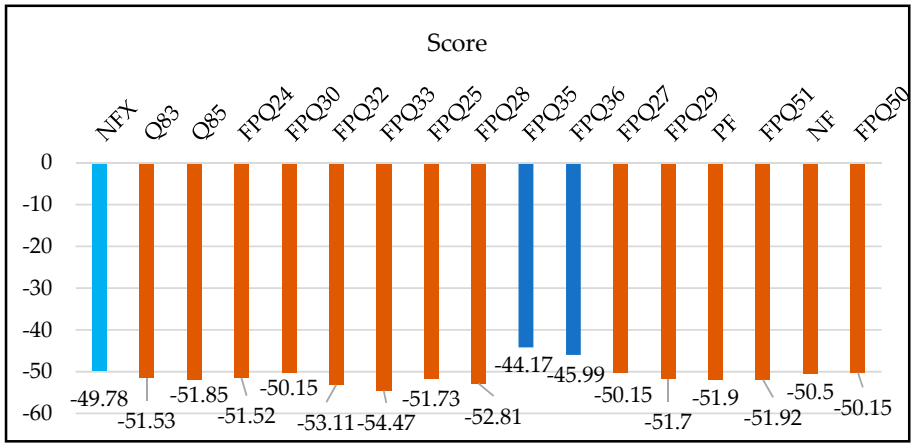

Figure 8. Docking score of fluoroquinolone compounds.

Author Contributions: L.P coordinated the study. L.P and A.S carried out design and molecular docking studies and contributed to the writing of the manuscript.

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Conflicts of Interest: "The authors declare no conflict of interest."

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Sample Availability: Samples of the compounds are available from the authors.