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Original Article

AN *IN SILICO* STUDY OF NOVEL FLUOROQUINOLONES AS INHIBITORS OF DNA GYRASE OF *STAPHYLOCOCCUS AUREUS*

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ABSTRACT

Objective: This study is an attempt to identifying an effective fluoroquinolones (FQ) s against *STAPHYLOCOCCUS AUREUS (S. aureus)* by *in silico* analysis of 150 (FQ) compounds using iGemDock v2.1 tool.

Methods: Structure of DNA gyrase (2XCT) was retrieved from the Protein Data Bank (PDB) and the structures of (FQ) compounds were selected from literature survey of 400 novel compounds and the physical, chemical and molecular characteristics of each compound were obeyed for drug-relevant properties based on "Lipinski's rule of five, then a total of 150 (FQ)s were docked against the protein of the 2XCT enzyme.

Results: From this study, it was found that the compound (1) [(3*R*,7*E*)-9-fluoro-7-(isonicotinoylhydrazono)-3-methyl-10-(4-methylpiperazin-1-yl)-2,3-dihydro-7*H*-[1,4]oxazino[2,3,4-*ij*]quinoline-6-carboxylic acid] and the compound (2) [1-cyclopropyl-6-fluoro-7-{4-[(8-hydroxyquinolin-2-yl)methyl]piperazin-1-yl}-4-oxo-1,4-dihydroquinoline-3-carboxylic acid] showed the best interaction value against 2XCT enzyme, the binding energy was (-104. 58 kcal/mol), (-26. 5kcal/mol) respectively whereas the reference ciprofloxacin (CIP) was (-74. 33 kcal/mol).

Conclusion: Further *in vitro* studies of these compounds against the enzyme will lead a new pathway to drug discovery.

Keywords: *S. aureus*, (FQ)s, 2XCT, DNA gyrase, Lipinski's rule, iGemdock, *In silico.*

INTRODUCTION

S. aureus is an opportunistic, anaerobic Gram-positive coccal pathogen, found on the mucous membranes and the human skin, which shows extreme adaptability to antibiotic pressure [1]. It can cause a range of illnesses from minor skin infections to life-threatening diseases [2], and it is still one of the five most common causes of nosocomial infection and community-acquired *methicillin-resistant S. aureus (MRSA)* [3]. Today, the spread of multi-resistant bacteria becomes major concern in the hospital environment, where the glycopeptides, vancomycin and teicoplanin are considered as the last resort drugs against *(MRSA)* [4-6]. Therefore, the search for new structural ligands and novel targets of attack as a means to overcome bacterial resistance is an important research goal [7, 8].

Modern approaches toward development of new potential inhibitors are based on knowledge of structure and function of proteins specific to bacteria like DNA gyrase which is member of the topoisomerase enzymes that are able to relax supercoiled DNA in a reaction coupled to the hydrolysis of ATP [9,10], whereas it is characteristic and essential bacterial enzyme when it is inactivated, it leads to bacterial cell death. For this reason, gyrases have been chosen as targets for antibacterial agents [11-13]. DNA gyrase consists of two subunits, A and B, of molecular mass 97 and 90 kDa, respectively, with the active enzyme being an A2B2 complex. The A subunit of DNA gyrase is involved in DNA breakage and reunion while the B subunit catalyzes the hydrolysis of ATP [14, 15]. There are many agents that target this enzyme such as (FQ)s coumarins, and cyclothialidines while all have their own limitations [16]. (FQs), e.g., ciprofloxacin, inhibit the DNA breakage-reunion cycle by forming a constant complex with DNA and the enzyme DNA gyrase [17]. They have gained immense importance during the last two decades because of their potent antibacterial activity against wide varieties of gram-positive and gram-negative pathogenic bacteria with minimum toxic side effects [18, 19]. The (FQs) were introduced in 1980s, they have a relatively simple molecular nucleus which consists of a bicyclic ring structure, and there is a substitution at position N-1, a carboxyl group at position 3, a keto group at position 4, a fluorine atom at position 6 and a nitrogen heterocyclic moiety at the C-7 position [20-23]. To date, many (FQ)s as antibacterial agents have been developed and synthesized to be used in clinical trials with significant improvement in the antibacterial spectrum and activity [24].

In silico methods are used to analyze the target structures for possible binding sites, generate candidate molecules, check for their drug-likeness, dock these molecules with the target, rank them according to their binding affinities, and further optimize the molecules to improve binding characteristics [25]. This work is an attempt to survey a number of novel (FQ)s that are synthesized in the last years, then do a virtual screening that allows studying the compounds *in silico* and comparing them with the reference and select, theoretically, the best compounds based on binding energy as inhibitors of DNA gyrase of *S. aureus*.

MATERIALS AND METHODS

Protein preparation

The receptor enzyme, required for the docking study that related to *S. aureus* has been retrieved from the(PDB) which is a key resource in areas of structural biology, and it is a fundamental repository for 3D structure data of large molecules [26]. The enzyme PDB ID-2XCT [27-30] was designated on this site and it had a resolution factor 3.35 A°. The enzyme was downloaded then saved in pdb file format and the 3D of it was shown in fig. 1. We defined the active site of (2XCT) based on the x-ray complex structure of protein (2XCT) and binding ligand (CIP), fig. 2, whereas that ligand was discovered and developed by Bayer A. G. and subsequently approved by the US Food and Drug Administration (FDA) in 1987, and it was the most widely used of the second-generation of (FQ)s antibiotic that came into clinical use in the late 1980s and early 1990s [31, 32].

Generation and optimization of ligands

The (FQ) s, fig. 3, which was reported here, had been selected after an extensive literature survey. In fact, we had selected a total of 400 new compounds of (FQ)s [33,34,35-40,41,42,65], and they were drawn in the two-dimensional (2D) structures using ACD chemsketch software [66]. Then the compounds were saved in mol

format and converted to mol2 format using the OPEN BABEL software [67]. After that a total of 150 (FQ) compounds had been selected for *in silico* study based on "Lipinski's rule of five"[68-69], where the molecular properties such as cLogp, number of hydrogen bond donors and acceptors and polar surface area were obtained from: www.molinspiration.com [70].

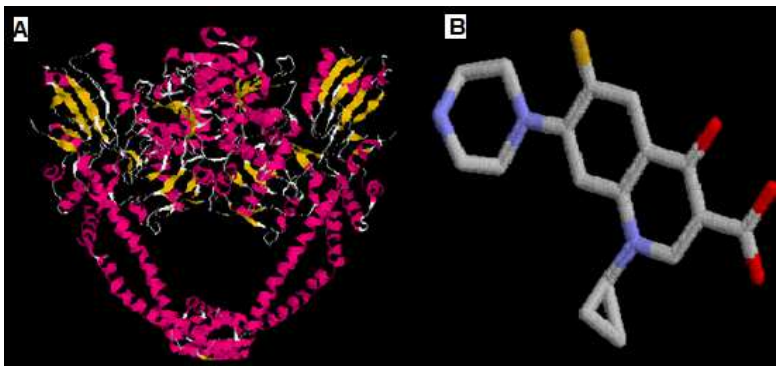


Fig. 1: (A) 3D structure of 2XCT protein, (B) the reference ligand (ciprofloxacin)

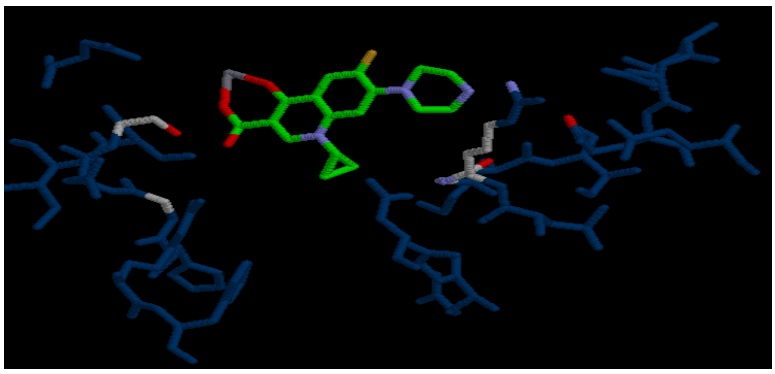


Fig. 2: 3D Binding site of 2XCT with reference inhibitor (Ciprofloxacin)

Fig. 3: the parent structure of fluoroquinolones

Protein-ligand docking

In this research, we used iGemdock software [71, 73] to dock the enzyme (2XCT) with 150 (FQ)s, which it is available for free and was used in various previous researches [74-77].

iGemdock v2. 1

In order to carry out docking simulation of the enzyme (2XCT) with 150 (FQ)s, we used the iGemdock v2. 1 as molecular docking tool. iGemdock is an integrated virtual screening (VS) environment from preparations through post-screening analysis with pharmacological interactions. iGemdock generates protein-compound interaction profiles by providing interactive interfaces to prepare both the binding site of the target enzyme and the screening compounds library. Then each compound in the library is docked into the binding site by using the in-house docking tool iGemdock. Afterward, iGemdock infers the pharmacological interactions and clusters the screening compounds for the post-screening analysis based on profiles of electrostatic (E), hydrogen-bonding (H), and Van der Waal's (V) interactions and compound structures. Finally, iGemdock ranks and visualizes the screening compounds by combining the pharmacological interactions and energy-based-scoring function of iGemdock.

Virtual screenings of the 150 compounds were performed in the docking tool iGemdock. The docking consisted protocol "accurate docking" by setting population size of 800 is set with 80 generations and 10 solutions. After the completion of the docking, the post-docking analysis was performed to find the docking pose and its energy values. The empirical scoring function of iGemdock was estimated using:

Energy = vdW+Hbond+Elec

Here, the vdW term is van der Waal energy; H bond and Elect terms are hydrogen bonding, energy, and electro statistic energy, respectively.

Table 1 illustrates the structure of 30 studied compounds and shows the structure and the IUPAC name of the compounds.

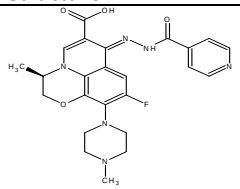
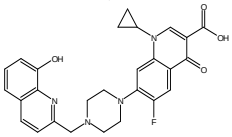
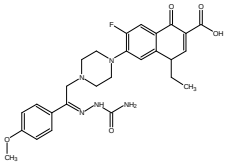
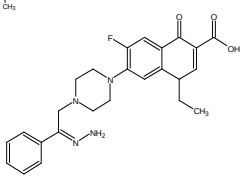
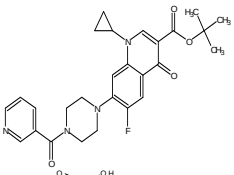
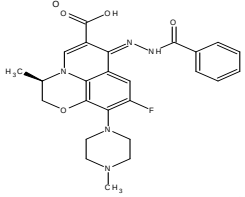
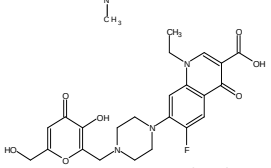
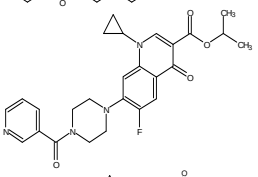
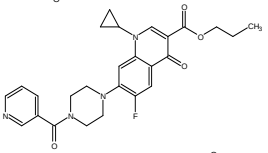
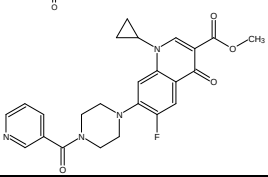
RESULTS AND DISCUSSION

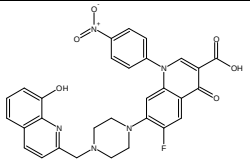
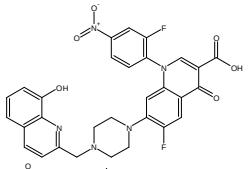
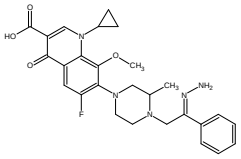
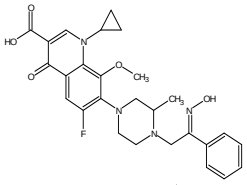
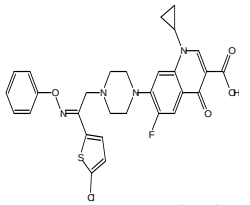
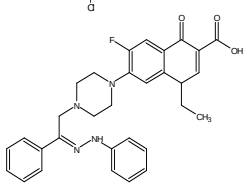
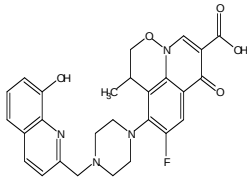
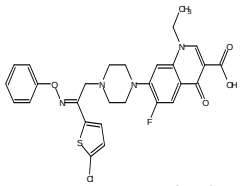
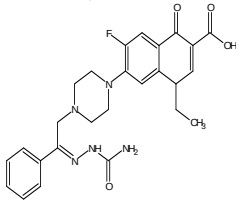
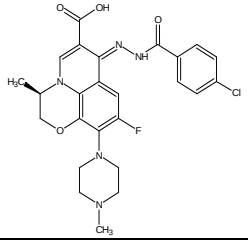
In silico docking is the best approach to check utility of any chemical as a drug before going through any *in vivo* or *in vitro* analysis to shorten out the experiments and cost cutting. A literature survey was done for new compounds of (FQ)s, then a total of 150 compounds were selected based on Lipinski's rule of five and they were docked against the enzyme DNA gyrase of *S. aureus* using iGemdock to understand its interactive analysis before they have been proposed to study its *in vitro* antibacterial activity.

The objective of the current work is to evaluate the theoretical antibacterial activity against *S. aureus* of the novel (FQ)s that have been synthesized in recent years by using the docking studies. In this perspective, synthesized compounds like that mentioned in table (1) were selected and (CIP), a known DNAgyrase inhibitor, was used as the standard, and then the docking studies were performed using iGemdock v2. 1, and the

results displayed that all the selected (FQs) showed lesser binding energy ranging between (-104. 58 kcal/mol) to (-47.33 kcal/mol) as it shows in table 2 when compared with the standard (-74.33 kcal/mol). So, these molecular docking analyses could deliver the most potent 2XCT inhibitors for the prevention and treatment of infections caused by *S. aureus.*

Table 1: The structure of 30 screened fluoroquinolone compounds

S. No.	IUPAC name	Structure	Ref.
1	(3*R*,7*E*)-9-fluoro-7-(isonicotinoylhydrazono)-3-methyl-10-(4-methylpiperazin-1-yl)-2,3-dihydro-7*H*-[1,4]oxazino[2,3,4-*ij*]quinoline-6-carboxylic acid		62
2	1-cyclopropyl-6-fluoro-7-{4-[(8-hydroxyquinolin-2-yl)methyl]piperazin-1-yl}-4-oxo-1,4-dihydroquinoline-3-carboxylic acid		43
3	6-{4-[(2*Z*)-2-[(aminocarbonyl)hydrazono]-2-(4-methoxyphenyl)ethyl]piperazin-1-yl}-4-ethyl-7-fluoro-1-oxo-1,4-dihydronaphthalene-2-carboxylic acid		64
4	4-ethyl-7-fluoro-6-{4-[(2*Z*)-2-hydrazono-2-phenylethyl]piperazin-1-yl}-1-oxo-1,4-dihydronaphthalene-2-carboxylic acid		64
5	*tert*-butyl 1-cyclopropyl-6-fluoro-4-oxo-7-[4-(pyridin-3-ylcarbonyl)piperazin-1-yl]-1,4-dihydroquinoline-3-carboxylate		46
6	(3*R*,7*E*)-7-(benzoylhydrazono)-9-fluoro-3-methyl-10-(4-methylpiperazin-1-yl)-2,3-dihydro-7*H*-[1,4]oxazino[2,3,4-*ij*]quinoline-6-carboxylic acid		62
7	1-ethyl-6-fluoro-7-(4-{[3-hydroxy-6-(hydroxymethyl)-4-oxo-4*H*-pyran-2-yl]methyl}piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid		63
8	isopropyl 1-cyclopropyl-6-fluoro-4-oxo-7-[4-(pyridin-3-ylcarbonyl)piperazin-1-yl]-1,4-dihydroquinoline-3-carboxylate		46
9	propyl 1-cyclopropyl-6-fluoro-4-oxo-7-[4-(pyridin-3-ylcarbonyl)piperazin-1-yl]-1,4-dihydroquinoline-3-carboxylate		46
10	methyl 1-cyclopropyl-6-fluoro-4-oxo-7-[4-(pyridin-3-ylcarbonyl)piperazin-1-yl]-1,4-dihydroquinoline-3-carboxylate		58

11	6-fluoro-7-{4-[(8-hydroxyquinolin-2-yl)methyl]piperazin-1-yl}-1-(4-nitrophenyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid		43
12	6-fluoro-1-(2-fluoro-4-nitrophenyl)-7-{4-[(8-hydroxyquinolin-2-yl)methyl]piperazin-1-yl}-4-oxo-1,4-dihydroquinoline-3-carboxylic acid		43
13	1-cyclopropyl-6-fluoro-7-{4-[(2*E*)-2-hydrazono-2-phenylethyl]-3-methylpiperazin-1-yl}-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid		60
14	1-cyclopropyl-6-fluoro-7-{4-[(2*E*)-2-(hydroxyimino)-2-phenylethyl]-3-methylpiperazin-1-yl}-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid		60
15	7-{4-[(2*E*)-2-(5-chloro-2-thienyl)-2-(phenoxyimino)ethyl]piperazin-1-yl}-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid		46
16	4-ethyl-7-fluoro-1-oxo-6-{4-[(2*Z*)-2-phenyl-2-(phenylhydrazono)ethyl]piperazin-1-yl}-1,4-dihydronaphthalene-2-carboxylic acid		65
17	5-fluoro-4-{4-[(8-hydroxyquinolin-2-yl)methyl]piperazin-1-yl}-3-methyl-7-oxo-2,3-dihydro-7*H*-[1,2]oxazino[4,3,2-*ij*]quinoline-8-carboxylic acid		43
18	7-{4-[(2*E*)-2-(5-chloro-2-thienyl)-2-(phenoxyimino)ethyl]piperazin-1-yl}-1-ethyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid		46
19	6-(4-{(2*Z*)-2-[(aminocarbonyl)hydrazono]-2-phenylethyl}piperazin-1-yl)-4-ethyl-7-fluoro-1-oxo-1,4-dihydronaphthalene-2-carboxylic acid		65
20	(3*R*,7*E*)-7-[(4-chlorobenzoyl)hydrazono]-9-fluoro-3-methyl-10-(4-methylpiperazin-1-yl)-2,3-dihydro-7*H*-[1,4]oxazino[2,3,4-*ij*]quinoline-6-carboxylic acid		62

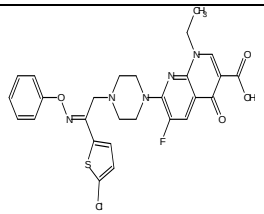
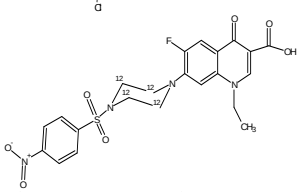
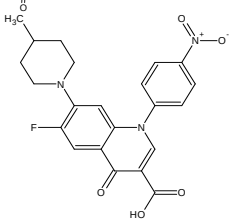
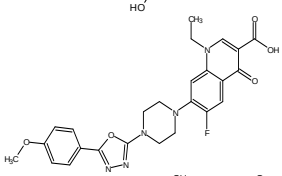
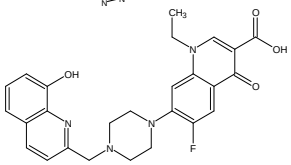
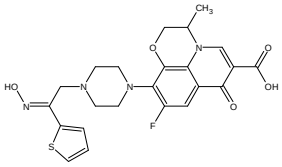
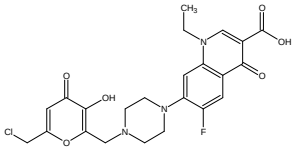
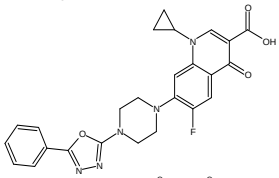
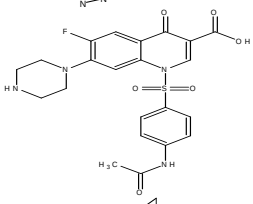
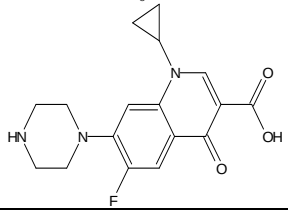
21	7-{4-[(2*E*)-2-(5-chloro-2-thienyl)-2-(phenoxyimino)ethyl]piperazin-1-yl}-1-ethyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid		46
22	1-ethyl-6-fluoro-4-oxo-7-[4-(phenylsulfonyl)piperazin-1-yl]-1,4-dihydroquinoline-3-carboxylic acid		36
23	6-fluoro-7-(4-methylpiperidin-1-yl)-1-(4-nitrophenyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid		48
24	1-ethyl-6-fluoro-7-{4-[5-(4-methoxyphenyl)-1,3,4-oxadiazol-2-yl]piperazin-1-yl}-4-oxo-1,4-dihydroquinoline-3-carboxylic acid		57
25	1-ethyl-6-fluoro-7-{4-[(8-hydroxyquinolin-2-yl)methyl]piperazin-1-yl}-4-oxo-1,4-dihydroquinoline-3-carboxylic acid		43
26	9-fluoro-10-{4-[(2*E*)-2-(hydroxyimino)-2-(2-thienyl)ethyl]piperazin-1-yl}-3-methyl-7-oxo-2,3-dihydro-7*H*-[1,4]oxazino[2,3,4-*ij*]quinoline-6-carboxylic acid		59
27	7-(4-{[6-(chloromethyl)-3-hydroxy-4-oxo-4*H*-pyran-2-yl]methyl}piperazin-1-yl)-1-ethyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid		63
28	1-cyclopropyl-6-fluoro-4-oxo-7-[4-(5-phenyl-1,3,4-oxadiazol-2-yl)piperazin-1-yl]-1,4-dihydroquinoline-3-carboxylic acid		57
29	1-{[4-(acetylamino)phenyl]sulfonyl}-6-fluoro-4-oxo-7-piperazin-1-yl-1,4-dihydroquinoline-3-carboxylic acid		50
30	1-cyclopropyl-6-fluoro-4-oxo-7-piperazin-1-yl-1,4-dihydroquinoline-3-carboxylic acid		54

Table 2: The docking binding energy values results using iGemdock

S. No.	VW. force (kcal/mol)	H Bond (kcal/mol)	Elec. energy (kcal/mol)	Total binding energy(kcal/mol)
1	-90.19	-14.49	0.1	-104.58
2	82.98	-18.42	0	-101.4
3	-68.74	-31.14	-1.45	-101.33
4	-73.13	-24.95	-1.15	-99.22
5	-82.91	-15.62	0	-98.52
6	-88.58	-9.63	0.16	-98.04
7	-89.07	-6.6	0	-95.67
8	-80.42	-15.17	0	-95.59
9	-79.28	-16.19	0	-95.57
10	-78.05	-16.58	0	-94.62
CIP	-60.38	-15.88	1.92	-47.33

Post-screening analysis

All the (FQ)s in the post-screening analysis PDB ID-2XCT, in comparison to the reference (CIP), were as potential antibacterial drugs of *S. aureus* with good docking energy with the target protein especially the compound No. 1[(3*R*,7*E*)-9-fluoro-7-(isonicotinoyl-hydrazono)-3-methyl-10-(4-methylpiperazin-1-yl)-2,3-dihydro-7*H*-[1,4]oxazino[2,3,4-*ij*]quinoline-6-carboxylic acid] and the compound No.2 [1-cyclopropyl-6-fluoro-7-{4-[(8-hydroxyquinolin-2-yl)methyl] piperazin-1-yl}-4-oxo-1,4-dihydroquinoline-3-carboxylic acid] which they had better drug activity, as they showed the most favorable binding energy whereas the first compound binds to DNA gyrase with high binding affinity (-104. 58 kcal/mol) and the second (-101. 4 kcal/mol). Our study showed that the compound No. 1 that was synthesized in 2013 by (Sahu Susanta K., Pandeya Surendra N.) and it evaluated as a new inhibitor of *E coli*. Whereas the compound No. 2 was synthesized in 2005 by(Yue-Ling Zhao, Yeh-Long Chen, *et al.*) as anti tubercular agent. Here in this study they were good agents against DNA gyrase of *S. aureus* based on binding energies, in comparison to the (CIP). Also the compound (3) [6-{4-[(2*Z*)-2-[(aminocarbonyl) hydrazono]-2-(4-methoxyphenyl)ethyl] piperazin-1-yl}-4-ethyl-7-fluoro-1-oxo-1,4dihydronaphthalene-2-carboxylic acid] and the compound (4) [4-ethyl-7-fluoro-6-{4-[(2*Z*)-2-hydrazono-2-phenylethyl] piperazin-1-yl}-1-oxo-1, 4-dihydro-naphthalene-2-carboxylic acid] that were synthesized in 2014 by (Mehul M. Patel and Laxman J. Patel) disappeared an acceptable energies, so they could be an effective against *S. aureus*.

The interactions and fitness scores of the compound suggest that these compounds can as an antimicrobial activities drug against gram-positive *S. aureus.*

Table 3 shows residues that are associated with the amino acids in the binding site of the compound No. 1 that it was the best in Elec energy and the reference. Fig. 4 illustrates the interactions of the compound No. 1 with protein pocket which have the most favorable binding energy.

Table 3: Pharmacological interactions and Residues involved in the binding site

PDB ID	Predicted pharmacologic interactions	Compound 1	CIP
	H-M GLU 435	-3.5	0
2XCT	H-S GLU 435	-3.5	0
	H-S ASP 437	-4.2	0
	H-S LYS 460	0	-3.5
	H-S ASN 475	0	-6.2
	H-S ARG 1122	-3.3	-12
	V-M GLU 435	-7.7	-6.1
	V-S GLU 435	-7.5	6.6-
	V-M GLY 436	-14.4	11.4-
	V-M ASP 437	-16.6	0
	V-S ASP 437	-12.8	3.6-
	V-M ARG 458	0	-3.2

The green and grey color represents the amino acids involved in(H)hydrogen bonding and(V) van der Waals are interaction types M and S are Main chain and Side chain.

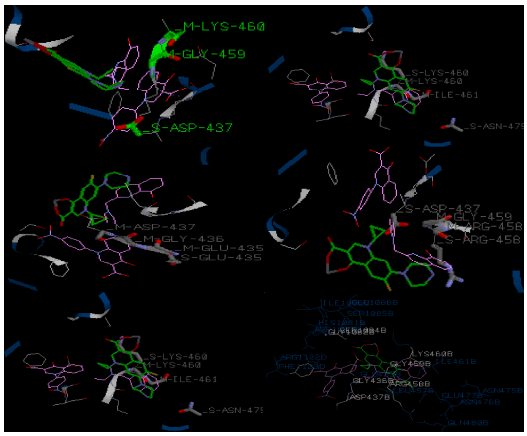


Fig. 4: The compound (1) with the reference CIP and their interactions with the amino acids of the binding site

Lipinski's rule

Lipinski *et al.* formulated the 'Rule of Five' to predict drug-likeness, which consists of four important properties, each related to the number 5. The rule is based on data in the literature for a large number of compounds, including all known drugs that correlate physical properties with oral bioavailability. The compounds are more likely to be membrane permeable and easily absorbed by the body if it matches the following criteria:

1. The molecular weight of less than 500 mg/mol

2. Has a high lipophilicity (log p less than 5)

3. Hydrogen bond donors less than 5

4. Hydrogen bond acceptor is less than 10

The rule describes molecular properties important for a drug's pharmacokinetics in the human body, including their Absorption, Distribution, Metabolism, and Excretion (ADME). The rule is important for drug development where a pharmacologically active lead structure

is optimized step-wise for increased activity and selectivity, as well as drug-like properties as described by Lipinski's rule.

The table 4 depicts the values related to the Lipinski's rule of five. From the table it is evident that all the ten studied compounds obey the Lipinski's rule. The molecular docking studies and Lipinski's rules facilitate drug development avoiding expensive post clinical experiments.

Veber rule and molar refractivity

1-Veber Rule: In particular, compounds which meet only the two criteria of:

a) Rotatable bond count≤10.

b) Polar surface area (PSA) equal to or less than 140 Å2 are predicted to have good oral bioavailability.

2-Molar Refractivity: between (40-130) is used as measurement of the real volume of the molecule and it is also related to the forces which govern the ligand-receptor interactions [79].

The 10 high ranked lead molecules were prioritized to follow Lipinski's guidelines of five, veber rule and molar refractivity based on the likeliness drug properties are listed in table 4.

Table 4: The Lipinski's and Veber properties of the selected 10 ligands

S. No.	Molecular Formula[1]	M W[2]* g/mol	logP[2#]	HD[2*]	HA[2*]	RB[2*]	PSA[2]	MR[1*]
	Value to be	**500<**	**5<**	**5<**	**10<**	**=10<**	**<140**	**40-130**
1	$C_{25}H_{26}FN_5O_4$	480.49	-1.43	2	9	4	112.30	126.4
2	$C_{27}H_{30}FN_5O_5$	488.51	0.679	2	8	5	98.90	130.4
3	$C_{27}H_{30}FN_5O_5$	464.5	1.22	2	7	6	137.56	137.01
4	$C_{25}H_{27}FN_4O_3$	450	0.735	2	7	6	99.23	122.69
5	$C_{27}H_{29}FN_4O_4$	492.5	2.09	0	7	6	84.75	129.19
6	$C_{25}H_{25}ClFN_5O_4$	479.50	-0.28	2	8	4	99.41	131.04
7	$C_{23}H_{24}FN_3O_2$	473.451	-2.331	3	10	6	136.45	115.42
8	$C_{26}H_{27}FN_4O_4$	478.5	2.69	0	7	6	84.75	125.27
9	$C_{26}H_{27}FN_4O_4$	478.51	2.84	0	7	5	84.75	125.32
10	$C_{27}H_{25}FN_4O_4$	450.46	1.97	0	7	5	84.75	128.74
CIP	$C_{17}H_{18}FN_3O_3$	331.34	-1.27	2	6	3	74.57	83.25

1-Calculated by ACD (Available Chemical Directory) 2-calculated by: www. molinspiration. Com, *PSA: Polar Surface Area,*MW: Molecular weight, *HD: H bond donor, *HA: H bond acceptor. *RB: rotatable bonds. *MR: Molar refractivity#Octanol/Water partition coefficient

CONCLUSION

The present study has given an insight into the searching of new fluoroquinolones as DNA gyrase of *S. aureus* inhibitors. Various *in silico* tools like Lipinski filter and molecular docking has been utilized to select the best compounds as antibacterial inhibitors of *S. aureus* whereas the synthesized derivative [(3*R*,7*E*)-9-fluoro-7-(isonicotinoyl-hydrazono)-3-methyl-10-(4-methylpiperazin-1-yl)-2,3-dihydro-7*H*-[1,4]oxazino[2,3,4-*ij*]quinoline-6-carboxylic acid] showed good antibacterial activity theoretically, then further *in vitro* studies should be applied to evaluate the biological activity. Thus, the *in silico* study has been helpful in promising molecules enabling the minimization of time spend for searching compounds and can be considered as good method for screening of novel fluoroquinolones to target another enzyme.

ABBREVIATION

(FQ)s: Fluoroquinolones (*S. aureus*: *S staphylococcus aureus*, *MRSA: Methicillin-Resistant S. Aureus*, CIP: Ciprofloxacin, iGemdock: iGeneric Evolutionary Method Docking, PDB: Protein Data Bank, ADME: Absorption, Distribution, Metabolism, and Excretion

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CONFLICT OF INTERESTS

Declared None

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