(RESEARCH ARTICLE)

Synthesis and *In-silico* design of a novel silver metal ciprofloxacin compound

Sudhanshu Kumar Jha [1, *], Sneep Kumar Chaturvedi [2], Shivam Kumar Singh [3], Sunny Chauhan [1], Prince Chauhan [4], Amit [2], Harshit Singh [5] and Chaitanya Kumar [5]

[1] Department of Pharmaceutical sciences, Maharshi Dayanand University, Rohtak, Haryana, India.
[2] Department of Pharmaceutical sciences, Kurukshetra University, Thanesar, Haryana, India.
[3] Department of Pharmaceutical sciences, Lovely Professional University, Phagwara, Punjab, India.
[4] Department of Pharmaceutical sciences, IIMT University, Meerut, Uttar Pradesh, India.
[5] Department of Pharmaceutical sciences, Siddhartha Group of institutions, Dehradun, Uttarakhand, India

Abstract

Ciprofloxacin is a quinolone derivative with antibacterial properties. Quinolones, which share structural similarities with nalidixic acid, function as unidentate, bidentate, and bridging ligands during chelation. A key factor in increasing quinolones' biological activity is the presence of metal ions. Many transition metals, including Ni^{2+}, Co^{2+}, Ca^{2+}, Zn^{2+}, Ag^{2+}, Au^{2+}, Mn^{2+}, Mg^{2+}, and Fe^{2+}, are often utilised as chelating agents. The ciprofloxacin silver ions was developed in the current study and then compared with two standard medications (ciprofloxacin and norfloxacin) and evaluated for *in-silico* investigations using (PDB ID: 2XCT). It was shown that the silver metal of the ciprofloxacin Analogue (L1) had a higher docking score and glide energy when compared to two standard medications like, norfloxacin and ciprofloxacin respectively. It has been demonstrated in *in-silico* studies that the synthesised novel silver metal of the ciprofloxacin analogue (L1) has significant potency against a wide range of bacterial and fungal diseases, making it an essential source for new antibacterial drugs that target bacterial and fungal diseases in the future.

Keywords: Silver metal ion; Ciprofloxacin Analogue (L1); *In-silico* design; Schiff base; Docking result; Glide energy.

1. Introduction

Antibiotics are chemical substances that either eradicate or prevent bacterial growth [1]. Penicillin, cephalosporin, tetracycline, fluoroquinolone, aminoglycoside, quinolone, streptogramin, and sulphonamide are just a few of the various families into which the antibiotics that have been discovered so far are divided [2]. The increased antibacterial activity of transition metal complexes with quinolones has been the subject of several researches [3-6]. Ciprofloxacin, a synthetic fluoroquinolone antibiotic with a broad spectrum of activity, is 1-cyclopropyl-6-flouro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3 quinolone carboxylic acid. The bacterial DNA gyrase, which is necessary for DNA replication, is inhibited by ciprofloxacin [7], and it has been postulated that intermediates of metal complexes are involved in this action [8, 9]. The complexation of the compounds with a metal ion increases their stability and adaptability, and the Schiff's base provides a greater range of options and flexibility. In this study, the ciprofloxacin-containing keto group and carboxylic acid group were combined to produce the Schiff base, which was then complexed with silver metal ions. Fig.1 depicts the ciprofloxacin imine's structural breakdown. The antibacterial and antifungal activity of the novel studied chemical and its metal complex was assessed against bacterial and fungal strains.

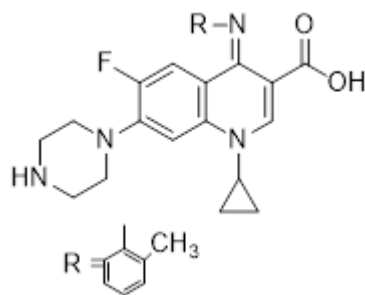* Corresponding author: Sudhanshu Kumar Jha[1]

Figure 1 Ciprofloxacin imines (Ligand)

Ciprofloxacin is a derivative of the quinolone, which has antibacterial activity, and Norfloxacin is the first antibiotic of the fluoroquinolone family. Pseudomonas aeruginosa, Haemophilus influenzae, and Neisseria gonorrhoeae are among the gram-negative enteric bacteria that ciprofloxacin and norfloxacin are effective against.Staphylococcus spp., particularly methicillin-resistant Staph. aureus, responds well to ciprofloxacin. In general, norfloxacin is less effective than ciprofloxacin, especially when used to treat Ps. aeruginosa and Staph. aureus. One to two hours after each medicine has been taken orally, peak concentrations happen. Both medications are widely metabolised, excreted by the kidneys, and dispersed throughout bodily tissues and fluids. In cases of serious renal impairment, dosage reductions are necessary. Both ciprofloxacin and norfloxacin are powerful medications for treating infections of the urinary tract, particularly those brought on by Pseudomonas aeruginosa. Adults should take 400 mg of norfloxacin orally every 12 hours to treat urinary tract infections; simple infections should be treated for 7 to 10 days, and severe infections should be treated for 10 to 21 days. The fluoroquinolones might be helpful in the management of persistent bacterial prostatitis. The antibiotic ciprofloxacin has the potential to be helpful in the treatment of STDs. Chlamydia spp. and N. gonorrhoeae, including strains that produce beta-lactamases and are tetracycline-resistant, are both susceptible to the antibiotic ciprofloxacin. It is promising to use ciprofloxacin to treat gastrointestinal infections and to decontaminate the gastrointestinal system only when necessary [10].

2. Material and methods

2.1. Synthesis of ciprofloxacin imine or Schiff base (L$_1$):

It took 4 hours to boil ciprofloxacin (0.03 mol; 9.9 g) and o-toluidine (0.03 mol; 3.2 ml) in a methanolic solution in the presence of glacial acetic acid. On a water bath, the concentrated solution was placed and allowed to cool at 0 °C. Filtered colored solid was then dried after being rinsed with methanol and ethanol. Figure 2 shows a schematic of the synthesis [11].
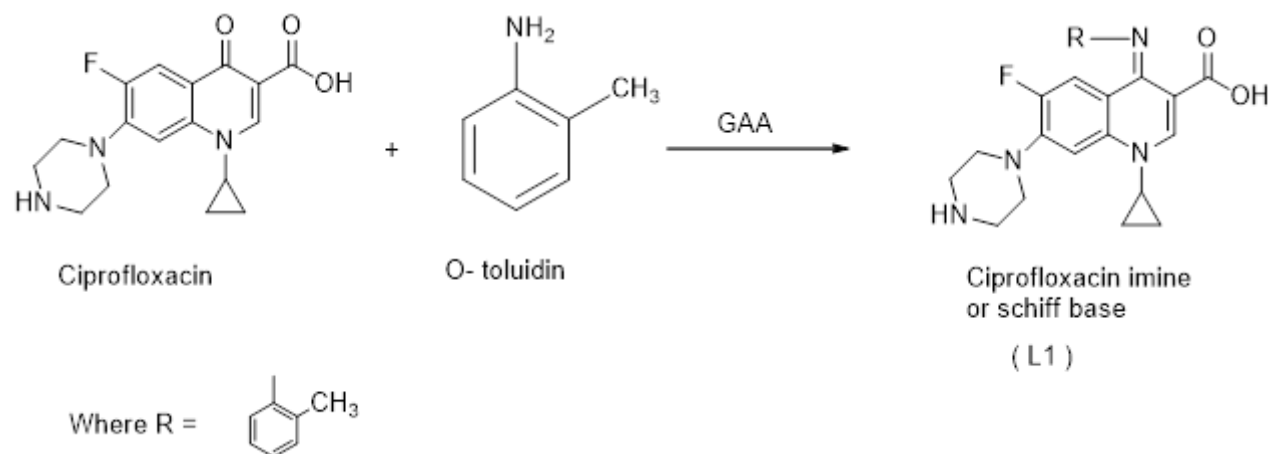

Figure 2 Synthesis scheme of ciprofloxacin imine or Schiff base (L$_1$)

2.2. Molecular docking

By simulating the interaction between a tiny molecule and a protein at the atomic level, the molecular docking method enables us to characterise how small molecules behave at the binding site of target proteins and to better understand fundamental biological processes [12]. The completion of the human genome project has opened up a growing number

of novel therapeutic targets for drug development. The study of a number of structural characteristics of proteins and protein-ligand complexes has also been aided by the advent of nuclear magnetic resonance spectroscopy, crystallography, and high-throughput protein purification techniques. Due to these advancements, computational approaches can now be applied across the entire drug discovery process [13–17]. The two primary steps in the docking procedure are prediction of the ligand structure, as well as its positioning and orientation within these sites (often referred to as pose), and assessment of the binding affinity. The sample methods and scoring frameworks that will be discussed in the theory section are impacted by these two actions. Knowing the location of the binding site before doing any docking operations considerably increases the efficiency of those processes. The binding site is typically known before ligands are docked into it; by knowing the binding site's position before docking processes, efficiency is considerably increased. The binding site is typically known prior to docking ligands into it. One can also learn more about the sites by contrasting the target protein with a family of proteins that carry out a similar function or with proteins that have been co-crystallized with various ligands. Further information about the sites can be obtained by comparing the target protein to a family of proteins that share a similar function or to proteins that have been co-crystallized with various ligands. Software or internet services like GRID [18–19], POCKET [20], Surf Net [21–22], PASS [23], and MMC [24] that detect cavities without knowing the binding locations.

2.3. Examples of the application of molecular docking to the discovery of new drugs

Molecular docking has been the approach that has been utilised most frequently. There have been some remarkable accomplishments in this field, despite the fact that its principal application is in structure-based virtual screening to discover novel compounds that are active against a particular target protein [25]. Molecular docking has been the approach that has been utilised most frequently. There have been some remarkable accomplishments in this field, despite the fact that its principal application is in structure-based virtual screening to discover novel compounds that are active against a particular target protein [25].

2.4. Docking investigations with Maestro 12.8

Molecular docking has been the approach that has been utilised most frequently. There have been some remarkable accomplishments in this field, despite the fact that its principal application is in structure-based virtual screening to discover novel compounds that are active against a particular target protein [26]. It is actually part of a workflow that includes numerous *in-silico* and experimental approaches and is not a stand-alone procedure [27].

2.5. Expected TPP and 1 ligand preparation for docking

The Maestro 12.8 software has tools for both protein and ligand optimization, such as assigning atomic charges to proteins to make them more polar, modifying ligands by assigning charge and rotatable bonds, figuring out the energy contribution of de-solvation during ligand-binding on proteins, and assigning grid maps on protein surfaces prior to ligand interaction by auto grid. Through the use of a new scoring method, efficient optimization, and multithreading, the aforementioned capabilities improve the speed, accuracy, and docking of molecular docking [28].

2.6. In a simulated TPP, protein docking with L1 metal ion molecules serves as the ligand

In the current work, we estimated the binding-free energy or docking, which represents the binding affinity of 1 ligand, which is silver metal of the ciprofloxacin analogue (L1), and Two prescription medications (Standard pharmaceuticals: Ciprofloxacin and Norfloxacin) to model TPP. The aforementioned docking research demonstrates that the silver metal of the ciprofloxacin analogue (L1) had a greater binding affinity and docking score (-5.338) than the prescription drugs Ciprofloxacin and Norfloxacin, whose docking scores were (-4.378 and -2.421 respecively). The ligands with the highest affinity for the model TPP are listed in Table: 1 for further study [29]. The Schrodinger program's Glide energy (Maestro 12.8) drug discovery tool was employed in the study as an alternative to Auto Dock Vina. Maestro 12.8 predicts binding affinity energies between (-5.338 kcal/mole to-2.421kcal/mole) when docking calcineurin with inhibitors, which is nearly identical to the results of the current study [30].

2.6.1. Ciprofloxacin's metal ions (L1) and standard drug chemical structure composition

(E)-1-cyclopropyl-6-fluoro-7-(piperazin-1-yl)-4-(o-tolylimino)-1,4-dihydro quinoline-3-carboxylic acid
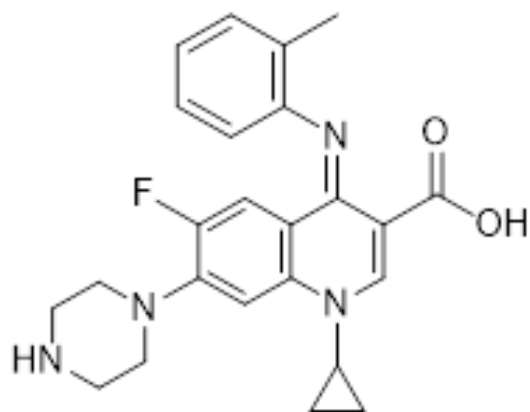
Figure 3 Chemical structure of Ciprofloxacin Analogue (L1)

1-cyclopropyl-6-fluoro-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid
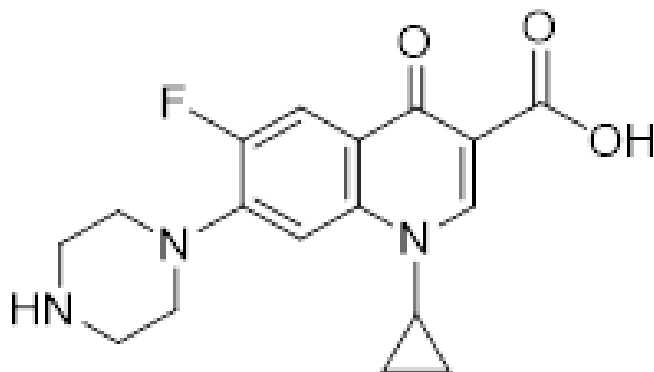

Figure 4 Chemical structure of Ciprofloxacin

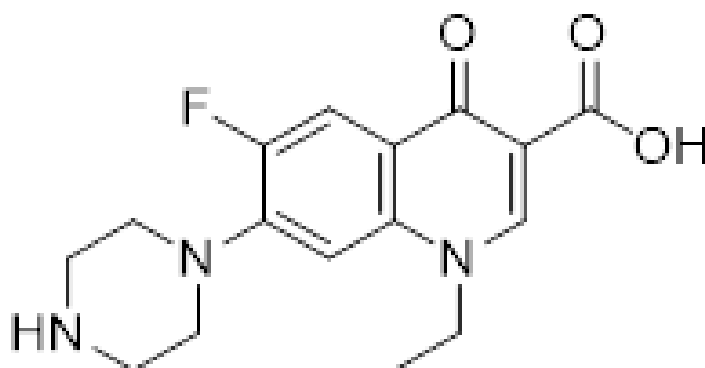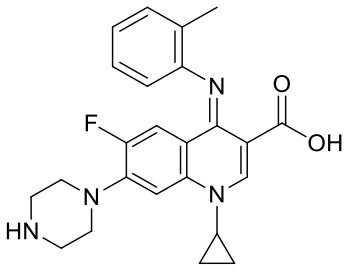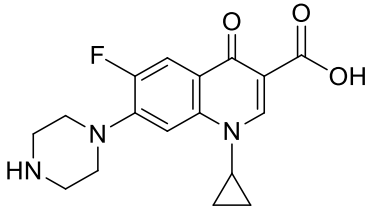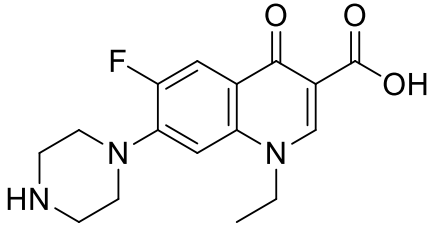1-ethyl-6-fluoro-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid

Figure 5 Chemical structure of Norfloxacin

3. Results and discussion

Table 1 Ciprofloxacin metal ions (L1) were screened for *In-silico* screening against standard prescription drug.

S.No	Name of Compounds	Chemical Structure	Docking score (PDB ID: 2XCT)	Glide energy	Molecular Weight	cLogP
1.	Ciprofloxacin Analogue (L1)		-5.338	-35.325	$C_{24}H_{25}FN_4O_2$	0.53
2.	Ciprofloxacin (Standard drug)		-4.378	-34.406	$C_{17}H_{18}FN_3O_3$	0.72
3.	Norfloxacin (Standard drug)		-2.421	-26.54	$C_{16}H_{18}FN_3O_3$	0.68

3.1. PDB ID

2XCT: The twinned 3.35A structure of s.aureus Gyrase complex with Ciprofloxacin and DNA [31].

- **Classification:** ISOMERASE/DNA/ANTIBIOTIC
- **Organism(s):** Staphylococcus aureus subsp. aureus N315, synthetic construct
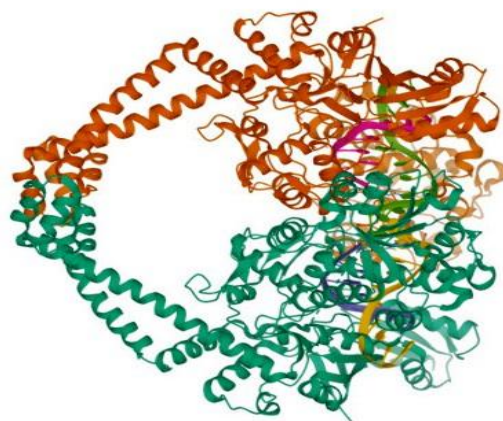- **Expression system:** Escherichia coli BL21(DE3)
- **Mutation(s):** Yes
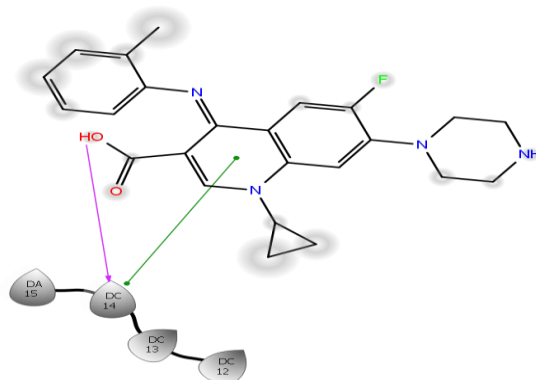
Figure 6 3D- Structure of protein (2XCT)

Figure 7 Ciprofloxacin Analogue (L1) 2D diagrams of docked conformation compound
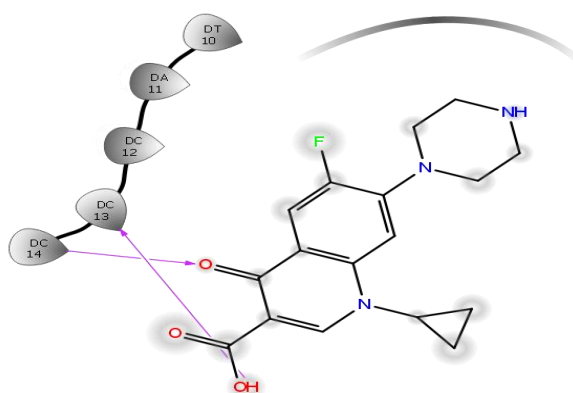

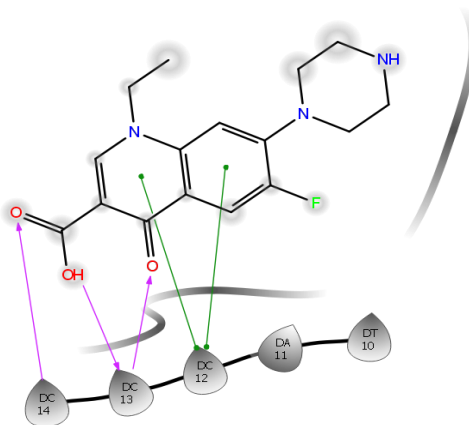**Figure 8** Ciprofloxacin 2D diagrams of docked conformation compound

Figure 9 Norfloxacin 2D diagrams of docked conformation compound

4. Conclusion

Despite the fact that our study is based on computational molecular docking, it is important that the scientific tool Maestro 12.8 used for molecular docking research proves its veracity. Our study finds that the medicine demonstrates robust and effective capabilities against a variety of bacterial and fungal diseases. It is based on the production and evaluation of the silver metal of the ciprofloxacin analogue (L1) in a computer simulation. Therefore, it has been demonstrated in *in-silico* studies that the silver metal in the recently synthesised ciprofloxacin analogue (L1novel) has significant potency against a number of bacterial and fungal diseases, making it a crucial source for new antibacterial drugs that focus on potent inhibition activity against various bacterial and fungal diseases in the future.

Compliance with ethical standards

Acknowledgments

The authors thank the reviewers for their insightful suggestions.

Disclosure of conflict of interest

We declare there is no conflict of interest in this study.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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