In-Silico Drug Designing, Synthesis and Biological Evaluation of Novel Ciprofloxacin Analogues

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ABSTRACT

Antibiotic resistance is one of the leading fears worldwide. Development of resistance against antimicrobial agents is one of the major purposes for research and development of new molecules. Ciprofloxacin analogues have caused continuous interests and their antibacterial potential is still a focus of research. For this purpose, in present research antibiotic ciprofloxacin has been selected as a parent compound and its analogues has been designed, synthesized and finally evaluated for their better antimicrobial activities. For that purpose, virtual screening has been performed by software Auto dock Vina 4.2.6 to analyze the binding energies between the receptor and designed ligands. Those designed ligands showing better binding affinities than parent compound CPFX were short listed for synthesis. The present study also describes insilico prediction of drug-like properties of newly designed analogues by using different online computational tools. The insilico screening of designed analogues indicated them qualified for the parameters of drug likeness also showing good bioactivity along with optimum pharmacokinetic properties. Overall results of insilico pharmacokinetic screening indicated that the newly designed compounds may be considered as a candidate for further drug development studies. Evidences from Structure activity relationship (SAR) studies of Ciprofloxacin indicated that C-3 position on quinolone nucleus is essential for DNA gyrase binding. In order to achieve this objective three analogues of ciprofloxacin by introducing new functional groups at carboxylic group position C-3 have synthesized. Structure of the analogues was confirmed by different techniques i.e., IR, 1 H NMR and mass spectroscopy. The antibacterial activity of the derivatives was also assessed with the parent against a series of Gram-positive and Gram-negative bacteria. The synthesized compounds 3a, 3b and 3c showed diverse antimicrobial profile possessed a better activity in comparison to the ciprofloxacin. Docking studies of synthesized molecules revealed them as good antimicrobial candidates and their docking scores prove better binding as compared to the standard CPFX.

Keywords: Analogues, Ciprofloxacin, Docking, DNA gyrase, Virtual screening.

INTRODUCTION

Ciprofloxacin (CPFX) is chemically named as 1-cyclopropyl-6-fluoro-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinolone-3-carboxylic acid[1, 2]. It is a member of second generation of fluoroquinolones. It showed strong antibacterial potential, excellent pharmacokinetic characteristics and few adverse effects[3]. As a result, Ciprofloxacin analogues have caused continuous interests and their antibacterial potential is still a focus of research. The main target for these compounds is two bacterial enzymes DNA gyrase and Topoisomerase IV. CPFX inhibits bacterial DNA synthesis by forming a ternary complex with these enzymes, and consequently blocks bacterial DNA supercoiling[4, 5]. In facilitating discovery of drug derivatives directed at selective multiple targets insilico approaches have shown appreciable potential[6]. *In-silico* studies are conducted for the identification of most suitable ligand in a known target structure. The method that predicts the conformation of a ligand at the target site is molecular docking[7].For drug discovery, combination of technologies including *in-silico* models can offer pronounced benefits in improving the probabilities of achievement in a discovery

programme[8]. This study also showed synthesis of new CPFX analogues with aromatic amide substitution at C-3 with selected reagent. The present research includes drug designing on the basis of structure, virtual screening on the basis of structure and insilico pharmacokinetics as these are the most recent approaches serve as an influential tool to propose new compounds in medicinal chemistry. Implementation of these approaches may assist to raise the worth of novel products.

OBJECTIVES

Drug discovery is the multi objective cyclic optimization process .The key objectives of this study are to design, synthesis and evaluation of ciprofloxacin derivatives. It will be include the following:

1. Molecule designing by using different softwares further analyzing their pharmacokinetic and pharmacodynamic properties.
2. Synthesis of novel analogues to get pronounced antimicrobial action against resistant pathogens.
3. Characterization of newly synthesized analogues through different analytical tools.
4. Biological evaluation of newly synthesized analogues.

METHODOLOGY

For derivative synthesis first compounds will be designed by ChemOffice software. Then virtual screening has been performed for 14 designed compounds. After that best 3 compounds have been selected.Then, ADMET (absorption, distribution, metabolism, excretion, toxicity) properties of the designed and selected compoundshave analyzed via different softwares, after that docking has done by using different protein targets. Then, synthesis of designed analogues occurred by refluxing at specific temperature for hours, timely TLC has taken to check the completion of reaction. After that Characterization of the synthesized compounds has done by the most appropriate available analytical tools such as UV, IR and elemental analysis. Further Biological evaluation of newly synthesized compounds has been performed.After that, by using the AutoDock Vina docking tool, compounds 3a-3c were docked into the active sites of DNA gyrase of (PDB ID: 2XCT) and (PDB ID: 3ILW) of *S. aureus.*Hydrogen bonds, non-covalent interactions, and docked positions with the lowest binding energies were observed and verified.

CONCLUSION

All of the newly designed synthesized analogues are found as active antimicrobial agents. Among all, the synthesized derivatives 3a, 3b 3c, 7b and 7c against all of the tested strains, demonstrated considerable bacterial inhibition activity. Molecular docking of the synthesized analogues indicated that the synthesized compound showed better affinity towards the proteins than the standard drug CPFX.

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