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In silico screening and molecular docking study of quinoline based compounds with Human kallikrein 7 in complex with 1,4-diazepane-7-one 1-acetamide derivative receptor target for potential antibacterials

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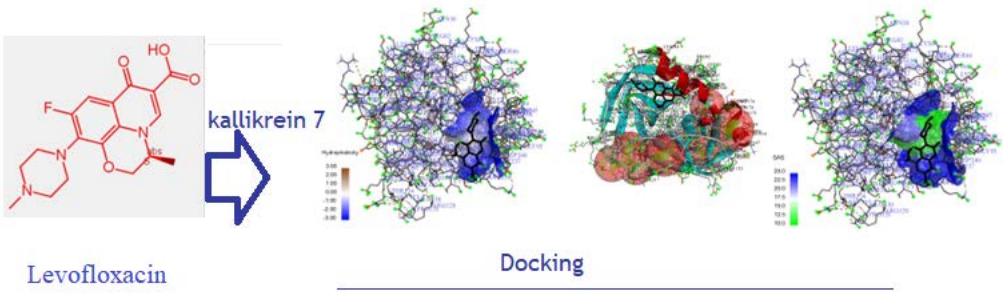
Article

ABSTRACT



The quinolines based drugs and its analogues are widely used as a medicinal drug. In this study, five compounds from quinoline-based pharmaceuticals have been discovered using virtual screening with Autodock software, with binding affinities ranging from 6.6 to 5.4 kcal/mol. The best suitable chemical is levofloxacin, which has a higher drug-likeness and a total drug score of 0.87. Improved receptor (kallikrein 7) Vander-waal bonding with ARG A:50, TRP A:51, LYS A:243, ASN A:239, ASN A:48 is also revealed by levofloxacin docking and bonding studies. Based on the affinity score, levofloxacin was found to have superior pharmacological properties and bonding when compared to other molecules from quinoline-based drugs and kallikrein 7. After thorough in silico research, levofloxacin from quinoline-based medications can be used as a potential treatment target towards development of antibiotic medicine.

Keywords: Quinoline, Interaction, Binding affinity, Residues, Biological activity, Antibiotic, Synthesis, Medicines

INTRODUCTION

Major components of natural products, active pharmacophores, and possessing excellent biological properties like antibacterial activity are compounds based on quinoline. This article describes a molecular docking study that used antimicrobial protein scaffolds with quinoline-based drugs and their equivalents.[1,2] These derivatives were subjected to an in silico molecular docking analysis to ascertain the binding affinity, residual interaction, and hydrogen bonding of several ligands against the protein. The results of this investigation are described here. The results of the current study showed that quinoline and its derivatives could function as powerful antibacterial agents to create antibiotic medicines. Ciprofloxacin is a fluoroquinolone antibiotic with a wide range of activity. It is effective against a variety of Gram-negative bacteria as well as a few Gram-positive bacteria. Topoisomerase IV and type II topoisomerase, which are necessary to divide bacterial DNA, are blocked, preventing cell division. The bacterial DNA (Deoxyribose Nucleic Acid) will fragment if the enzymes are inhibited.[3,4] Levofloxacin is a powerful antibiotic that works well against both Gram-positive and Gram-negative bacteria. Like all quinolones, it functions by obstructing DNA gyrase and topoisomerase IV, two bacterial type IIA topoisomerases. Topoisomerase IV is required for the separation of duplicated (doubled) DNA prior to bacterial cell division.[5,6] Because the DNA is not divided, the process is halted, and the bacterium cannot divide. DNA gyrase is in charge of supercoiling the DNA to make it fit in the newly produced cells on the opposite side of the process. Both techniques successfully eliminate the bacteria. A bactericide, levofloxacin has several qualities. Corynebacterium pseudodiphtheriticum is one of many Gram-positive and Gram-negative eye infections that the fluoroquinolone besifloxacin is effective against in vitro.[7,8]

Some quinolones can increase the toxicity of medicines that are metabolized by the cytochrome P450 system when taken concurrently. Norfloxacin[9] and other quinolones, such as warfarin or its derivatives, may exacerbate the effects of oral anticoagulants. Prothrombin time or other relevant coagulation

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tests should be closely monitored when these medications are taken together.[10,11] Coadministration may riskily increase the activity of coumadin and warfarin; INR should be carefully watched. Moxifloxacin is not absorbed as well when used with antacids that include aluminium or magnesium ions. The QT interval-lengthening medication pimozide, for example, may have an additive effect on QT lengthening and raise the risk of ventricular arrhythmias.[12,13] Patients using warfarin may experience an increase or decrease in the international normalized ratio.[14–16]

METHOD

Receptor structure identification

The serine proteases known as human tissue kallikreins (KLKs) (KLK1–KLK15) are involved in a variety of physiological and pathological processes. Recently, 1,2 KLKs have drawn interest as desirable therapeutic targets. Among these, chymotryptic serine protease kallikrein 7 (KLK7, stratum corneum chymotryptic enzyme, SCCE) is widely expressed in the skin. KLK7 contributes significantly to epidermal desquamation through the degradation of corneodesmosome proteins. Several proteases, notably KLK7 and their intrinsic inhibitors like lympho-epithelial Kazal-type-related inhibitor (LEKTI), maintain the function of the skin barrier in a normal epidermis. Increased protease activity in the epidermis, however, has the potential to disrupt the skin barrier's homeostasis and cause epithelial dysfunction, which could lead to increased moisture loss and microbial and allergen penetration. The PDB (protein data bank) file is get from from rcsb protein data bank (https://www.rcsb.org).

Binding/Active site identification

To find the amino acids thought to be involved in receptor interaction, the putative active site was determined using the SCFBIO Tool (http://www.scfbio-iitd.res.in/). According to a literature search, the amino acids GLY133, GLY184, PRO186, A8VX301, and LYS161 are crucial for receptor binding and function. These amino acids can be targeted to lessen or stop abnormal signaling. The size of the active and binding sites was chosen based on the amino acids necessary for receptor binding.

Compounds screening

The compounds were obtained from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/), and Chem Draw software (Chem Draw Professional 15.0) was used to develop the chemical structure. Further, we prepare the protein and the ligand from PDB to PDBQT format by the help of Auto dock Tools-1.5.7. The library of ligand molecules was subsequently put through a virtual docking-based screening process using Auto dock software. According to their binding affinity, which reflects the receptor interaction with the highest potential, Auto dock categorized the ligands. For additional drug property research, the compounds with the lowest binding affinity (Kcal/mol) were selected.

Identification of drug properties

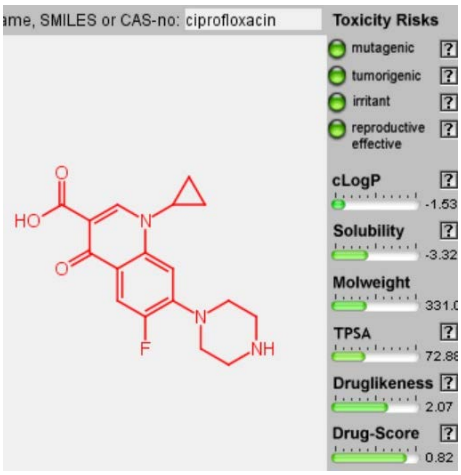
The OSIRIS properties explorer identified the ligand compounds' pharmacological characteristics. The Lipinski's rule, molecular weight, clogp, drug similarity, and drug score were all examined as part of the investigation.[17] They were also examined for their mutagenic, tumorigenic, irritating, and reproductive effects using the aforementioned programme. Then, the molecular weight, clogp, topological polar surface area (TPSA), solubility, H-donor, H-acceptor, druglikeness, and overall drug score of the compounds were examined. To determine compound hydrophilicity, the software used the logarithm of the partition coefficient between n-octanol and water, log (Coctanol/Cwater). Substances having a clogp value less than 5.0 are more likely to be well absorbed because high values indicate poor absorption. Topological polar surface area (TPSA) has been used to determine drug absorption, including intestinal absorption, bioavailability, and blood-brain barrier penetration. It is a useful tool for forecasting drug transport properties. The degree to which a substance is soluble in water affects both its absorption and distribution properties. Since poor absorption is frequently correlated with low solubility, the general objective is to steer clear of such substances.[18]

Docking verification and analysis

The selected ligand molecule is once more confirmed by AutoDock VINA based on the drug properties and docking potential. Additionally, the shortlisted docked complexes are visualized and analyzed using the discovery studio visualizer.[19] A flexible molecular docking programme called AutoDock VINA[20] provides five different docked ligand molecule modes with the receptor. For different bonding distances and interactions with the binding site residues, the best mode with the lowest binding energy was selected and researched.

RESULTS

The earlier mentioned literature search revealed the kallikrein 7 amino acids that are predisposed to ligand molecule binding **(Figure 1**). These circumstances raise the chance of sensitization, which triggers a range of inflammations. A persistent, inflammatory skin condition with multiple underlying causes is atopic dermatitis (AD).



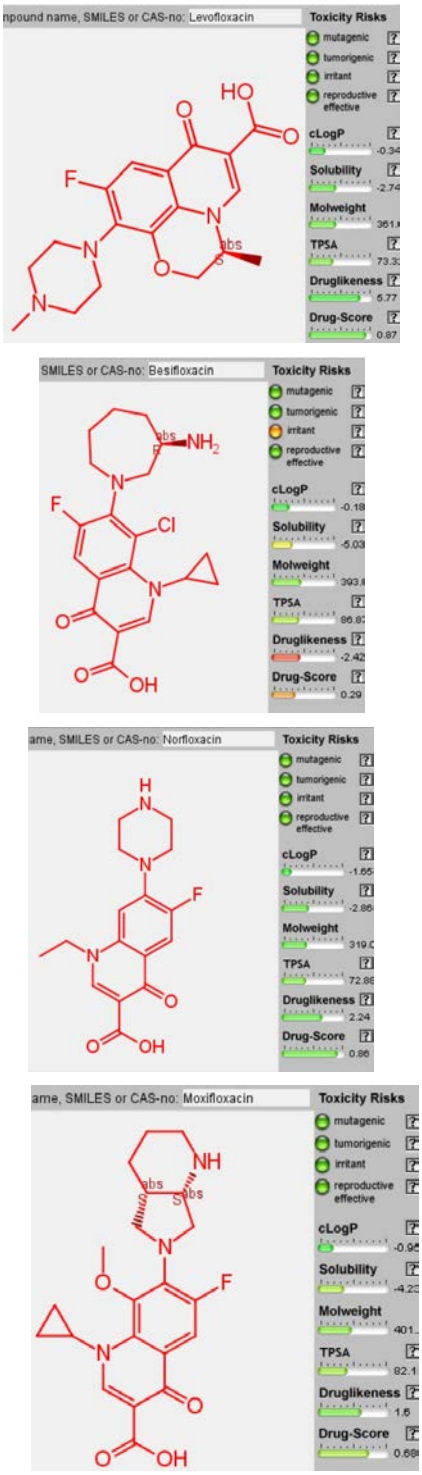


Figure 1 Comparative study of Ciprofloxacin, Levofloxacin, Besifloxacin, Norfloxacin and Moxifloxacin interaction with kallikrein 7 target.

One of the major contributing causes to the onset of AD is failure of the skin barrier, and studies have shown that AD patients have prominently raised KLK7 levels in their epidermis. The best match template was chosen via a BLAST search against the (Protein Data Bank) PDB database, and homology modelling.

The prediction of active site

The kallikrein 7 active site was predicted by SCFBio Tools (http://www.scfbio-iitd.res.in/), and the outcomes were compared to references in the literature. Chosen amino acids with potential functions in functionality and abnormal signalling were looked into for the binding site identification. The projected site of docking's selected cavity points was 20.476, 41.419, and 26.237, and the cavity's volume is 1373 Å cubic centimetres (Cavity 2=PFLTVINGAQCDSHYMEWKR). The cavity dimensions were further employed for docking-based screening based on the chosen amino acids.

Table 1 Compound screening from quinoline analogues

S. No.	Name of compound	Binding Energy	Pub Chem ID
1	Ciprofloxacin	-6.0	CID= 2764
2	Levofloxacin	-6.6	CID=149096
3	Besifloxacin	-5.4	CID=10178705
4	Norfloxacin	-5.7	CID=4539
5	Moxifloxacin	-6.0	CID=152946

The designing and virtual screening of ligand

These compounds' structures were created using ChemDraw 3D (ChemDraw Professional 15.0), and all of the chemical structures were converted from sdf to pdb format using pymol (Version 2.5). With kallikrein 7 as the target protein, Pymol software was used to screen a library of ligand compounds in pdb format. The grid box dimension (Å) (X=98 Å, Y=122 Å, Z=100 Å) was utilized in the Auto Grid engine configuration file for the Auto Dock Tool software. For further examination, compounds with binding energies between -6.6 and -5.4 kcal/mol were chosen (**Table 1**).

Pharmacokinetic properties of the selected ligands

The examination of the chosen molecule reveals that ciprofloxacin, levofloxacin, and norfloxacin have overall drug scores of 0.82, 0.87, and 0.86 with molecular weights of 331.0, 361.0, and 319.0 respectively. Among the other compounds besifloxacin and moxifloxacin shows the 0.29, and 0.68 overall the drug score with the molecular weight of these compounds is 393.0 and 410.0. The drug score shows a compound's overall likelihood of meeting the criteria to become a drug candidate in light of the drug likeness, cLogp, solubility, molecular weight, and toxicity hazards. Additionally, as indicated in **Table 2**, the examination demonstrates no toxicity and follows the Lipinski rule. Ciprofloxacin, Levofloxacin, Besifloxacin, Norfloxacin, Moxifloxacin, docking is once more verified using Auto Dock VINA. Ciprofloxacin shows Vander Waals interaction with the SER A:153, LEU A:73, TRP A: 141, GLN A:39, A8VX: 301, hydrogen bonds with PHE A: 151, LEU A:40, halogen with PRO A: 152 are shown in **Figure 2**, whereas Levofloxacin shows the Vander Waals with ARG A:50, TRP A:51, LYS A:243, ASN A:239, ASN A:48, halogens with the MET A:242 and Pi-Alkali bonding with ARG A:246 are shown in **Figure 3**.

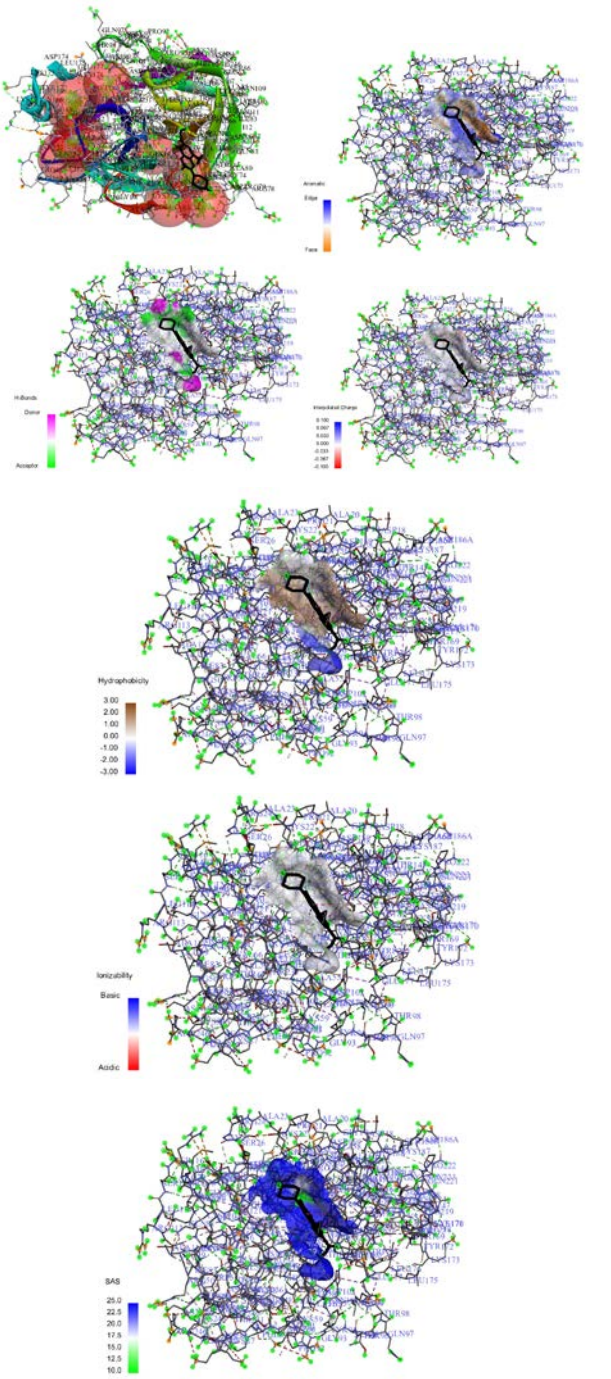


Figure 2 Ciprofloxacin docking with kallikrein 7 and cavity properties. **a** Interaction. **b** Aromaticity view **c** cavity H-bond view. **d** Interpolated charge View. **e** Cavity hydrophobicity view. **f** Cavity ionizability view. **g** Show good solvent accessibility.

As shown in **Figure 4** vander waals interaction with ALA A:56, HIS A: 99, HIS A:57, HIS A:41, THR A:96, A8VX: 301, the hydrogen bond with TYR A:94, ARG A:90, LYS A;59 shows by the Norfloxacin (**Table 3**).

Interaction of Besifloxacin shows vander waals with ILE A:185, GLY A:133, GLY A:184, PRO A:225, CYS A:168, VAL A:171, ASN A:223, ASP A:167, alkyl with ILE A:163 as well as

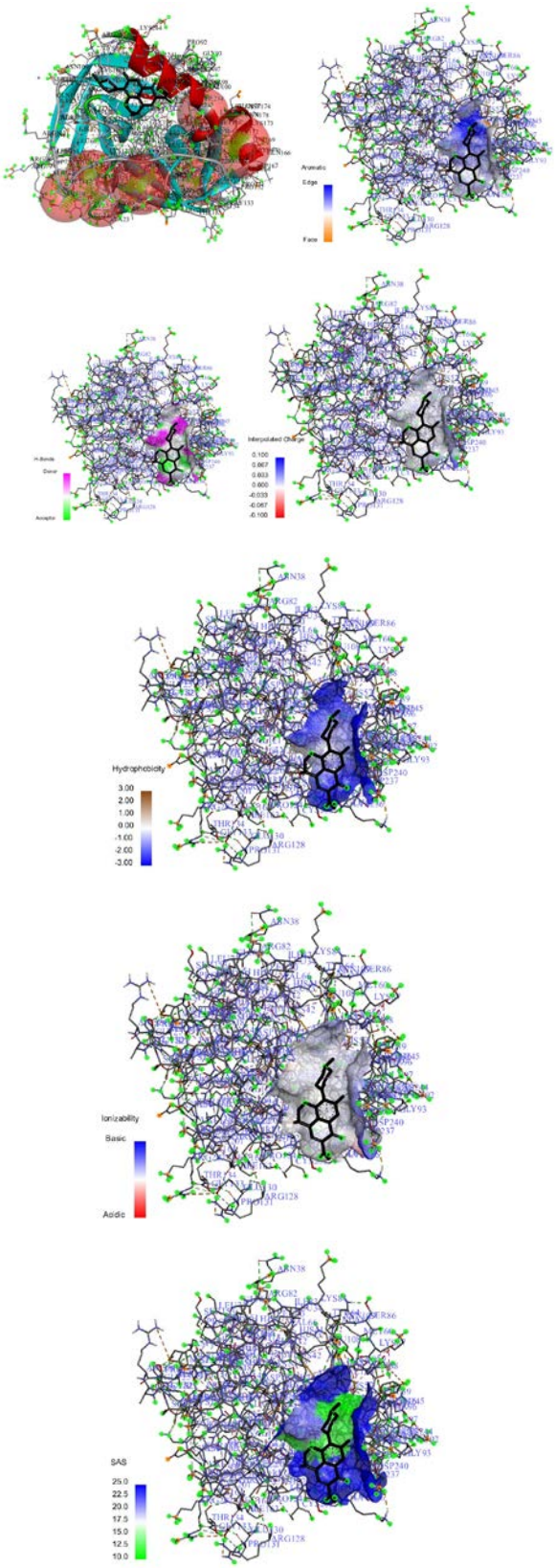


Figure 3 Levofloxacin docking with kallikrein 7 and cavity properties. **a** Interaction. **b** Aromaticity view c cavity H-bond view. **d** Interpolated charge View. **e** Cavity hydrophobicity view. **f** Cavity ionizability view. **g** Show good solvent accessibility.

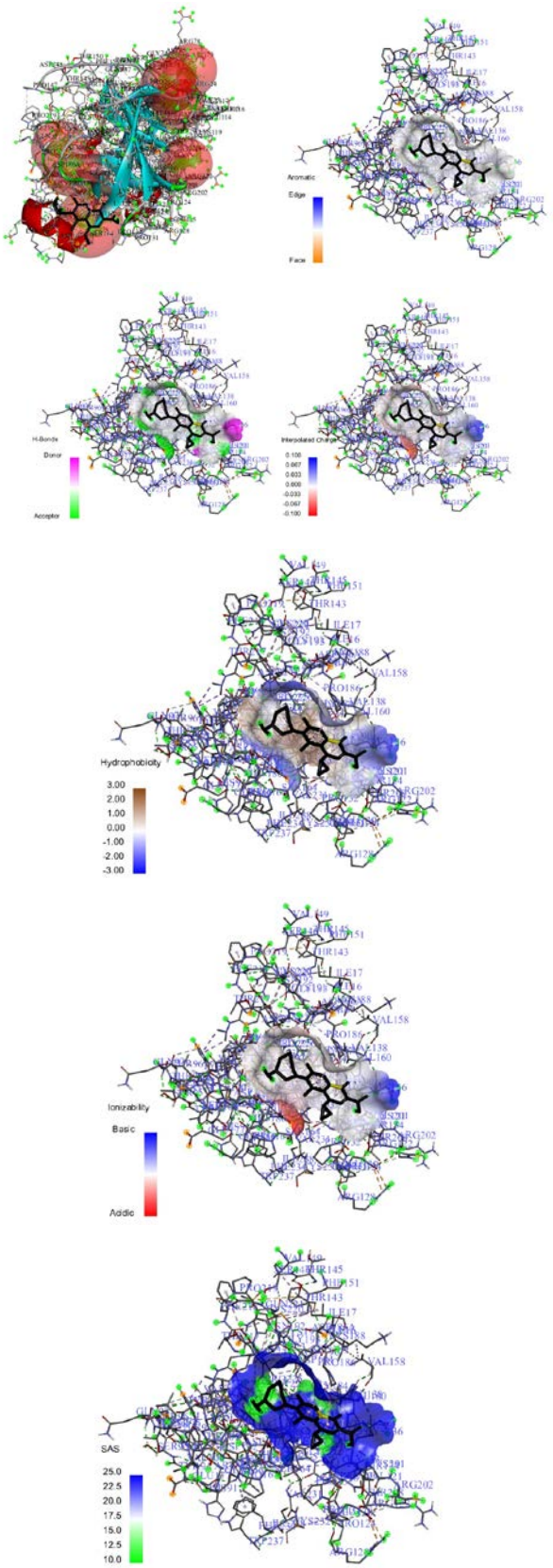


Figure 4 Besifloxacin docking with kallikrein 7 and cavity properties. **a** Interaction. **b** Aromaticity view **c** cavity H-bond view. **d** Interpolated charge View. **e** Cavity hydrophobicity view. **f** Cavity ionizability view. **g** Show good solvent accessibility**.**

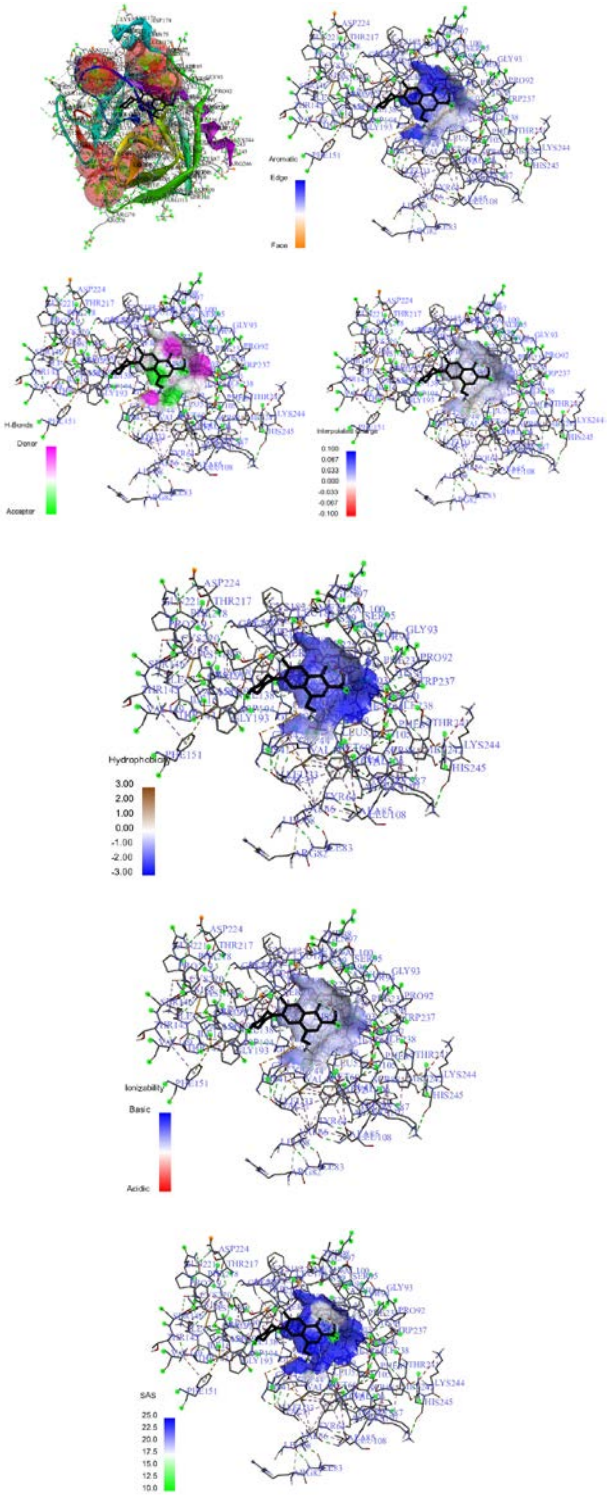


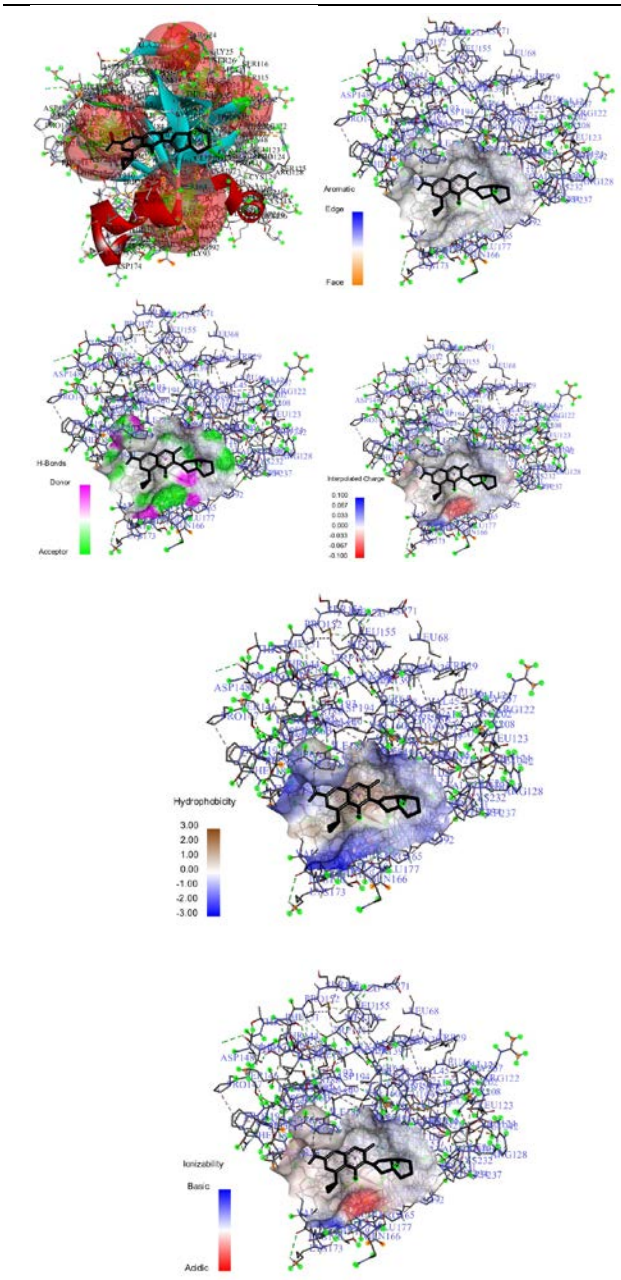
Figure 5 Norfloxacin docking with kallikrein 7 and cavity properties. **a** Interaction. **b** Aromaticity view **c** cavity H-bond view. **d** Interpolated charge View. **e** Cavity hydrophobicity view. **f** Cavity ionizability view. **g** Show good solvent accessibility.

hydrogen bonding with PRO A:186, LYS A:161 are shown in **Figure 5**. As shown in **Figure 6**, And moxifloxacin shows the hydrogen binding with the ILE A:185, PRO A:186, halogen with

LEU A:162, pi-sigma with ILE A:163, alkyl with PRO A:132 and the vanderwaal with ASN A:223, ASP A:167, GLY A:133, GLY A:184, SER A:164, LYS A:161, ASP A:186, PRO A:225 residues involved in receptor binding **Figure 7** (**Table 3**).

Table 2 Properties of the selected compounds as a drug candidate

S. No.	Name of compd.	Mol. weight	Clog p	TPSA	Solubility	Drug-likeness	Drug score
1	Ciprofloxacin	331.0	-1.53	72.88	-3.32	2.07	0.82
2	Levofloxacin	361.0	-0.34	73.22	-2-74	5.77	0.87
3	Besifloxacin	393.0	-0.18	86.87	-5.03	-2.42	0.29
4	Norfloxacin	319.0	-1.66	72.88	-2.86	2.24	0.86
5	Moxifloxacin	401.0	-0.95	82.11	-4.23	1.6	0.68



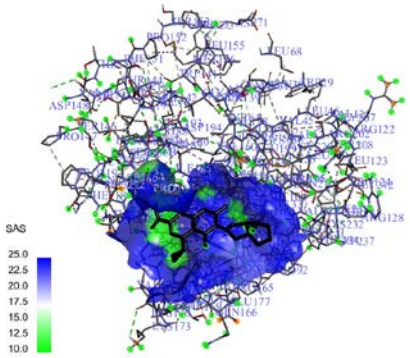
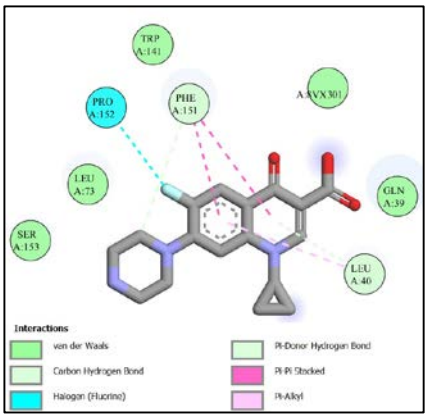
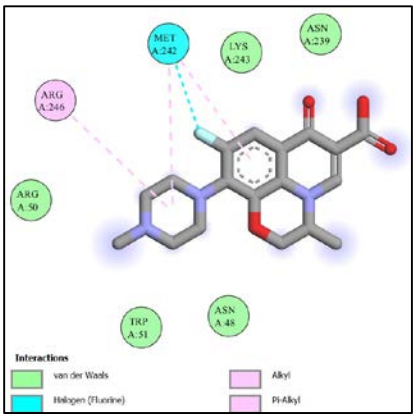
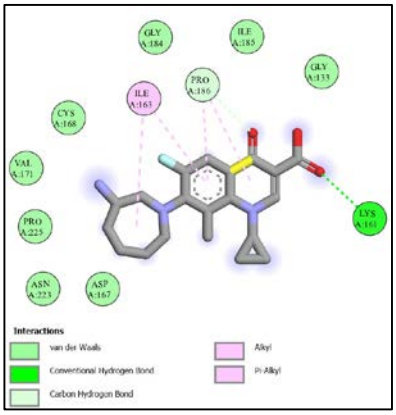


Figure 6 Moxifloxacin docking with kallikrein 7 and cavity properties. **a** Interaction. **b** Aromaticity view **c** cavity H-bond view. **d** Interpolated charge View. **e** Cavity hydrophobicity view. **f** Cavity ionizability view. **g** Show good solvent accessibility.







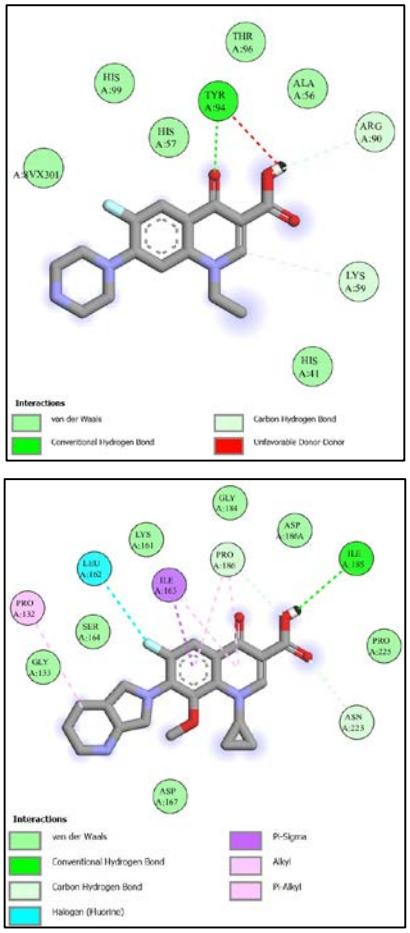


Figure 7 Interaction representation (H-bonding, Vander Waals, Pi-Cation, Pi-Pi Stacked, Alkali, conventional H-bonding) of kallikrein 7 with **a.** Ciprofloxacin, **b.** Levofloxacin, **c.** Besifloxacin, **d.** Norfloxacin, **e.** Moxifloxacin.

DISCUSSION

In order to determine which complex can be further examined in an in vitro investigation, kallikrein 7 and quinoline and its analogues were docked and analyzed. Mostly quinoline derivatives shows antibacterial property. According to the Kallikrein 7 docking-based screening of compound drug properties, luteolin with molecular weights of 331.0, 361.0, and 319.0 exhibits the best properties when compared to other compounds, while Ciprofloxacin, Levofloxacin, and Norfloxacin show better pharmacological properties. In addition, when ciprofloxacin is compared to besifloxacin and moxifloxacin, it forms Vander Waals (SER A:153, LEU A:73, TRP A:141, GLN A:39, A8VX:301), hydrogen bonds (PHE A:151, LEU A:40), and halogen (PRO A:152) with the important amino acids that may play a role in pathogenesis. Levofloxacin shows the Vander Waals (ARG A:50, TRP A:51, LYS A:243, ASN A:239, ASN A:48), halogens (MET A:242) and Pi-Alkali (ARG A:246). Vander waals (ALA A:56, HIS A: 99, HIS A:57, HIS A:41, THR A:96, A8VX: 301), hydrogen bond (TYR A:94, ARG A:90, LYS A;59) the key amino acids having potential role. All the compounds have antibacterial property. Based on the in-silico analysis, quinoline and its analogues-based drugs can be used as potential drug candidates. Additionally, in vitro research will confirm the aforementioned finding.

Table 3 Types of bonding and interacting amino acids of kallikrein 7 with compounds.

Name of compound	Binding Energy	H-bonding	Vander waal	Halogen	Pi-alkyl	Pi-sigma
Ciprofloxacin	-6.0	PHE A: 151, LEU A:40	SER A:153, LEU A:73, TRP A: 141, GLN A:39, A8VX: 301	PRO A: 152	-	-
Levofloxacin	-6.6	-	ARG A:50, TRP A:51, LYS A:243, ASN A:239, ASN A:48	MET A:242	ARG A:246	-
Besifloxacin	-5.4	TYR A:94, ARG A:90, LYS A;59	ALA A:56, HIS A: 99, HIS A:57, HIS A:41, THR A:96, A8VX: 301	-	-	-
Norfloxacin	-5.7	PRO A:186, LYS A:161	ILE A:185, GLY A:133, GLY A:184, PRO A:225, CYS A:168, VAL A:171, ASN A:223, ASP A:167	-	ILE A:163	-
Moxifloxacin	-6.0	ILE A:185, PRO A:186	ASN A:223, ASP A:167, GLY A:133, GLY A:184, SER A:164, LYS A:161, ASP A:186, PRO A:225	LEU A:162	PRO A:132	ILE A:163

CONCLUSION

The interaction of amino acids with the receptor is revealed by molecular docking-based screening of molecules from quinoline and its analogues with kallikrein 7 target. The pharmacokinetic and therapeutic properties of ciprofloxacin, Levofloxacin, Besifloxacin, Norfloxacin, and Moxifloxacin have been enhanced. Levofloxacin, however, was determined to be the best suitable ligand when compared to other drugs based on the quantity of factors and overall drug score. The strongest receptor bonding and the finest pharmacological characteristics of luteolin were determined by the type of bonding contact.

Abbreviations

PDB: Protein data bank; AD: Atopic dermatitis; DNA: Deoxyribose nucleic acid; KLK: kallikrein; RMSD: Root mean square distribution; TPSA: Topological polar surface area.

Ethics approval and consent to participate: Not Applicable

Consent for publication: This is an original work, and the result is promising to scientific community.

Availability of data and material: Available in the department of chemistry, Amity University Madhya Pradesh.

Competing interests: The authors declare that they have no competing financial interests.

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