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INSILICO DESIGN, SYNTHESIS AND ANTIBACTERIAL EVALUATION OF NOVEL IMIDAZOLE DERIVATIVES AGAINST A RECEPTOR FimH OF *E. COLI*

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ABSTRACT

Molecular docking is a widely used computational technique in drug discovery that predicts interactions between small molecules and target proteins, helping to identify potential drug candidates. This study aimed to design and evaluate novel imidazole derivatives as antibacterial agents against *Escherichia coli* by integrating *in silico* and experimental approaches. Molecular docking was performed using AutoDock Vina to assess the binding affinities of 20 imidazole derivatives (labeled 3A-3J) against the E. coli receptor FimH (PDB ID: 4XO8). Predictions for ADME (Absorption, Distribution, Metabolism, and Excretion) and toxicity were also conducted to evaluate the drug-like properties of these compounds. The results revealed binding affinities that were stronger than that of ciprofloxacin. Among the compounds tested, compound 3J demonstrated the highest binding affinity. It was synthesized and characterized using infrared (IR) spectroscopy. The antibacterial properties of the compound 3J was evaluated using the cup plate method, with ciprofloxacin as a reference. The results confirmed that compound 3J exhibited superior antibacterial activity. This study emphasizes the significant role of molecular docking in drug design and supports the further development of imidazole derivatives as effective antibacterial agents.

KEYWORDS: Molecular docking, Imidazole derivatives, *E. coli*, FimH receptor, Schiff base, Antibacterial activity, ADMET analysis.

INTRODUCTION

The quest for new pharmaceuticals with enhanced efficacy and reduced toxicity is a persistent priority within the field of drug discovery. Despite the critical need for innovative therapies, the journey from initial idea to market-ready medication is fraught with challenges, often requiring significant financial investment and time. The inherent hurdles, including target validation, hit identification, and the high attrition rates observed during clinical trials due to poor pharmacokinetics or adverse effects, necessitate an optimized approach to each phase of drug development.

Recent computational power and technology advancements have paved the way for computer- aided drug design (CADD), a transformative method that expedites the discovery process. This approach allows for the *in-silico* identification and design of potential drug candidates through sophisticated molecular modeling and simulation techniques. By employing various CADD methodologies, including virtual ligand screening and structure prediction, researchers can significantly enhance the likelihood of success while alleviating some of the time and cost burdens traditionally associated with drug development.[1,2]

Molecular docking techniques are essential in Computer-Aided Drug Design (CADD) because they enable researchers to predict how small molecules interact with target proteins. Grasping this understanding is vital for dissecting the complexities of these interactions, which in turn will lead to the development of more powerful and effective therapeutic agents. Recently, significant attention has been given to the study of *Escherichia coli (E. coli)*, a gram-negative bacterium associated with various human health problems. By exploring key proteins, such as FimH, which plays a crucial role in bacterial adhesion and pathogenesis, researchers are discovering new opportunities for targeted therapies.[3-5](PDB ID:4XO8).

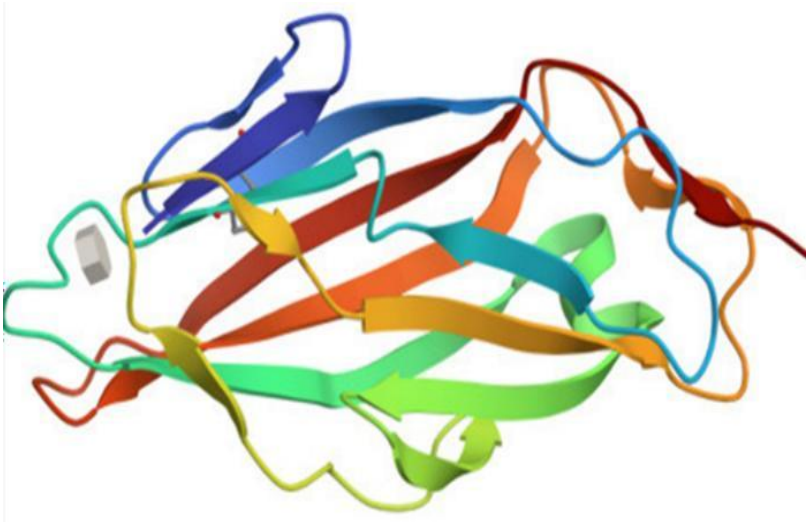


Fig. 1

Crystal structure of the FimH lectin domain from E. coli K12 in complex with heptyl alpha-D-mannopyrannoside

The imidazole ring is not just a structural element, it is a key player in many biologically active compounds, offering a wealth of intriguing pharmacological properties. Its distinct chemistry presents exciting opportunities for drug development and therapeutic innovation. With demonstrated activities ranging from antibacterial to anticancer, imidazole derivatives are gaining attention as potential leads in the ongoing battle against antibiotic resistance and other critical health challenges. In light of these developments, this work aims to explore the integration of advanced computational methods in drug discovery and the potential impact of imidazole compounds in combating multidrug-resistant infections.[6-9]

MATERIALS

- Chem sketch
- Molinspiration
- preADMET
- pkCSM
- Binding site prediction
- AutoDock Vina
- ProTOX
- Discovery studio
- pyMOL

METHODOLOGY

I. Synthesis of Schiff base

Weigh about 0.01 M of an aromatic aldehyde and 0.01 M of a substituted aromatic primary amine and transfer both into a round-bottom flask. Then, add 20 mL of ethanol and stir the mixture well until the aldehydes are fully dissolved.[10]

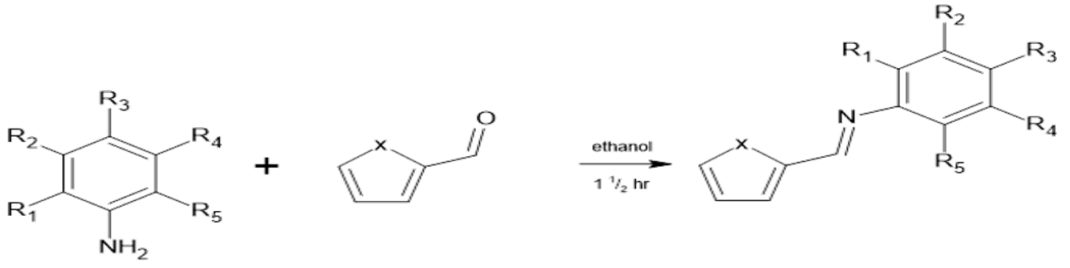
While heating the mixture, add small porcelain chips to prevent bumping. Allow the mixture to undergo condensation for 1.5 hours.

After 1.5 hours, pour the reacted mixture into a beaker filled with crushed ice. Once the solid product has formed, filter it out and allow it to dry. The product can be further purified through recrystallization using alcohol.

II. Synthesis of novel substituted imidazole derivative

A 0.01 M solution of the purified Schiff base was treated with 0.001 M ammonium acetate and 0.01 M benzil in the presence of ethanol. The mixture was refluxed for 12 hours to produce the desired imidazole derivatives. Once the reaction is complete, cool the mixture on ice and filter out the solid product. Wash the solid product with cold water. Finally, recrystallize the purified imidazole from ethanol and allow it to dry.[11]

SCHEME STEP: 1

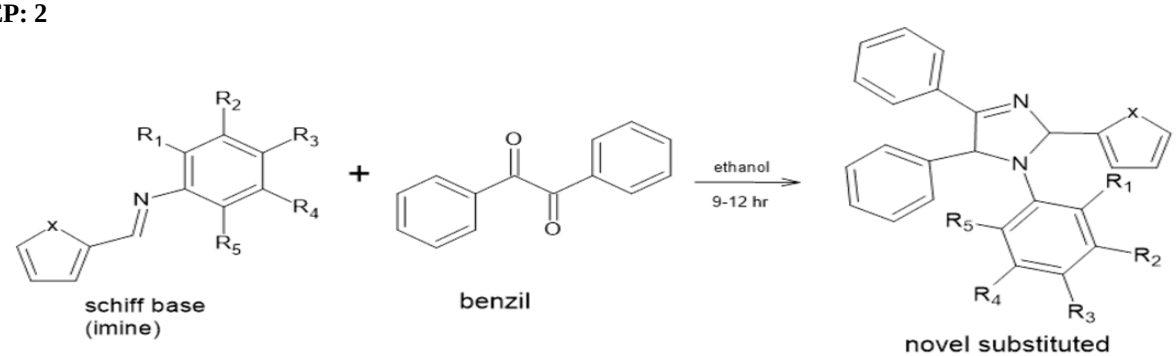


substituted aromatic primary amine **(1A-1T)**

substituted aldehyde

schiff base (imine) **(2A-2T)**

STEP: 2



(2A-2T) **(3A-3T)**

III. Anti-bacterial activity

It was determined by the cup plate method using the standard drug Ciprofloxacin(100µg/ml). The test concentrations were 50µg/ml and 100µg/ml respectively. The control used was DMF.

RESULTS AND DISCUSSIONS

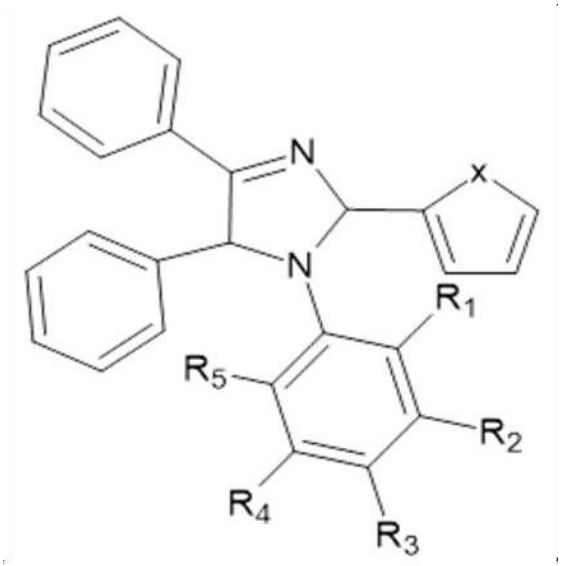


Fig. 2

Table 1: General structure of novel substituted imidazole derivatives.

R1	R2	R3	R4	R5
H	H	SO_2NH_2	H	H
Cl	H	H	Cl	H
H	H	F	H	H
H	H	OCF_3	H	H
H	CF_3	H	CF_3	H
NO_2	H	NO_2	H	H
H	H	OCH_3	H	H
H	H	CH_3	H	H
OCH_3	H	H	Br	H
H	Cl	OCH_3	F	H

X= S, O

Table 2: Binding affinity and toxicity prediction of derivatives.

Compound	Binding Energy	Carcinogenicity	Mutagenicity
3A	-9.1	+ve (59%)	+Ve (73%)
3B	-9.8	+ve (50%)	-ve

3C	-9.3	+ve (52%)	-ve
3D	-9.6	+ve (51%)	-ve
3E	-9.5	+ve (55%)	-ve
3F	-9.6	+ve (76%)	+ve (90%)
3G	-9.5	+ve (55%)	+ve (54%)
3H	-9.8	+ve (60%)	-ve
3I	-9.1	+ve (50%)	-ve
3J	-9.4	-ve	-ve
3K	-8.8	+ve (72%)	+ve (92%)
3L	-9.6	+ve (59%)	-ve
3M	-8.9	-ve	-ve
3N	-9.1	-ve	-ve
3O	-9.2	+ve (50%)	-ve
3P	-9.1	-ve	+ve (57%)
3Q	-9.2	+ve (73%)	+ve (92%)
3R	-9.4	+ve (50%)	-ve
3S	-8.8	-ve	-ve
3T	-9.0	-ve	-ve
Ciprofloxacin	-7.4	-ve	+ve (53%)

Docking studies revealed that compounds 3B and 3H have the lowest binding energy and highest binding affinity, but both show potential carcinogenic effects. In contrast, compounds 3J, 3M, 3N, 3S, and 3T test negative for carcinogenicity. Compound 3J has the lowest binding energy, no carcinogenicity, and mutagenicity making it an ideal candidate for antibacterial research, as it forms a hydrogen bond with serine at position 78. Notably, ciprofloxacin has higher binding energy than the 20 novel substituted imidazole derivatives, indicating it may be less effective against the *E. coli* receptor. Synthesized compound obtained in 70-72% yield. The antibacterial property of compound 3J was evaluated using the cup plate method, with ciprofloxacin as a reference. The results confirmed that compound 3J exhibited good antibacterial activity with a zone of inhibition of 11-13mm.

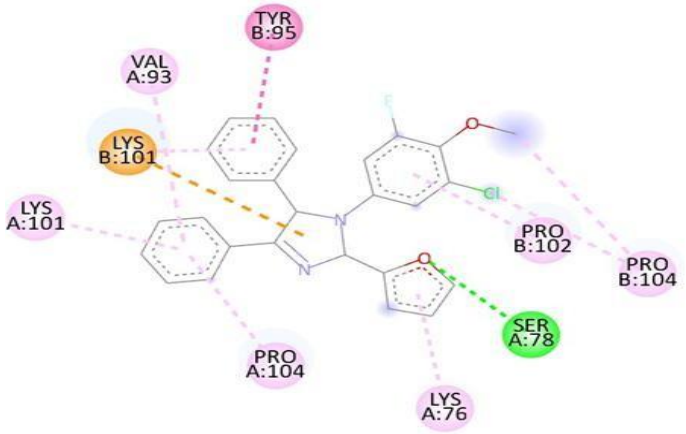


Fig. 3

Binding mode of 3J with SER A: 78

Fig.4: Prepared 2J

Fig.5: Prepared 3J

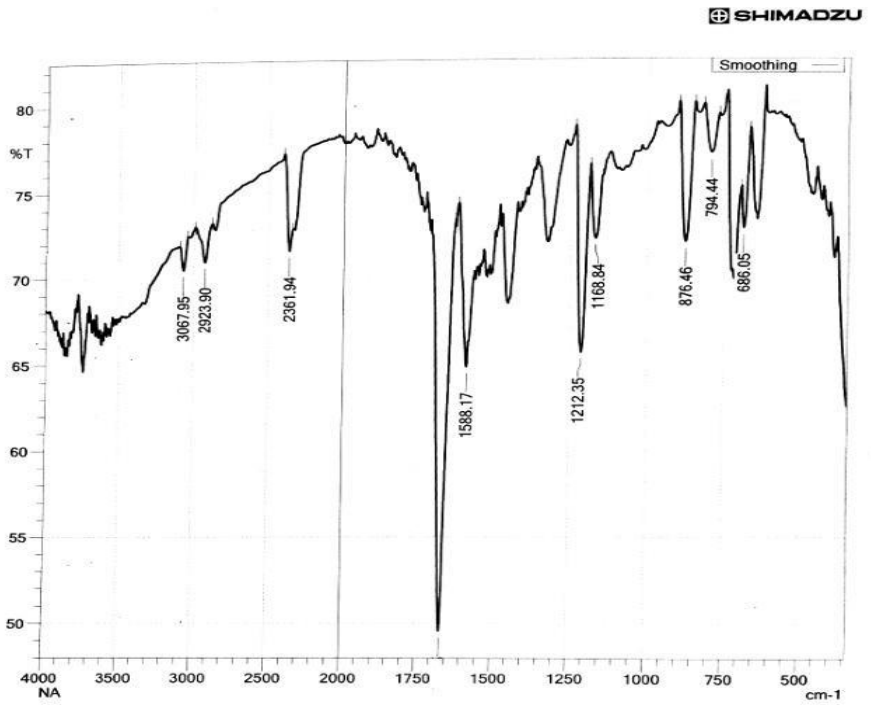


Fig. 6: IR SPECTRUM OF COMPOUND 3J.

CONCLUSION

Compound 3J has emerged as the most promising antibacterial candidate due to its strong receptor binding, favorable toxicity profile, and significant antibacterial activity. In contrast to compounds 3B and 3H, which showed potential carcinogenic effects, 3J exhibited a safer toxicity profile. Additionally, its superior binding affinity compared to ciprofloxacin underscores its potential as a novel antibacterial agent against E. coli. These findings support the need for further preclinical studies and the development of compound 3J as an effective antibacterial agent.

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