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Insilico identification of novel compound against Urinary Tract Infection

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Abstract

Urinary tract infections are one of the widest diseases in India nowadays. There are only limited diagnoses about the major cause of infection to initiate UTIs in humans. Most of the UTIs are caused by bacteria and fungus and are one of the most common indications for rapid increase in antibiotics usage for UTIs. FimH are surface organelles of Escherichia coli, responsible for UTIs, found on the tip of Escherichia coli *pili that interact with oligomannose on urothelial cells of urinary tract. We selected six Benzimidazole derivatives, that exhibits antimicrobial activity, were docked against the FimH protein. The docking analysis of FimH against six Benzimidazole derivatives revealed that all six* Benzimidazole derivatives *have potential to work against UTIs, but 1-{1-[(2Z)-3-(3-chlorophenyl) prop-2-enoyl]-1H-benzimidazol-2-yl}ethanol (-8.04 kcal/mol) fits better than the rest. Some of the commonly used drugs to treat UTIs include Ciprofloxin, Fosfomycin, Levofloxacin and Nitrofurantoin these drugs were subjected to docking analysis for comparative studies.*

Keywords: Urinary tract infections, *Escherichia coli*, FimH, AutoDock 4.2 and FimH.

Introduction

A urinary tract infection (UTI) involves different parts of urinary tract that get infected like kidney, bladder, ureter, and urethra[1]. Main cause of UTIs are microbes, an uropathogenic Escherichia coli bacteria[2], found in bowel, is responsible for more than 85 percent of all UTIs[3]. Infections in soft tissues are majorly caused due to infections in UTI and infect the urinary tract. Females having shorter urethra are more likely to get a UTI, because it is easier for *E. coli* and other bacteria or microbes to reach the bladder easily. About 50-60% females have at least once faced UTI during their lifetime in comparison to males. In present scenario UTI falls under the same category of "blooming diseases" as malaria and tuberculosis. Detrimental conditions and lack of knowledge about infection is the major cause behind spreading of UTI. If suspected, indiscriminate use of antibiotics results in making the bacteria resistant against the antibiotic. Benzimidazole *derivatives* are heterocyclic aromatic organic compounds with bicyclic in nature and have its existence with fusion between benzene and imidazole. It plays an important role in various pharmacological activities and has antibacterial, antiviral, antidiabetic, antimicrobial and anticancer property. Benzimidazoles are stunning effective compounds and many biochemical and pharmacological studies have inveterate that these molecules are implicit against various microorganism strains. *Benzimidazole derivatives* development is the one of the most possible and hopeful area where this issue can be overcome easily and safely further leading to develop a new drugs[4]. The present study assumes to develop a new antimicrobial drug against uropathogens. All the compounds were screened and analysed using bioinformatics softwares to develop new drug against UTIs. In present study FimH protein was used as the target protein which is present Escherichia coli and is responsible for infection of the urinary tract[5]. D-mannose-sensitive binding to the host surfaces is mediated by the Type 1 fimbriae surface organelles of Escherichia coli[6]. This binding is conferred by the minor fimbrial component FimH (Figure-1). Different forms of FimH protein of Escherichia coli[7-8], that are available naturally, have been selected because of their ability to recognize specific receptor targets.

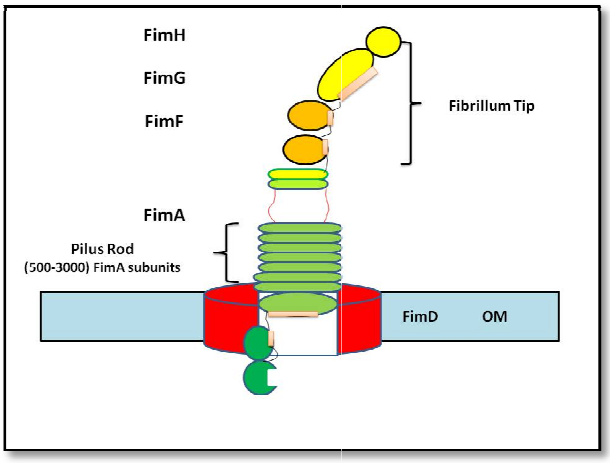


Figure-1
Localized FimH protein

Materials and Methods

Softwares required: Cygwin[9], Molecular graphics laboratory (MGL) tools and AutoDock 4.2[10-11], Discovery studio visualizer 2.5.5[12].

Target Identification: The FimH protein (Figure-2) structure of *Escherichia coli* bacteria was retrieved from Protein Data Bank (PDB)[13] with pdb ID: 4XOA and was cleaned using Discovery Studio.

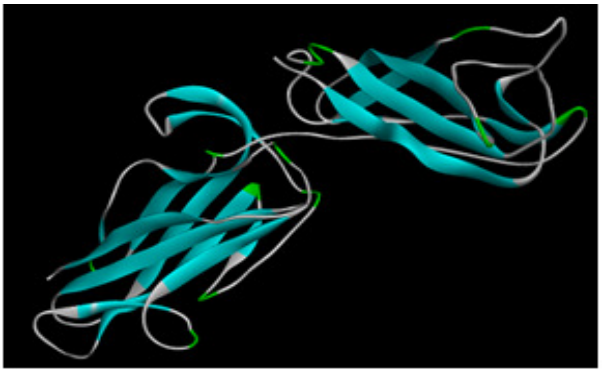
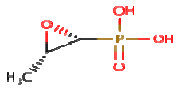
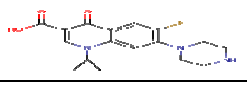
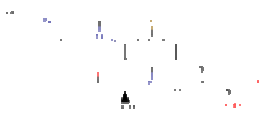


Figure-2
FimH protein structure

Ligand Identification: Benzimidazole derivatives were used as the ligand (Table-2). The present antibacterial drugs that are used for UTIs are Ciprofloxin, Fosfomycin, Levofloxacin and Nitrofurantoin were included in docking and comparative studies and was retrieved from Drug Bank database[14] (Table-1). The known structures were downloaded in *.sdf* format and then converted to *.pdb* format by using Open Babel software[15] and further used for docking studies using AutoDock version software.

Docking FimH with *Benzimidazole derivatives* using AutoDock 4.2: Lamarckian genetic algorithm (LGA) was used as the Docking algorithm. The docking preparation was done by setting grid box size to include all the amino acid residues of the target protein. Each docking experiment comprises of 10 different runs. Main goal has been to provide a computational tool to determine of biomolecular complexes. FimH protein was selected as target in our study. Docking of the selected Benzimidazole derivatives and known drug against FimH was carried out using AutoDock4.2 and Cygwin (provides Linux environment to windows). The interactions of the ligands with the target (docked complex) was analyzed and visualized using Pymol software[16] and Discovery studio.

Table-1
Showing Structures and Drug bank IDs of known drug

Ligand	Drug Bank ID	Structures
Fosfomycin	DB00828	
Nitrofurantoin	DB00698	
Ciprofloxin	DB00537	
Levofloxacin	DB1137	

Results and Discussion

The computational analysis suggested that when the unknown benzimidazol derivatives were docked with *FimH* protein, it was found that -{1-[(2Z)-3-(3-chlorophenyl)prop-2-enoyl]-1H-benzimidazol-2-yl}ethanol showed the best result (Table-3). Also FimH protein when docked with four present antibacterial drugs, Levofloxacin showed the best result among the rest three drugs.

Comparative analysis of benzimidazol derivative and Levofloxacin showed that the benzimidazol derivative have comparatively less binding energy (Table-4) making it more efficient as a drug in comparison to the present drugs.

In-depth study of the best compound may help in search of novel agents as inhibitors of UTIs.

Table-2
Showing structures of Benzimidazole derivatives used as ligands

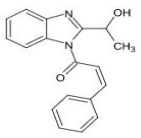
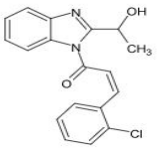
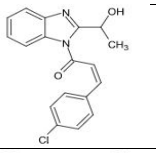
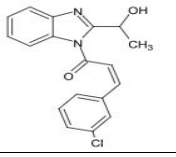
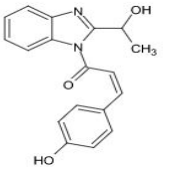
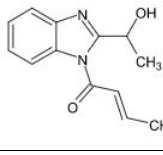
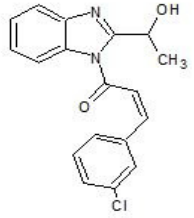
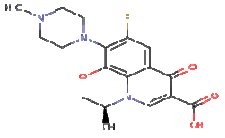
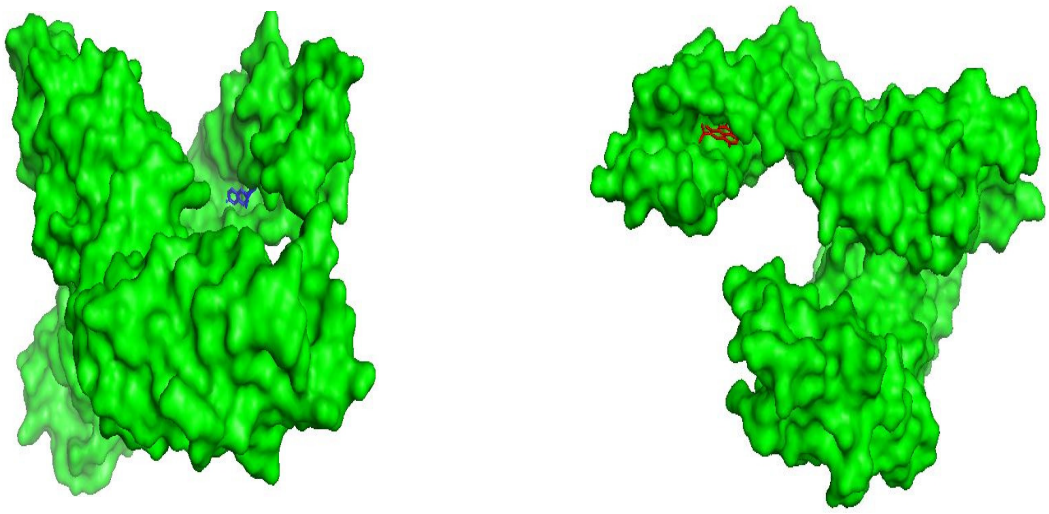
IUPAC /Ligand name	Structures
1-{1-[(2Z)-3-phenylprop-2-enoyl]-1H-benzimidazol-2-yl}ethanol	
1-{1-[(2Z)-3-(2-chlorophenyl)prop-2-enoyl]-1H-benzimidazol-2-yl}ethanol	
1-{1-[(2Z)-3-(4-chlorophenyl)prop-2-enoyl]-1H-benzimidazol-2-yl}ethanol	
1-{1-[(2Z)-3-(3-chlorophenyl)prop-2-enoyl]-1H-benzimidazol-2-yl}ethanol	
4-{(1Z)-3-[2-(1-hydroxyethyl)-1H-benzimidazol-1-yl]-3-oxoprop-1-en-1-yl}phenol	
1-{1-[(2E)-but-2-enoyl]-1H-benzimidazol-2-yl}ethanol	

Table-3
Docking result of protein with different ligands

Antibiotics/Derivatives	Confirmation	Binding energy (kcal/mol)	Ligand efficency	Inhibit constant (µM)
Ciprofloxacin	5	-5.99	-0.25	40.52
Fosfomycin	3	-4.21	-0.53	816.56
Levofloxacin	10	-6.49	-0.19	207.44
Nitrofurantoin	7	-5.01	-0.29	212.87
1-{1-[(2Z)-3-phenylprop-2-enoyl]-1H-benzimidazol-2-yl}ethanol	3	-7.59	-0.35	2.75
1-{1-[(2Z)-3-(2-chlorophenyl)prop-2-enoyl]-1H-benzimidazol-2-yl}ethanol	6	-7.73	-0.34	2.17
1-{1-[(2Z)-3-(4-chlorophenyl)prop-2-enoyl]-1H-benzimidazol-2-yl}ethanol	8	-7.84	-0.34	1.79
1-{1-[(2Z)-3-(3-chlorophenyl)prop-2-enoyl]-1H-benzimidazol-2-yl}ethanol	1	-8.04	-0.35	1.29
4-{(1Z)-3-[2-(1-hydroxyethyl)-1H-benzimidazol-1-yl]-3-oxoprop-1-en-1-yl}phenol	8	-8.02	-0.35	1.31
1-{1-[(2E)-but-2-enoyl]-1H-benzimidazol-2-yl}ethanol	8	-6.13	-0.36	31.84

Table-4
Comparative Analysis of the drug and novel compound

Binding energy (kcal/mol)	Ligand efficiency	Inhibit constant (µM)	Drug	Structure
-8.04	-0.35	1.29	1-{1-[(2Z)-3-(3-chlorophenyl)prop-2-enoyl]-1H-benzimidazol-2-yl}ethanol	
-6.49	-0.19	207.44	Levofloxacin	



(a) (b)

Figure-3
(a): 1-{1-[(2Z)-3-(3- chlorophenyl)prop-2-enoyl]-1H-benzimidazol-2-yl}ethanol (b): Levofloxacin

Conclusion

We concluded that the Benzimidazole derivatives acts as an antibacterial agent against UTI pathogenic bacteria, i.e. *Escherichia coli,* hence it may be used as new drug to treat UTI. The results of our study not only give a base for further research but also is useful for a novel drug development to control bacterial infection. Hence our study will therefore play a significant role in experimental design and development of novel antibacterial drug in future to treat UTI.

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