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Molecular docking study and antibacterial activity of novel chalcone derivatives

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Abstract
Chalcones are the natural phytoconstituents widely distributed in plants originate in fruits, vegetables, grains, bark, roots, stems, flowers, tea and wine. Chalcones with different substituents have revealed a variety of biological activities that may benefit human heaths, with marked biological significance such as Antimicrobial, Anti-inflammatory, Anticancer activity and Antioxidant. Hence, Chalcones are considered as an indispensable component in a variety of nutraceutical, pharmaceutical, medicinal and cosmetic applications with versatile health benefits. Present research a novel series of synthetic Chalcone derivatives (a-j) have been synthesized after 3D QSAR studies. This work deals with a molecular docking study of novel chalcone derivatives was performed by using Schrodinger (Maestro 11.5v) with PDB Id: 4PVR for drug protein interaction study. Synthesize novel chalcone are carried out using Acetophenone and substituted aldehydes to form Chalcone derivatives. Novel chalcone derivatives were assess for antibacterial activity against *Escherichia coli, Staphylococcus aureus*. Among the synthesized compounds (h, i and j) showed good antibacterial activity; whereas compounds (d, f, g) shows moderate antibacterial activity comparable to the reference drug Chloramphenicol. Thus, the conclusion can be made that the designed moiety can exhibit a good antibacterial activity. Compounds (h, i and j) derivatives were most active with (-8.286, -8.056, -8.000) docking score and (-8.286, -8.078, -8.112) Glide score respectively comparatively higher than standard (Chloramphenicol) Docking Score (-7.564) and standard Glide Score (-7.725).

Keywords: Chalcone, molecular docking, antibacterial, escherichia coli, staphylococcus aureus

Introduction
Chalcones are the natural phytoconstituents having functional group is an aromatic ketone and an enone that forms the important moiety for a variety of important for biological significance, which are jointly known as chalcones. The presence of a reactive α, β unsaturation keto function in chalcone found to be responsible for their Antimicrobial, Anti-inflammatory, Anticancer activity and Antioxidant. In current scenario the most serious problem in human health is microbial diseases in world hence newly design and synthesis numbers of drug resistant microbes. Chalcones are natural phytoconstituents widely distributed in plants originate in fruits, vegetables, grains, bark, roots, stems, flowers, tea and wine that can also be obtained synthetically using a relatively simple synthesis procedure. The general method applied to synthesize chalcone is the Claisen - Schmidt reaction, while a modern alternative to synthesize chalcones by only starring mechanism. Chalcone derivatives have well known for their broad spectrum of pharmacological activities, including Antimicrobial, Anti-inflammatory, Anticancer activity and Antioxidant. Some chalcones having Hydroxyl, Halogen (Cl, Br, I, *etc*.) groups in different position have been reported to possess Antimicrobial activities. Chalcones have very well-known Antimicrobial agents, and they exert their activity against *Escherichia coli, Staphylococcus aureus*. Present research a novel series of synthetic Chalcone derivatives (a-j) have been synthesized after 3D QSAR studies. This work deals with a molecular docking study of novel chalcone derivatives was performed by using Schrodinger (Maestro 11.5v) with PDB Id: 4PVR for drug protein interaction study. Synthesize novel chalcone are carried out using. Acetophenone and substituted aldehydes to form Chalcone derivatives. Novel chalcone derivatives were assess for antibacterial activity against Escherichia coli, Staphylococcus aureus.

Objective
The objective of the present research is to perform molecular docking studies of novel chalcone derivatives as potent inhibitors of *Escherichia coli, Staphylococcus aureus*.

Material and Methods

Molecular modeling simulations (MDS) are a very much investigated technique for recognizing the potent compound without putting excessively exertion and investment in research. Maestro 11.5 Schrodinger software is used by us to investigate the activity in terms of binding affinity (Kcal/mol), and there after the outcomes are compared in binding affinity score for best-docked conformation. For the molecular dockings, the all novel chalcone derivatives (ligand) and protein structures were generated within software. Ligands were sketched and minimized with Maestro 11.5 Schrodinger and further converted to the 3D structure. All the designed structures were optimized by energy minimization using MM2 method. To identify the potential, a protein 4PVR was selected and which was downloaded from protein data bank. The outcomes of results were analyzed by Docking score, Glide score, and Binding energy with various bonding interactions. For the molecular dockings, the all novel chalcone derivatives (ligand) and protein structures were generated within software. Ligands were sketched and minimized with Maestro 11.5 Schrodinger.

Experimental Method

Docking protocol

Molecular docking of proposed 10 novel Chalcone derivatives were done with the help of Maestro 11.5 Schrodinger software in order to choose the derivatives which shows good interactions with target protein with PDB Id: 4PVR taken from the Protein Data Bank (www.rscb.org).

Following steps are taken in to consideration for molecular docking study

Ligand preparation

Protein preparation and its refinement

Receptor grid generation

Protein ligand docking

Ligand preparation

The Schrödinger ligand preparation was done by using Lig Prep panel application which consists of series of steps that perform conversion of 2D structures to 3D structure, apply correction to the structure by minimizing the proper bond angles and distances and optimize the structure by minimizing its energy through force-field OPLS3.

Protein preparation and its refinement

For molecular docking study protein is the essential component and it is necessary to minimize the energy of protein molecule prior to docking studies with ligands. Both the Protein for ligand docking study was prepared by using protein preparation wizard tool in which was used to import proteins for the protein data bank (PDB). Proteins obtained from the PDB, vendors and other sources frequently have missing hydrogen, partial charges, side chain and whole loops region. So, to overcome all these barriers in docking study the proteins to undergone through pre-processing and it was done by selecting following parameters

- Add hydrogen
- Create zero order bonds to metals
- Create disulphide bonds
- Filling missing side chains using prime
- Fill in missing loops using prime
- Delete water beyond 5.00 Å From het group
- Generate het state using Epik: PH 7.0+/- 2.0

Receptor grid generation

Grid generation must be performed prior to running a virtual screen with glide. The shape and properties of the receptor are represented in a grid by field that provides progressively more accurate scoring of the ligand poses. For receptors that adopt more than one conformation on binding, Glide prepares grids for each conformation, to ensure that possible actives are not missed.

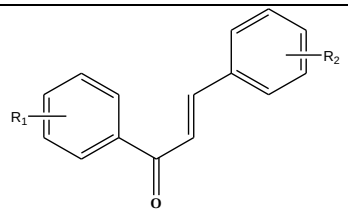
- Receptor
- Site
- Constraints

Protein ligand docking simulation

The docking was done flexible using Standard Precision (SP) and further refinement was done by using Extra Precision (XP) mode. The ligand docking process helps to predict ligand conformation and orientation (posing) within a targeted binding site and thus helps to interpret interactions of ligand atoms with amino acids of proteins, and to understand the binding affinity. The ligand docking was carried out in the following steps:

- Firstly Ligand docking application was selected from Glide in the Application menu.
- Next to receptor grid, click Browse and choose generated receptor grid.
- The LigPrep file of flavones was then browsed and entered into ligands to be docked.
- The ligand docking was carried out in the extra precision (XP) mode.

Table 1: Chalcone derivatives considered for molecular docking studies



Code	R_1	R_2
a	H	H
b	H	2-Chloro
c	H	3-Chloro
d	H	3-Methyl
e	H	3-Methoxy
f	H	2,4-Dichloro
g	4-Chloro	H
h	4-Chloro	2-Chloro
i	4-Chloro	4-Methyl
j	4-Chloro	2,4-Dichloro

Table 2: Glide score (G-score), docking score, potential energy and amino acids involved in interaction of newly designed chalcone derivatives and chloramphenicol

Code	Glide score	Docking Score	Potential Energy	Amino acids involved in interaction
a	-7.125	-7.214	101.923	GLY102, TYR109, LYS103
b	-7.015	-7.018	112.826	GLY102, LYS103
c	-7.336	-7.335	103.880	GLY102
d	-8.002	-8.012	106.840	TYR109
e	-7.923	-7.924	123.109	ASN46, TYR109
f	-7.103	-7.104	107.343	MG402, GLY102
g	-8.071	-8.071	87.896	LYS103, GYL102
h	-8.286	-8.286	97.896	GLY102, TYR109, LYS103
i	-8.078	-8.056	108.774	GLY102, LYS103
j	-8.112	-8.000	102.630	GLY102, LYS103
Chloramphenicol	-7.725	-7.564	97.896	GLY102, TYR109, LYS103

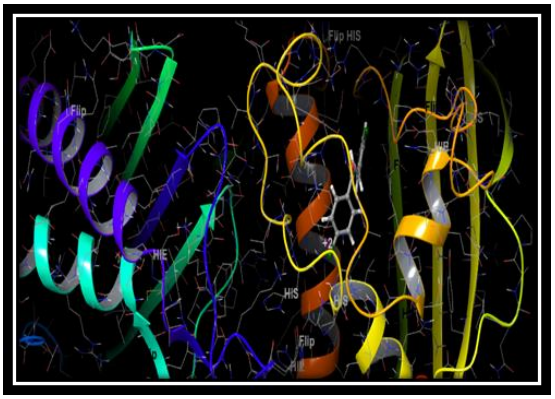


Fig 1: Ribbon structure of enzyme with (h)

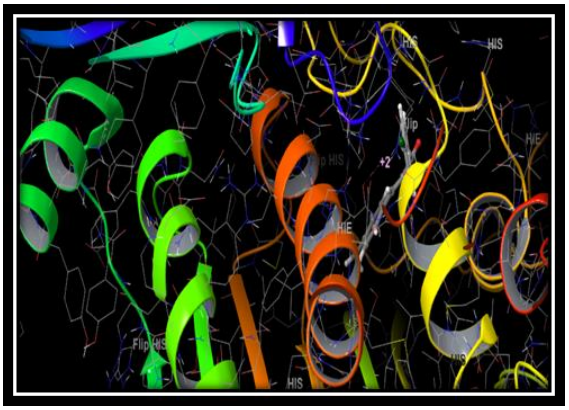


Fig 2: Ribbon structure of enzyme with (i)

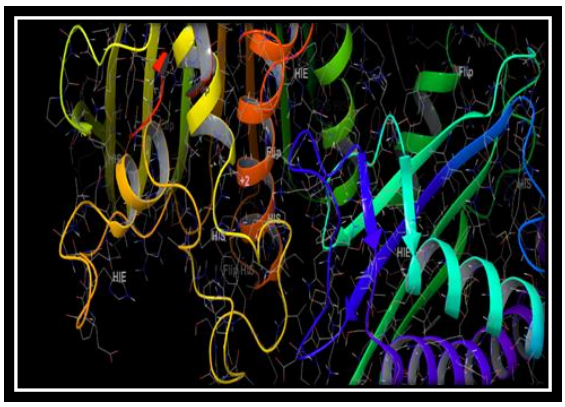


Fig 3: Ribbon structure of enzyme with (j)

Result and Discussion

All the newly designed chalcone derivatives were docked into the binding site of the receptor PDB ID 4PVR using Schrodinger (Maestro 11.5v) software. After preparation of ligand and protein, protein grid was generated under three heading, Receptor, Site and Constraints and defines the size if grid box in which ligand were projected to dock. Docking result shows that binding of ligand to protein occurs as per applied constriction with interaction with preferred manner as shown in Table 2. Best docking score and glide score of newly designed chalcone derivatives were compared using docking score and glide score and potential energy. Compounds (h, i and j) were most active with (-8.286, -8.056, -8.000) docking score and (-8.286, -8.078, -8.112) Glide score respectively comparatively higher than standard (Chloramphenicol) Docking Score (-7.564) and standard Glide Score (-7.725).

From the Molecular simulation study compound, 1-(4-Chloro)-phenyl-3-(2-chloro)-phenyl prop-2-en-1-one, 1-(4-Chloro)-phenyl-3-(4-methyl)-phenyl prop-2-en-1-one and 1-(4-Chloro)-phenyl-3-(2,4-dichloro)-phenyl prop-2-en-1-one as shown in Fig.1, Fig.2 and Fig.3 respectively.

Conclusion

From present research it is prove that the newly designed chalcone derivatives have better binding sites and better protein ligand interaction with *Escherichia coli*, *Staphylococcus aureus* cell wall protein. The highly precised binding protein interaction leads to greater field interaction with crystalized domain. This can be appreciated for synthesis thereafter biological screening of promising hits.

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