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IN-SILICO DESIGN OF NEW CHALCONE DERIVATIVES WITH PYRIDINE MOIETIES AND IT'S ANTI-MICROBIAL ACTIVITIES

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ABSTRACT

In the present dissertation, different novel Chalcone derivatives with pyridine moieties were designed using ACD/Lab ChemSketch 12.0 and their properties were predicted using Molinspiration software. The designed lead having required physiochemical properties, drug likeness and compliance with Lipinski Rule of Five were selected for docking studies via Biovia Discovery Studio 2021. The novel compounds are selected for their antibacterial and antifungal studies.

Among newly identified compounds 1-(2' pyridyl)-3-(3''-bromo-5''-hydroxyphenyl)-2-propene-1-one i.e., 3(g) showed highest antibacterial activity and antifungal activity with PDB ID: 4E81 and PDB ID: 6UEZ respectively.

KEYWORDS: - Chalcone, Pyridine, ACD/Lab ChemSketch 12.0, Molinspiration, Lipinski Rule of Five, Biovia Discovery Studio, Antibacterial study, Antifungal study, 4E81, 6UEZ.

INTRODUCTION

In the past most drugs have been discovered either by identifying the active ingredient from traditional remedies or by serendipitous discovery. But now we know diseases are controlled at molecular and physiological level. Drugs are essential for the prevention and treatment of disease. Human life is constantly threatened by many diseases and thus ideal drugs are always in great demand. Drug designing[1] is the inventive process of finding new medications based on the knowledge of biological target. Drug designing or "tailor-made compound" aims at developing a drug with high degree of chemotherapeutic index and specific action. Drug design frequently but not necessarily relies on computer modelling techniques. This type of modelling is often referred to as Computer Aided Drug Designing[3]. In general modelling approaches are categorized into structure based and Ligand[2] based methods. These structure-based approach consists of using the 3D structure of the target for the generation or

screening of potential ligands. Chalcones (1,3-diphenyl-2-propen-1-ones) are an important class of natural products. They are found in a plant and are considered to be precursors of flavonoids and isoflavonoids, natural and synthetic chalcones exhibit a wide range of biological activities such as antimalarial, antileishmanial, antitumoral and antimicrobial effects. Chalcones are a valuable molecule of medicinal importance due to presence of reactive keto-ethylenic group –CO–CH=CH–, belonging to the flavonoid family. These reactive α, β unsaturated keto function in chalcones are responsible for their biological activity.

MATERIALS & METHODS

Preparation of protein Structure

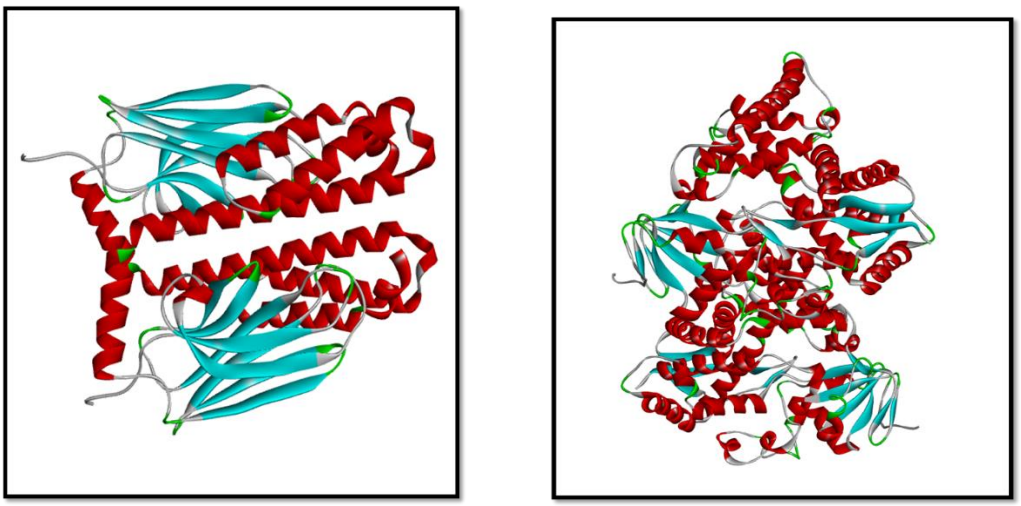
The crystal structure of <name of the protein> (PDB id: 4E81 with resolution 1.90A°) and <protein name> (PDB id: 6UEZ with resolution 1.98A°)was retrieved from the Protein Data Bank (PDB). The protein was prepared, for docking by removing the water and hetero atoms using Biovia Discovery Studio 2021 and then defined the sphere in the active site through an option “Define and Edit Binding site”, and the radius of the SBD_Site_Sphereset to 8.000. The values of X, Y and Z axis of the sphere defined are 15.077902, 21.606804 and 45.214753 respectively.

Ligand Preparation

The chemical structures of the ten compounds were downloaded from the PubChem database (http://pubchem.ncbi.nlm.nih.gov) in 3D sdf format, by using Discovery Studio tool; they were saved in PDB format. These ligands were then subjected to prepare ligands protocol of DS. They were subjected to include stereo chemical, ionization, tautomeric variations, as well as energy minimization and optimized for their geometry, desalted and corrected for their chiralities and missing hydrogen atoms. The bonds orders of these ligands were fixed and the charged groups were neutralized. The ionization and tautomeric states were generated between pH of 6.8 to 7.2. In the final stage of Ligand preparation, compounds were minimized using CHARMM force field. All the low energy conformers per ligand were generated and the optimized ligands were used for docking analysis.

Molecular Docking

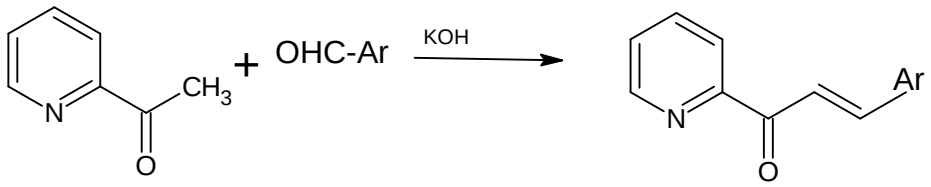
LibDock uses protein site features, referred to as hot spots, consisting of two types states (polar and apolar). The protocol allows the user to specify several modes for generating ligand conformations for docking. Scoring function of the LibDock calculates the binding affinity score or docking score (LibDock score) of protein-ligand complex. Also, possible hydrogen bonding and various interaction poses are calculated. The top ranked docked complexes of each compound are selected on the basis of LibDock Score. Binding poses with highest LibDock Score with maximum interactions are preferred as the best pose.



A) PDB ID: 4E81 B) PDB ID: 6UEZ

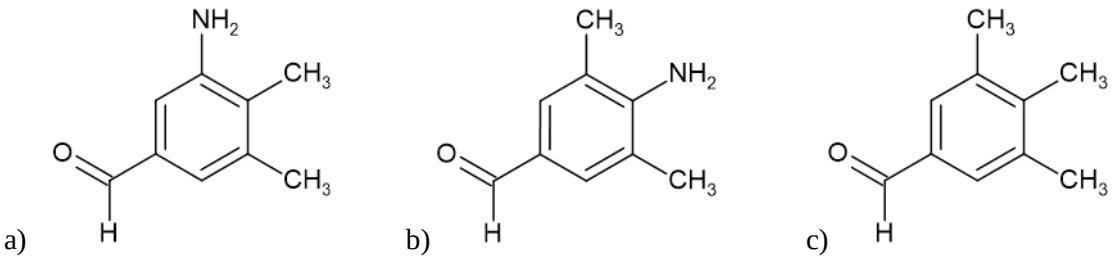
FIG: Three-Dimensional structure of proteins taken for the study

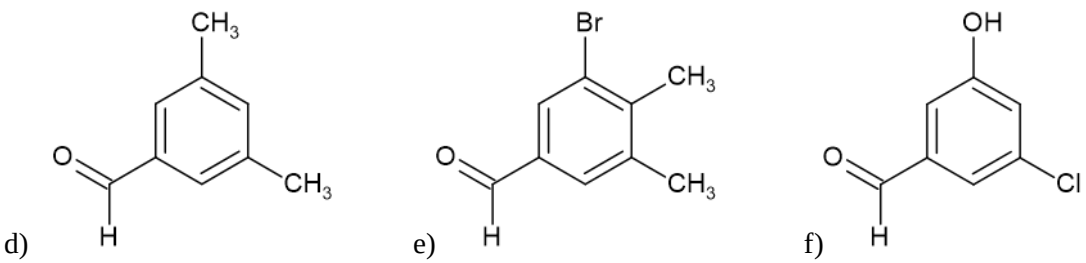
SCHEME OF WORK

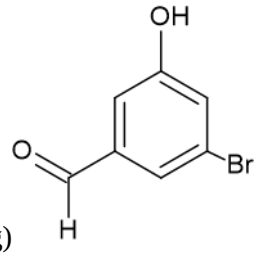


2 Acetyl pyridine Aldehyde Chalcone incorporated with pyridine

Various aldehydes







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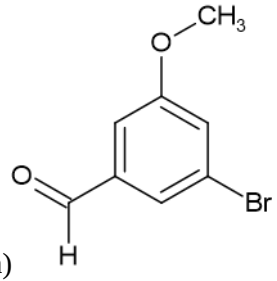

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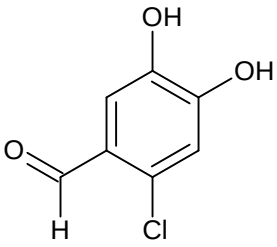

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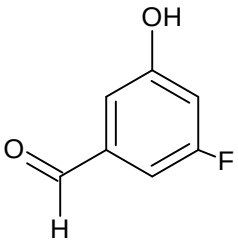


j)

RESULTS AND DISCUSSION

25 analogues which are the chalcone derivatives of 2-acteyl pyridine were designed using the software, ACD Lab Chemsketch 12.0.

Initially the designed 25 analogues were subjected to Lipinski rule analysis using Molinspiration software. From the results of Lipinski rule analysis, 10 compounds were selected for further studies, since the compounds did not show any violation from the Lipinski rule of five.

Further the selected 10 analogues were subjected to docking studies against to PDB ID: 4E81, PDB ID: 6UEZ. Among the Chalcone derivatives, compounds 3g showed the highest docking scores for antibacterial and antifungal activity respectively

Table : Lipinski rule analysis

Compound	miLogP	natoms	MW	nON	nOHNH	Violation	nrotb
3a	3.38	20	282.73	3	0	0	3
3b	2.88	19	253.32	3	2	0	3
3c	2.66	22	293.28	6	0	0	4
3d	1.97	23	304.26	7	0	0	4
3e	4.20	19	316.20	2	0	0	3
3f	2.77	18	259.69	3	1	0	3
3g	2.90	18	304.14	3	1	0	3
3h	3.44	19	318.17	3	0	0	4
3i	2.10	19	275.69	4	2	0	3
3j	2.25	18	243.24	3	1	0	3

Summary

Chalcone & pyridine-based compounds on literature review showed promising scope for exhibiting various biological activities so it was planned to do docking studies of certain novel chalcone derivatives and to explore its antibacterial and antifungal activities. The investigation that has been compared out during the present work is divided into following sections:

Design of novel compounds and Lipinski Rule

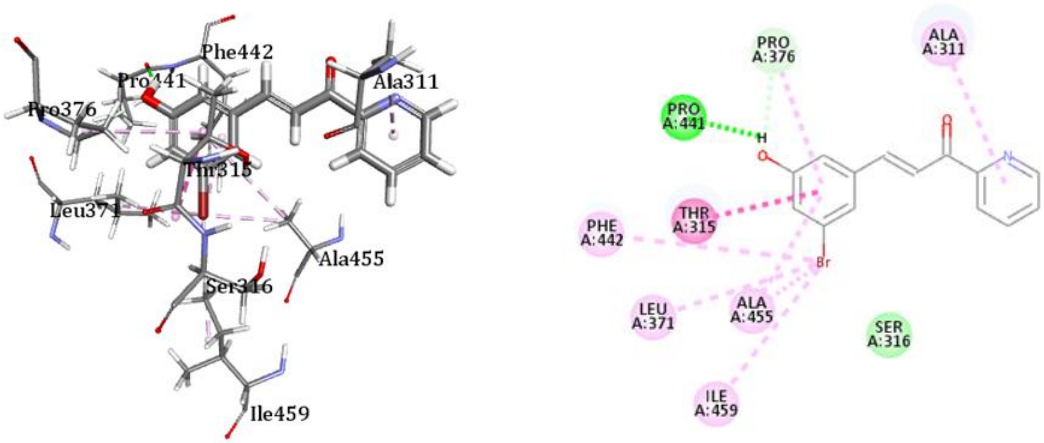
From the literature survey it was revealed that chalcone derivatives can event anti-bacterial & antifungal activities. So, several hybrid molecules bearing pyridine nucleus were designed using ACD/Lab ChemSketch 12.0 Software The molecules so designed were subjected to Lipinski Rule Analysis using Molinspiration to identify the theoretically active one. The result of the analysis yield 10 molecules for subjecting to next step

Docking studies

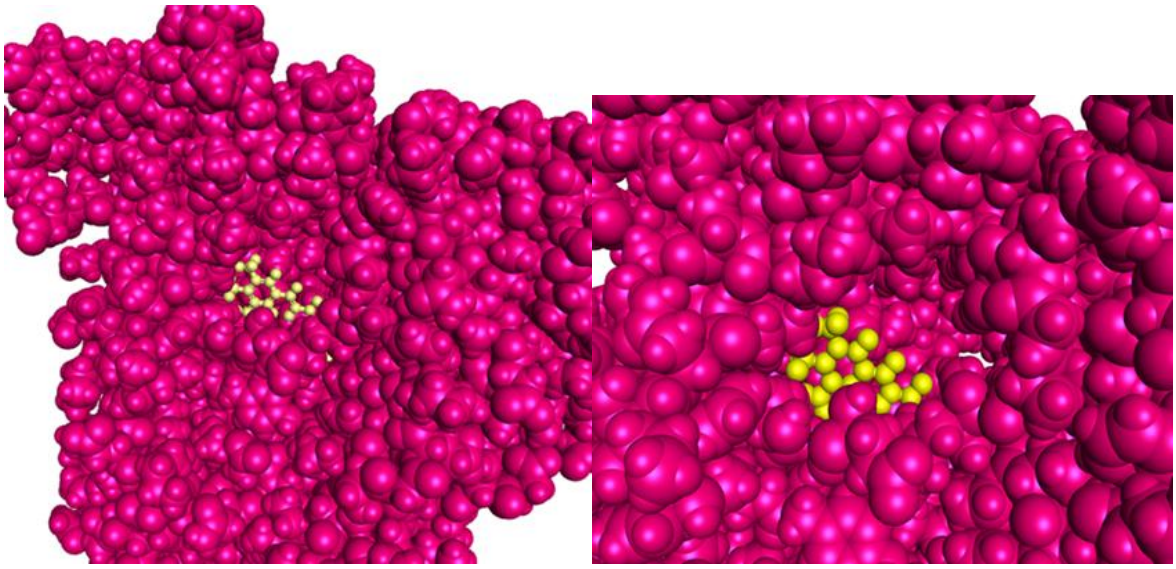
The 10 theoretically active compounds Identified above were subjected to docking study against 4E81 & 6UEZ for antibacterial and antifungal activity respectively

TABLE: Docking scores of PDB ID 6UEZ

Compound Code	LibDock Score
3a	96.68
3b	76.52
3c	79.62
3e	93.83
3f	97.82
3g	97.87
3h	71.47
Griseofulvin (std)	101.18



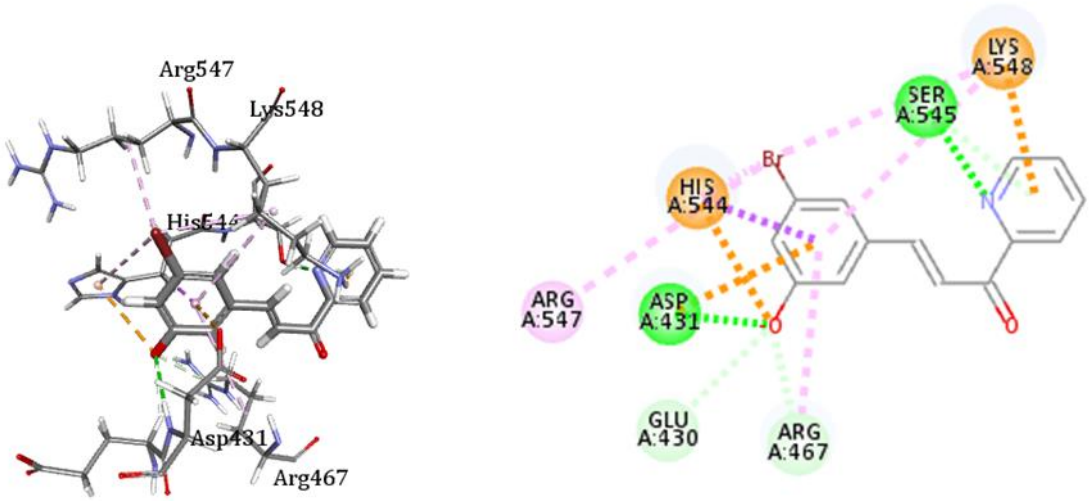
Interaction of 3g with 6UEZ



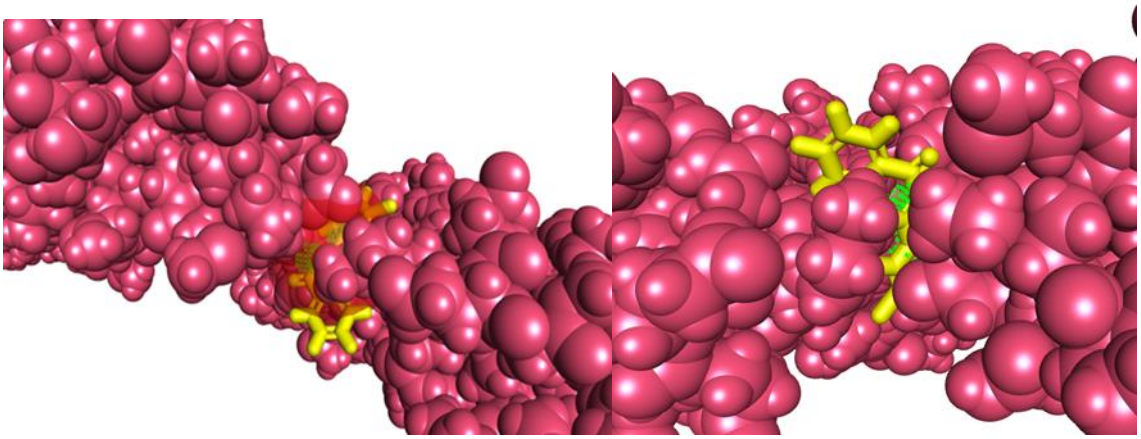
Docking of 3g with 6UEZ

Table: Docking scores with PDB ID 4E81

Compound code	LibDock score
3f	49.501
3g	71.47
3j	70.62
Ampicillin (std)	75.18



Interaction with 3g with 4E81



Docking with 3g with 4E81

CONCLUSION

The results of antibacterial and antifungal studies performed on novel compounds help to draw conclusion regarding the possibilities of proposing lead moieties from the newly synthesised compounds 3 (a-j) which can be a useful lead for development of anti- microbial agents

Compound 3g: 1-(2’ pyridyl)-3-(3’’-bromo-5’’-hydroxyphenyl)-2-propene-1-one emerged to be the most promising potential lead out of entire series of 10 novel compounds, owing to wide spectrum of activities displayed by molecules with significant antibacterial activity exhibited against DnaK of *E coli*

The compound 3g: 1-(2’ pyridyl)-3-(3’’-bromo-5’’-hydroxyphenyl)-2-propene-1-one showed promising anti-fungal activity against alpha demethylase which was higher than that exhibited by other members of the series which shows the potential of that compound to be developed as an antifungal agent

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