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In-silico EVALUATION OF OXADIAZOLE-BASED MOLECULES FOR POTENTIAL ANTIFUNGAL APPLICATIONS

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ABSTRACT

Oxadiazole derivatives have emerged as a promising class of compounds with notable antifungal potential. The binding interactions of certain oxadiazole derivatives with the crystal structure of a new antifungal protein (PDB ID: 1P9G) generated from Eucommia ulmoides Oliver were assessed in the current investigation using molecular docking techniques. With final energy values of 31.43 and docking scores as high as -47.86 kcal/mol, the data showed good binding affinities. At the enzyme's active site, notable molecular interactions were detected, especially aromatic interactions involving the residue HIS72A, which seem to support the stability of the enzyme–inhibitor complex. These results demonstrate the potential of scaffolds based on oxadiazole as effective antifungal medicines.

Keywords: Oxadiazole Derivatives, Molecular Docking, Ecommia Ulmoides Oliver, Antifungal Potential.
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INTRODUCTION

Fischer's lock-and-key model introduced the idea of ligand-receptor binding, positing that a ligand precisely fits into a receptor's active region in a similar manner to how a key fits into a particular lock. The foundation for the first molecular docking techniques, which saw the ligand and receptor as inflexible, rigid entities, was established by this early hypothesis.[1-2] Koshland subsequently created the induced-fit theory, which proposed that ligand contact can result in conformational changes in the receptor. This theory states that throughout the binding process, both the ligand and the receptor are rather flexible.[3] Due to computing limitations, most docking simulations have traditionally relied on a flexible ligand–rigid receptor paradigm, even though induced-fit provides a more dynamic and realistic perspective of molecular interactions.[4-5] Because it strikes a balance between accuracy and efficiency, this simplified model is still often employed in docking research today, even with advances. About 70–80% of plant infections are caused by phytopathogenic fungi, which present serious problems for crop management and agricultural output. These pathogens frequently generate identifiable signs, like sunken necrotic lesions with crimson borders that are

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typical of anthracnose infections brought on by Colletotrichum species.[6] Colletotrichum, Botrytis, Alternaria, and Fusarium are some of the most researched and troublesome fungal genera that impact plants; they are all linked to significant losses in agriculture.[7-8] Even with significant recent progress, it is still very difficult to include entire receptor flexibility, particularly backbone movements, into docking models. When trying to precisely represent such dynamic changes, current docking approaches frequently fail. [9] This is made possible by a number of software programs, such as Discovery Studio, which allow the creation of ligand structures in PDB format. Additionally, these systems help rate ligands according to their expected affinities for binding to a particular biological target, such as a protein or nucleic acid. In order to find the most advantageous complex structure based on interaction energy and geometric complementarity, docking simulations systematically sample potential ligand orientations and conformations within the target macromolecule's binding pocket.[10-11] The scoring algorithms built into docking software are crucial for accurately predicting the binding affinity of ligands and their molecular targets. Our ability to precisely determine the three-dimensional structures of both small chemical compounds and big biomacromolecules has been transformed by structural biology techniques like nuclear magnetic resonance (NMR) spectroscopy and X-ray crystallography. We now have a far better grasp of molecular recognition and interaction because to these structural discoveries. Homology modeling, which is based on sequence similarity with known protein structures, is a useful technique for predicting protein conformations when experimental evidence is scarce. In structure-based drug design, this modeling technique is essential because it makes it possible to create trustworthy target models for virtual screening.[12] However, rather than calculating protein–ligand binding affinities with complete precision, scoring systems frequently make assumptions and simplify the process.[13] The electrostatic terms are determined using a Coulombic framework[14]. Because simple point-charge models are not enough to adequately depict real biological conditions, a distance-dependent dielectric constant is frequently used when analyzing charge–charge interactions in order to better simulate the complicated electrostatic environment within proteins.[14] The Lennard-Jones potential, which accounts for both the repulsive and attractive forces between atoms depending on their distance from one another, is commonly used to simulate van der Waals interactions. Certain parameter sets inside the function can be changed to modify the hardness of this potential, which affects how closely ligand and receptor atoms can approach one another.[15] Computational inefficiencies can occasionally impede force-field-based scoring functions, despite their utility. Cut-off distances are used to restrict the range of non-bonded interactions taken into consideration in order to maximize performance.[16] Nevertheles, long-range interaction predictions may become less accurate as a result of this simplification. More complex force-field extensions provide more realism in binding simulations by incorporating extra elements such as solvation effects, entropic contributions, and hydrogen bonding. These functionalities are offered by software programs, including DOCK, GOLD, VlifeMDS, and AutoDock, which vary slightly in their energy function formulations, hydrogen bond treatment, and scoring methods. Additionally, techniques like free energy perturbation (FEP) and linear interaction energy are frequently employed to improve docking predictions, increasing the accuracy of binding energy estimations beyond the original score results.[17]

EXPERIMENTAL

Computational Details

ChemSketch was used to initially sketch all chemical structures (ACD/ChemSketch 12.0, 2009). After that, each molecule was cleaned and prepped for additional computational study in three dimensions. The Merck Molecular Force Field (MMFF) was used to minimize energy in order to get the ideal shape, and molecular docking was performed on VlifeMDS Software. In order to guarantee structurally stable and energetically advantageous conformations appropriate for docking experiments, using a distance-dependent dielectric model, the optimization process was carried out repeatedly until the energy gradient converged to a threshold of 0.001 kcal/mol.[18]

Conformational Analysis and Molecular Docking Analysis

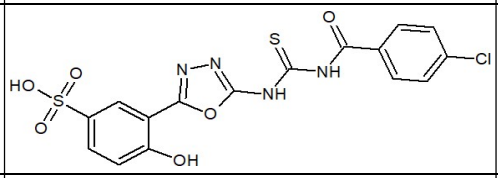
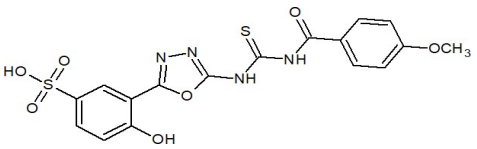
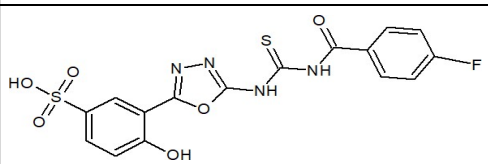
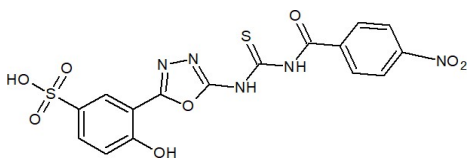
Based on empirical force field calculations that characterize atomic interactions, conformational analysis entails rearranging a molecule's atomic locations to produce a configuration with the least amount of potential energy. The optimized compounds in this study were subjected to a Monte. The Merck Molecular

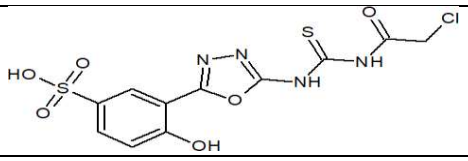
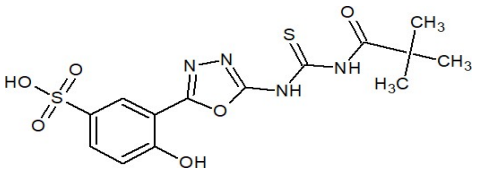
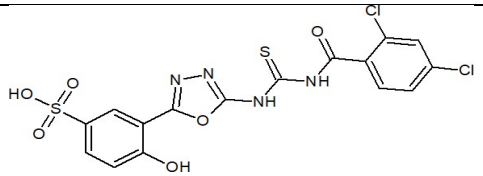
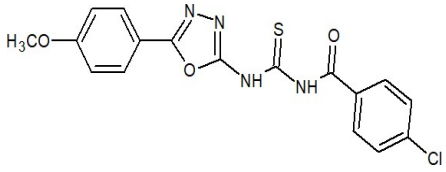
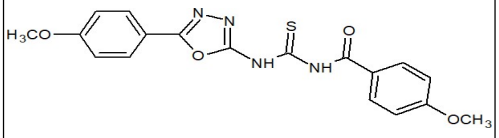
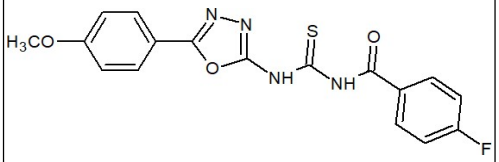
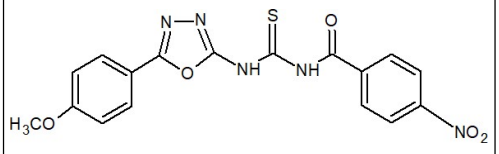
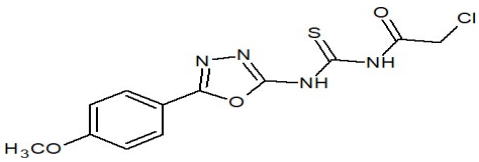
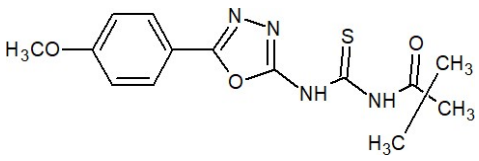
Force Field (MMFF) and an RMS energy gradient convergence threshold of 0.001 kcal/mol were applied in a Monte Carlo conformational search. The Monte Carlo method is a stochastic technique that randomly creates several conformations and assesses them using the Metropolis criterion, which establishes whether a particular conformer is accepted. The lowest-energy conformer was chosen from the pool of conformers produced for each of the 20 optimized molecules since it is the most stable structure and is therefore best suited for additional molecular docking research. For molecular docking investigations, the target receptor's three-dimensional structure—which was identified by PDB ID: 1P9G—was obtained from the PDB. This protein is an antifungal that is generated from Eucommia ulmoides Oliver. Prior to docking analysis, the receptor was meticulously prepared by checking the structure for missing atoms, incomplete bonds, and absent contacts to guarantee accuracy. Only the basic structural components needed for docking remained after all water molecules and unnecessary residues were eliminated. To guarantee structural stability, ligand molecules were built using a molecular builder, and then each one was put through energy minimization. A grid box was then used to delineate the receptor's active site, allowing for precise targeting during the docking simulations. A stable and precise environment for assessing ligand–receptor binding interactions was guaranteed by this preparation.[19-20]

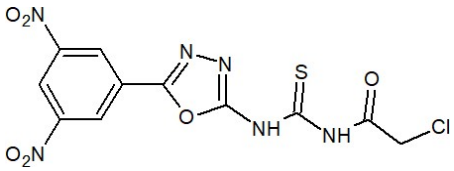
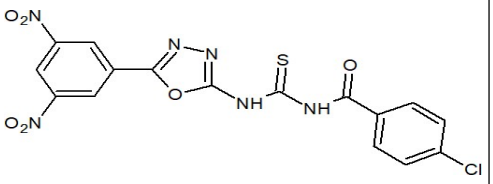
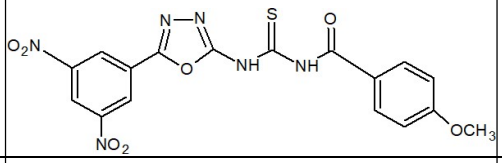
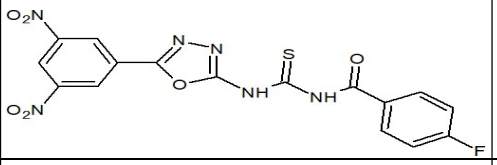
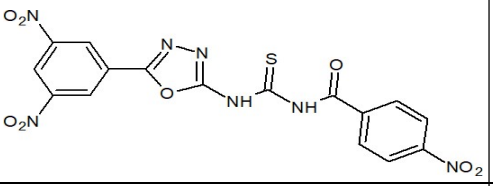
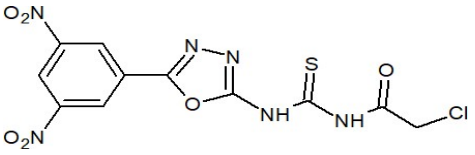
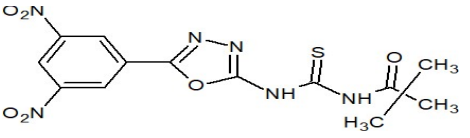
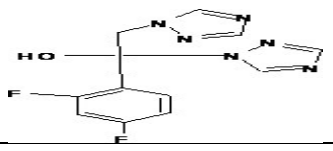
RESULTS AND DISCUSSION

Molecular docking research was conducted to assess the synthetic chemicals' antifungal properties. The preceding table provides a summary of the docking scores for the compound series, which are designated 3a through 3t and the docking score of -47.86 kcal/mol. Compound 3l showed the most favorable binding affinity among them, suggesting a stronger interaction with the target protein than the other derivatives. This finding implies that chemical 3l has encouraging binding potential for the antifungal receptor (PDB ID: 1P9G) in comparison to the body of previous literature. Figure-1 depicts the ideal binding pose produced by docking simulations. Within the binding cavity, every designed molecule showed a similar orientation, and the complex was stabilized by important interactions. The 2D interaction in Fig.-2 shows the notable aromatic stacking with the HIS72A residue, hydrogen bonding with TYR80A, van der Waals forces with LEU83A, and hydrophobic interactions, also including LEU83A. Furthermore, Fig.-3 shows an image of compound 3l docked inside the receptor, showing its ideal orientation and fit.

Table-1: Antifungal Activity Result of Molecular Docking Studies by using GRIP Batch Docking

S. No.	Compound code	Structure of compound	Final energy	Final GRMS	Dock score
1	3a		39.8671	0.8036	-23.20
2	3b		39.7175	0.5890	-28.91
3	3c		38.4819	0.6931	-32.18
4	3d		39.8759	0.5864	-24.92

5	3e		20.4603	0.5248	-29.42
6	3f		9.3422	0.5063	-35.82
7	3g		42.2353	0.4912	-19.35
8	3h		49.2688	0.5784	-43.78
9	3i		49.2688	0.5784	-31.55
10	3j		46.58	0.822	-47.73
11	3k		50.3581	0.6297	-43.54
12	3l		31.4335	0.5457	-47.86
13	3m		20.7862	0.6458	-35.17

14	3n		50.2214	0.8185	-22.94
15	3o		51.0464	0.8635	-44.72
16	3p		53.0934	0.8635	-21.41
17	3q		49.8718	0.8147	-28.12
18	3r		53.6959	0.8514	-30.71
19	3s		33.4813	0.4293	-28.20
20	3t		22.4727	0.7277	-37.69
21	Standard (Fluconazole)		83.1066	0.6270	-49.23

The possibility of the developed oxadiazole derivative as a promising antifungal candidate was further supported by the fact that the typical antifungal medication fluconazole produced a docking score of −49.23 kcal/mol, which is comparable to compound 3l.

Table-2: Data for the Interaction of Compound Code 3l with Amino Acid

Amino acid	Atom of ligand	Distance	Interaction type
HIS72A	8C	4.308	AROMATIC_INTERACTION
TYR80A	9O	1.695	HYDROGENBOND_INTERACTION
TYR80A	29H	2.558	HYDROGENBOND_INTERACTION

TYR80A	15N	3.730	VDW_INTERACTION
LEU83A	20C	3.915	VDW_INTERACTION
LEU83A	17C	3.510	HYDROPHOBIC_INTERACTION

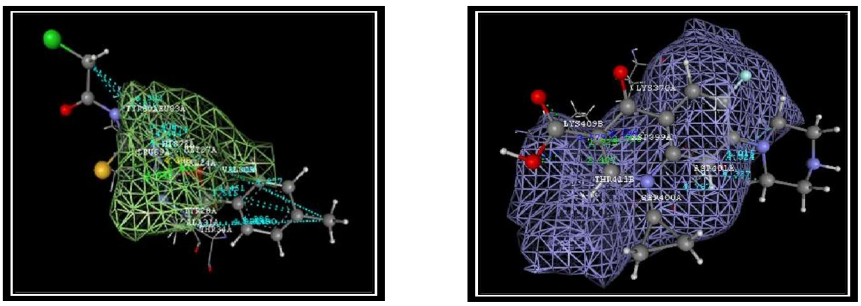


Fig.-1: Docking Poses of Compound Code 3l and Standard Drug

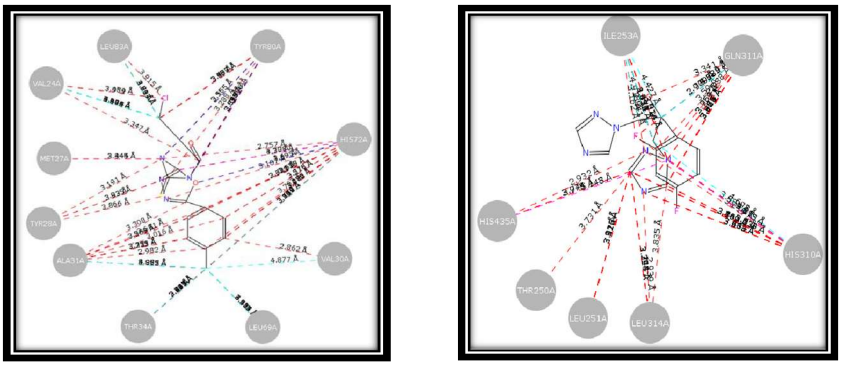


Fig.-2: 2D Representation of Docking Poses of Compound Code 3l and Standard Drug

Fig.-3: Superimposed Image Representation of Docking Poses of Compound Code 3l and Standard Drug

CONCLUSION

With substantial binding affinities and important interactions involving residues like HIS72A that contribute to complex stability, the molecular docking analysis concludes that the synthesized oxadiazole derivatives have promising antifungal potential. Their good fit into the active site is further supported by the existence of hydrophobic and aromatic interactions. These results imply their potential as antifungal drugs and offer important new information about their mode of action.

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CONFLICT OF INTERESTS

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

The present work is related to *SDG-3: Good Health and Well-being*. All the authors contributed significantly to this manuscript, participated in reviewing/editing and approved the final draft for publication. The research profile of the authors can be verified from their ORCID ids, given below:

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