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Molecular Docking Analysis of Some Azole Derivatives with CYP51 for Anti-fungal Activities

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ABSTRACT: *In this study, some of the azole derivatives were randomly selected and subjected to Molecular Docking analysis in order to test their anti-fungal activity. For this purpose, the crystal structure of CYP51 was selected and the downloaded from protein data bank whose pdb id is 3LD6. After Docking procedure, it was found that the molecule 1,3-diphenylpyrazole-4-propionic acid (DPPA) possess good binding affinity and low inhibitory constant. So the protein – ligand interactions of DPPA with 3LD6 were analyzed and their intermolecular interactions were presented. It was concluded that DPPA can serve better for anti-fungal activity and hence it can be used after doing necessary biological examinations.*

Keywords: *Anti-fungal, azoles, CYP51, Docking, 1, 3-diphenylpyrazole-4-propionic acid.*

I. INTRODUCTION

Heterocyclic azole molecules are well known for their pharmacological activities such as anti-cancer, hypoglycemia [1], analgesic [2], anti-inflammatory [3], anti-fungal [4-5], anti-microbial, anti-convulsant [6], anti-bacterial and HIV inhibitory activities. Omar H.EL-Garhy [7] reported in detail the antifungal activities of azoles likely the management of invasive mycoses. The azole anti-fungal drugs focus on the fungal CYP51 (Sterol 14α-demethylase) and they selectively inhibit the yeast and fungal CYP51 on the plant and human counterparts [8]. Even though a number of azole derivatives have been developed as potent antifungal agents, the number of disease causing fungi has also increased simultaneously due to modern medical practices, natural diseases, mobile population, *etc*., which urges the need of anti-fungal reagents. In the present study, the anti-fungal activity of some azole derivatives such as 3,5-dimethylisoxazole (DMI); 4-chloromethyl-3,5-Dimethyl iosxazole (CDMI); 1-(2,5-Dichloro-4-sulfophenyl)-3-methyl-5-pyrazolone (DSMP); 1,3-diphenylpyrazole-4-propionic acid (DPPA) and 5-(4-Chlorophenyl)Oxazole-2-Propionic acid (COPA) were tested for their anti-fungal activity under Molecular docking analysis and the results were reported.

II. MATERIALS AND METHODS

The azole derivatives DMI, CDMI, DSMP, DPPA and COPA were selected and optimized using Gaussian 09 [9] and Gauss View [10] software packages. The crystal structure of CYP51 in complex with ketoconazole was obtained from the protein data bank (pdb: 3LD6) and the docking analysis was performed with the aid of Auto dock tools version 1.5.6 software package [11]. All the ligand protein interactions were visualized and presented using pymol [12], Ligplot+ [13] and Discovery studio visualization [14] terminals.

III. RESULTS AND DISCUSSION

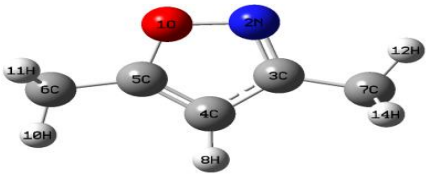
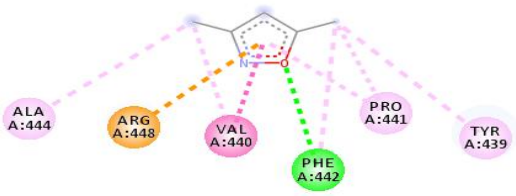
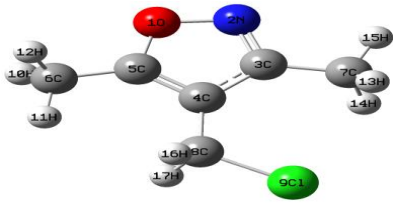
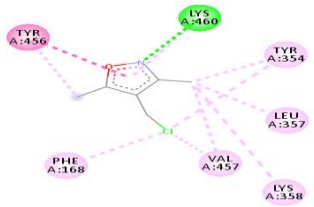
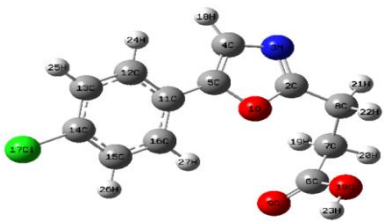
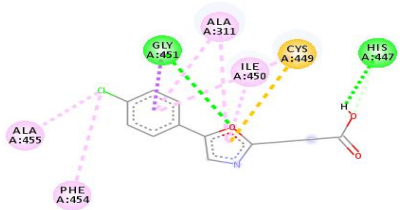
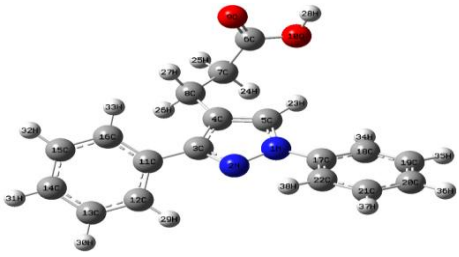
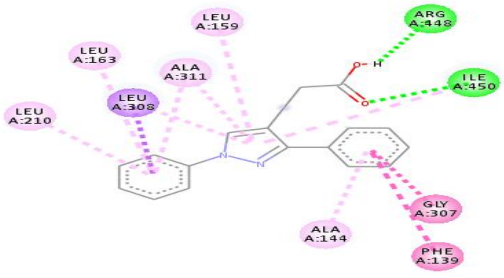
The ligands for docking were prepared by optimizing the molecular structure of DMI, CDMI, DSMP, DPPA and COPA at ground state minimum energy level. The protein was prepared by removing the co crystal ligands, water and co-factors from the downloaded crystal structure. The Autodock tools graphical interface was used to calculate the Kollman charges and to add polar hydrogens. Torsion and rotatable bonds were also defined. The active site of the enzyme was defined to include in the preferred grid size of 80Å x 80Å x 80Å. The docking analysis of the compounds were carried out using Lamarckian Genetic Algorithm (LGA) available in auto dock tools based on the steps described in the literature [15]. After docking, the binding energy and inhibitory constants were found out using Autodock program and the findings were tabulated in Table1. The ligand enzyme interactions were visualized using pymol and Discovery studio Visualizer. The ligand binds at the active sites of the target by weak non-covalent interactions such as H-bonding, alkyl, alkyl-π, π- π, π-σ interactions. From the table 1, it can be found that the DPPA molecule exhibits a good binding affinity of -9.8k cal/mol whose corresponding inhibitory constant is 128.52nM. The table 2 shows all the docked complex poses of the best conformers. The DPPA molecule possess a good conventional bond of length 1.92 and 2.73 Å.

Table 1: The Binding energy and Inhibitory constant of various azole molecules docked with 3LD6

Conformer	DMI		CDMI		COPA		DPPA		DSMP	
	B.E	Ki	B.E	Ki	B.E	Ki	B.E	Ki	B.E	Ki
1	-4.37	625.25 µM	-4.83	288.38 µM	-7.06	6.73 µM	-8.81	350.03nM	-8.09	1.18 µM
2	-4.37	622.80 µM	-4.84	284.31 µM	-7.02	7.09 µM	-9.37	135.87nM	-7.98	1.40 µM
3	-4.37	621.30 µM	-4.73	341.61 µM	-5.93	44.63 µM	-8.66	447.69nM	-7.62	2.62 µM
4	-4.40	591.37 µM	-4.83	288.78 µM	-7.09	6.39 µM	-9.24	168.37nM	-8.05	1.27 µM
5	-4.37	621.71 µM	-4.84	283.39 µM	-7.04	6.90 µM	-9.32	147.72nM	-7.92	1.58 µM
6	-4.37	622.76 µM	-5.15	168.92 µM	-7.28	4.58 µM	-9.36	137.27nM	-7.61	2.64 µM
7	-4.37	632.78 µM	-4.84	285.55 µM	-7.19	5.38 µM	-9.40	128.52nM	-7.53	3.02 µM
8	-4.43	566.90 µM	-4.84	282.44 µM	-7.15	5.74 µM	-9.26	162.47nM	-8.01	1.34 µM
9	-4.55	464.10 µM	-5.02	210.47 µM	-7.22	5.12 µM	-8.82	343.74nM	-8.52	565.28nM
10	-4.54	466.10 µM	-4.84	285.00 µM	-7.08	6.42 µM	-8.87	317.48nM	-8.28	847.65nM

B.E-Binding Energy (kcal/mol) **Ki**- Inhibitory constant

Table 2: The Optimized structures and Docked complexes of corresponding Azole derivatives

Molecule	Optimized structure	Docked complex
DMI		
CDMI		
COPA		
DPPA		

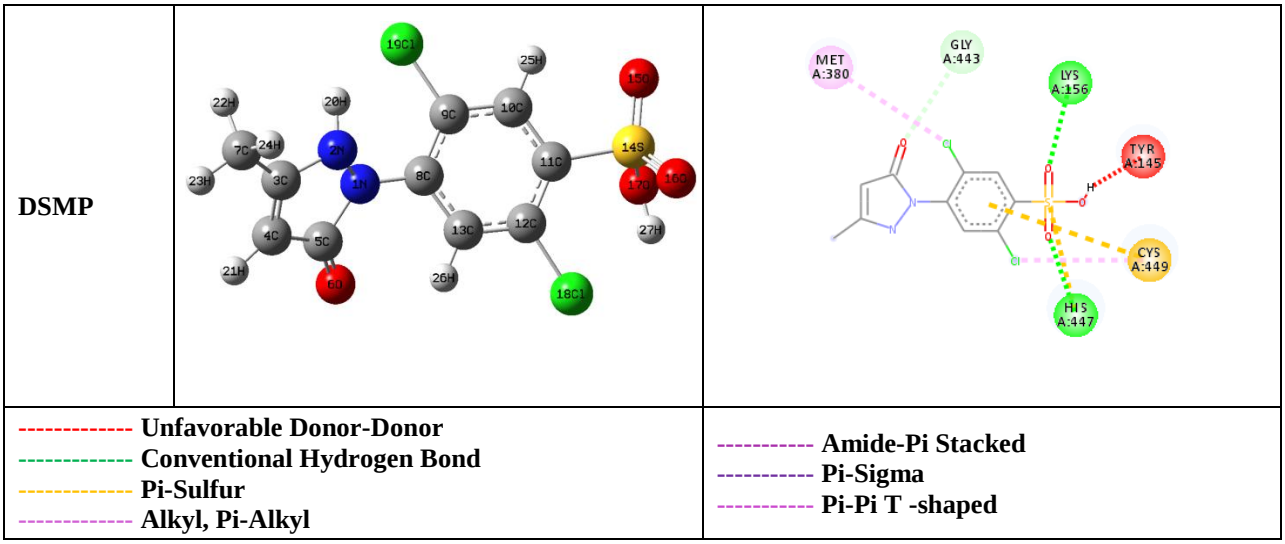


Figure 1: The protein ligand interactions of DPPA molecule with 3LD6

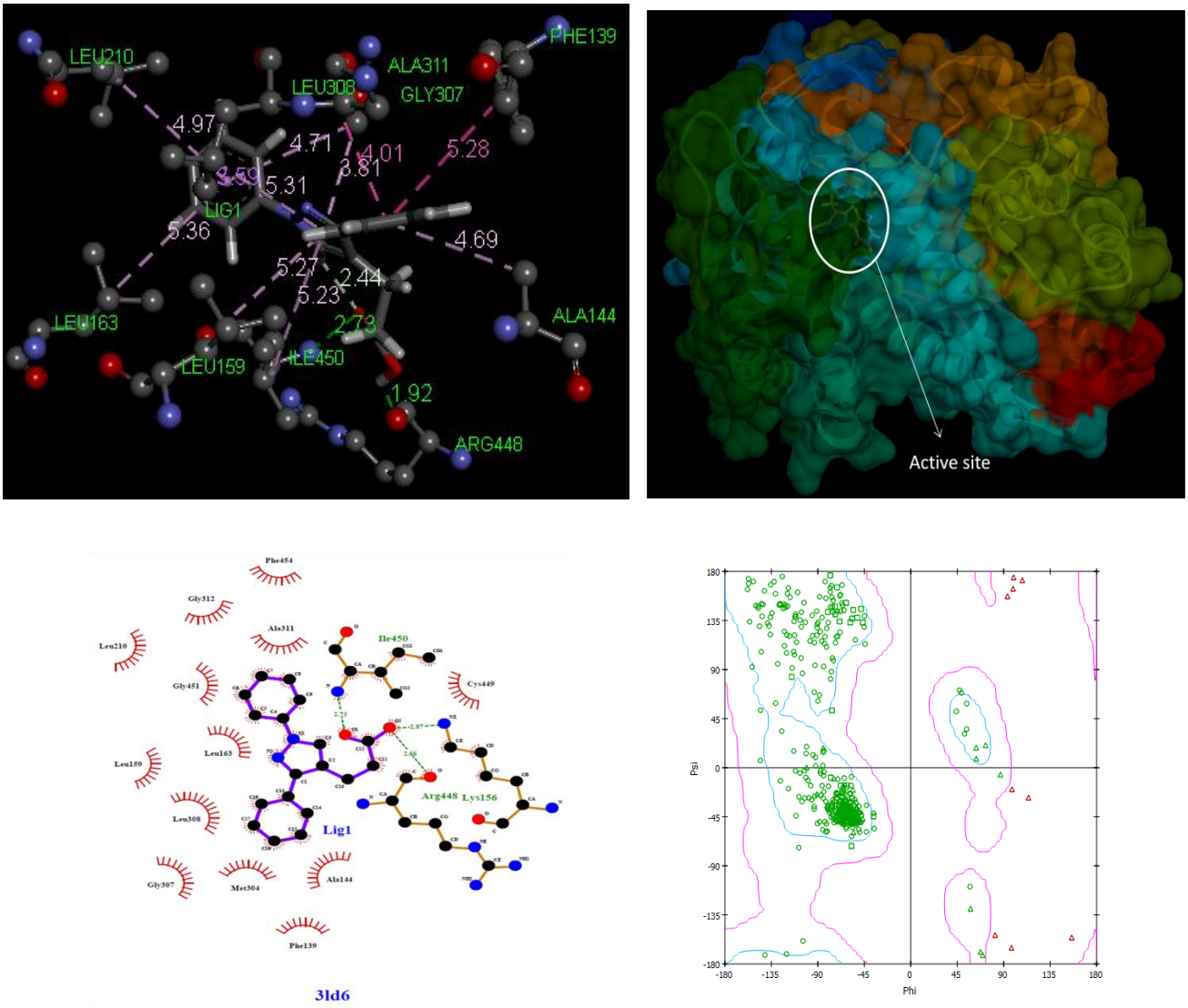


Figure 2: Ligplot representation and Ramachandran plot of the possible interactions of DPPA with 3LD6

The distances of other interactions and the surface view of DPPA protein- ligand interactions can be observed from the Fig 1.The ligplot presented in Fig 2 shows the important interactions of the ligand DPPA with the protein. The residues Ile450, Arg448 and Lys156 interact well with the ligand showing the conventional bond length of 2.73, 2.66 and 2.87Å respectively. The Ramachandran plot of DPPA molecule has also been constructed with 3LD6. In the figure, the green colour triangle shows the residues with acceptable angles and red colour triangles indicate angles which are not acceptable. From the figure it can be observed that there are very few red triangles which indicate that the interaction between the protein and ligand DPPA is quite acceptable. However biological tests need to be carried out to validate the computational predictions.

IV. CONCLUSION

The molecules 3,5-dimethylisoxazole; 4-chloromethyl-3,5-Dimethyl isoxazole; 1-(2,5-Dichloro-4-sulfophenyl)-3-methyl-5-pyrazolone; 1,3-diphenylpyrazole-4-propionic acid; 5-(4-Chlorophenyl) Oxazole-2-Propionic acid after minimum energy structure optimization were subjected to Molecular docking analysis with the protein 3LD6 for predicting their anti-fungal activity. From the observed results, the molecule DPPA was found to exhibit good binding affinity and low inhibition constant. The docked complex poses of DPPA with 3LD6 were presented. It can be revealed that DPPA may be used as an anti-fungal agent after making necessary biological tests.

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