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Research Article

Docking studies and adme/toxicity parameter of azole derivatives for antifungal activity

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ABSTRACT

This study aims to perform molecular docking of various miconazole derivatives against antifungal proteins (8VLK and 4UYL) using ArgusLab and AutoDock. Additionally, MolInspiration software is utilized to predict the ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) properties of these compounds. Azole derivatives are well-known antifungal agents that function by inhibiting ergosterol synthesis in the fungal cell membrane. Fifty miconazole derivatives have been identified using ChemSketch software, and their novelty has been confirmed through PubChem, ensuring that these compounds do not already exist. The study compares the binding energy of these derivatives with that of the original miconazole drug to identify potential candidates with lower energy, reduced toxicity, or enhanced antifungal potency.

Introduction

Invasive fungal infections such as candidiasis have become a major cause of mortality and morbidity. The term “antifungal” encompasses all chemical compounds, pharmacologic agents and natural products used to treat fungi i.e mycoses [1]. Azoles, allylamines, polyenes are the four classes of antifungal drugs used to treat fungal infections such as candidiasis in humans. Their extensive use has led to the emergence of drug resistance, complicating antifungal therapy for yeast infections in critically ill patients. The fungistatic nature and prolonged use of azoles to treat fungal infections, has promoted the selection and emergence of drug resistant fungal strains.

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This necessitates either a development of novel antifungal drugs or improved therapeutic strategy to overcome drug resistance problem by C. albicans [2]. Some of the noted antifungal agents are listedhere: Anidulafungin, Amorolfine, Amphotericin B, Caspofungin, Ciclopirox, Clotrimazole, Fluconazole, Flucytosine, Griseofulvin, Itraconazole, Ketoconazole, Micafungin, Miconazole, Naftifine, Nystatin, Pimaricin, Posaconazole, Terbinafine, and Terconazole, which are extensively used in medicine [3]. Miconazole act by inhibiting the enzyme 14-α demethylase, which is responsible for the conversion of lanosterol to ergosterol (a necessary component of the fungal cell membrane). Loss of ergosterol production increases the cell membrane permeability, ultimately causing leakage of cellular contents. Miconazole may also inhibit endogenous respiration, interact with membrane phospholipids, inhibit the transformation of yeast to mycelial forms [4]. Since synthesizing and testing of antimicrobial activity by microbiological protocols is a

tedious and time-consuming process here docking software is used for the prediction of antimicrobial activity. The computer software used in the present studies are

1. ACD/Chemsketch [5]
2. Argus lab [6]
3. Discovery studio [7]
4. Auto dock 1.5.7 [8]
5. Molegro molecular viewer [9]
6. Molinspiration [10]

Here, ligand-protein docking was done using the AutoDock (1.5.7) program. By employing score functions, one can use knowledge of the preferred orientation to forecast the strength of the contact or binding affinity between two molecules. An empirical scoring function in AutoDock (1.5.7) adds up the contributions of several separate terms to determine the affinity, or fitness, of protein-ligand interaction [11].

The Molinspiration web tool was utilized in this instance. It offers unrestricted access to a collection of quick and dependable predictive models for ADME analysis and moreover shows bioavailability radar for an expedient evaluation of drug-likeness [12] Fig. 1 depicted the fundamental docking procedure.

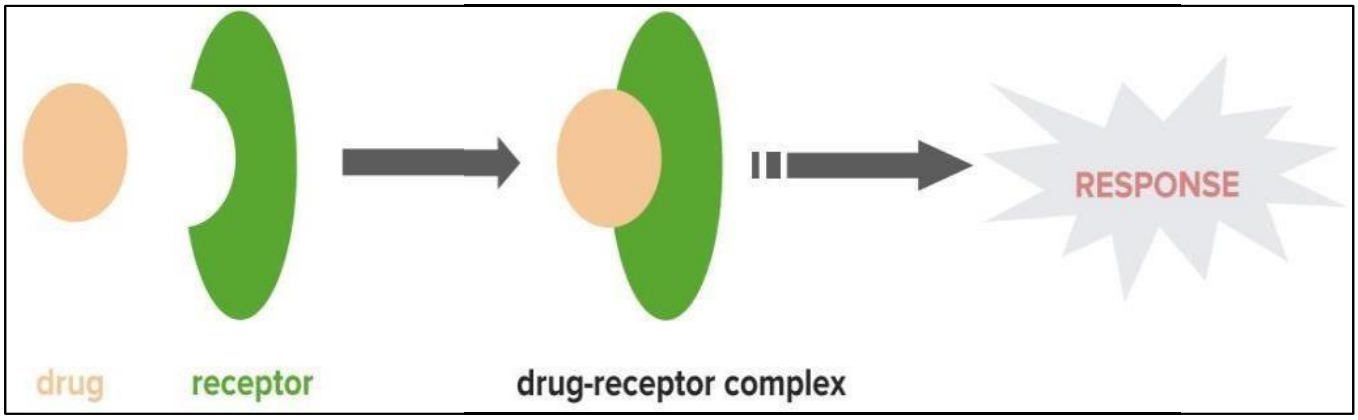


Figure 1: Schematic illustration of docking a small molecule ligand (drug) to a protein target (receptor) producing a stable complex.

Materials and Methods

Molecular Docking [13]

Molecular docking has become an essential part of in-silico drug development in recent years. This technique involves predicting the interaction between a small molecule and a protein at the atomic level [14]. Molecular docking aims to predict the ligand-receptor complex through computer-based methods [15]. The process of docking involves 2 main steps which includes sampling the ligand and utilizing the scoring function [16]. Thus, the following phases are involved in the docking process:[17]

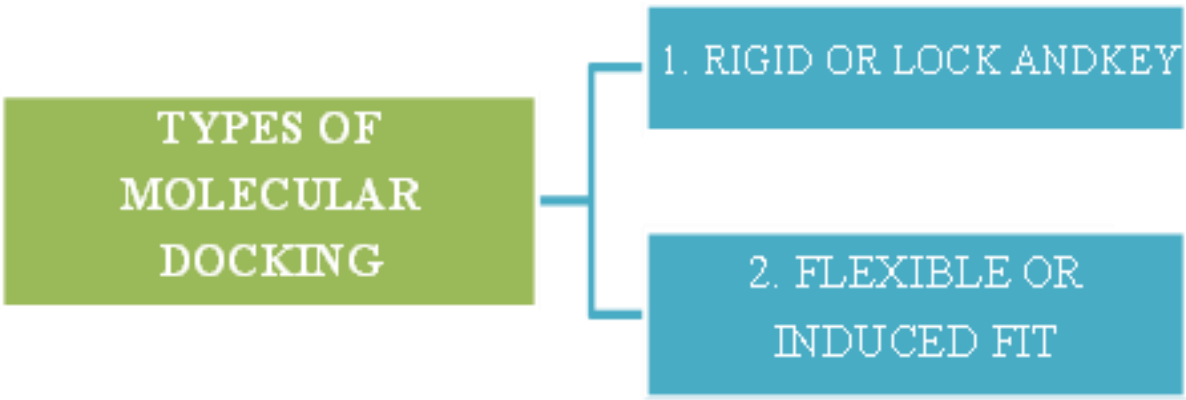


Figure 2: Types of molecular docking.

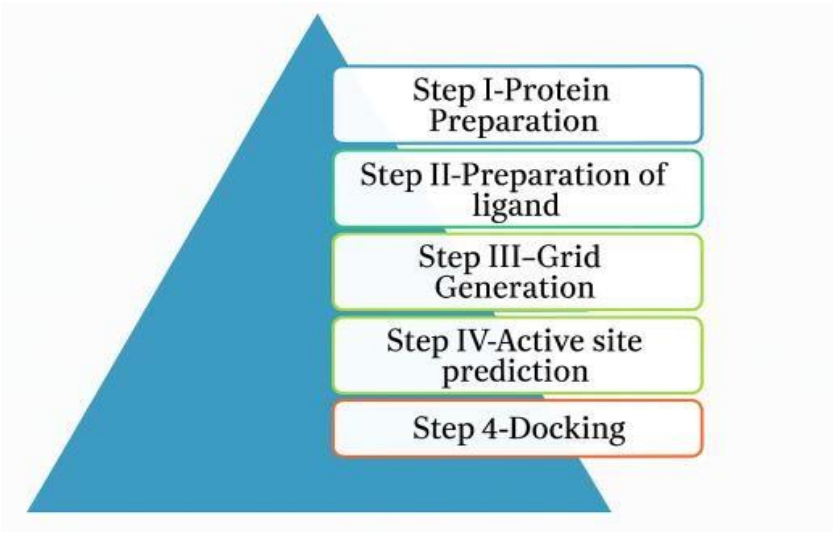


Figure 3: Molecular docking mechanics steps.

Step I: Protein preparation

The protein's three-dimensional structure (8VLK, 4UYL) should be obtained from the Protein Data Bank (PDB) the structure should then undergo pre-processing. Imported the protein files and followed the necessary instructions.

Step II: Ligand preparation

The given derivatives of miconazole were drawn using chemsketch and Lipinski's Rule of 5 should be applied while selecting the ligand. Regarding selecting a ligand that complies with Lipinski's Rule [18,19].

Table 1: Lipinski's rule of five.

Properties	Lipinski's Rule of 5
Molecular weight	< 500 g/mol
Log P	< 5
H- bond donor	< 5
H- bond acceptor	< 10
Polar surface area	< 140 A^0

Step III: Active site prediction

Predicting the prepared protein's active site is the most important step. The receptor may have several active sites; only the one that poses the greatest risk needs to be selected. If heteroatom's or water molecules are present, they are eliminated.

Step IV: Docking

Programs like Argus Lab 4.0.1 and Autodock tools 1.5.7 are used to investigate the interactions between the docked ligand and protein. The scoring function assigns a score based on the selection of the best docked ligand complex.

ADMET Property Prediction:

Molinspiration [10]

Structure of all the chemical compounds were drawn by using ACD labs Chemsketch version 12.1 and their SMILES notation were generated. Smiles notation of the compound were fed in the online molinspiration software version 2022.09 (www.molinspiration.com) for calculation of molecular properties (Log p, Total polar surface area, numbers of the hydrogen bond donors and acceptors, molecular weight, number of atoms, number of rotatable bonds etc.) and prediction of bio activity score drug targets (GPCR ligands, kinase inhibitor, ion channel modulators, enzyme and nuclear).

AUTODOCK 1.5.7 [7]

Autodock is an automated procedure for predicting the interaction of ligands with biomolecular targets [12]. AutoDock is a molecular modeling simulation software. It is especially effective for protein-ligand docking.

AutoDock consists of two main programs:

- AutoDock for docking of the ligand to a set of grids describing the target protein;
- AutoGrid for pre-calculating these grids.

Following fig.4. depicting the fundamental docking procedure for Autodock 1.5.7 [20].

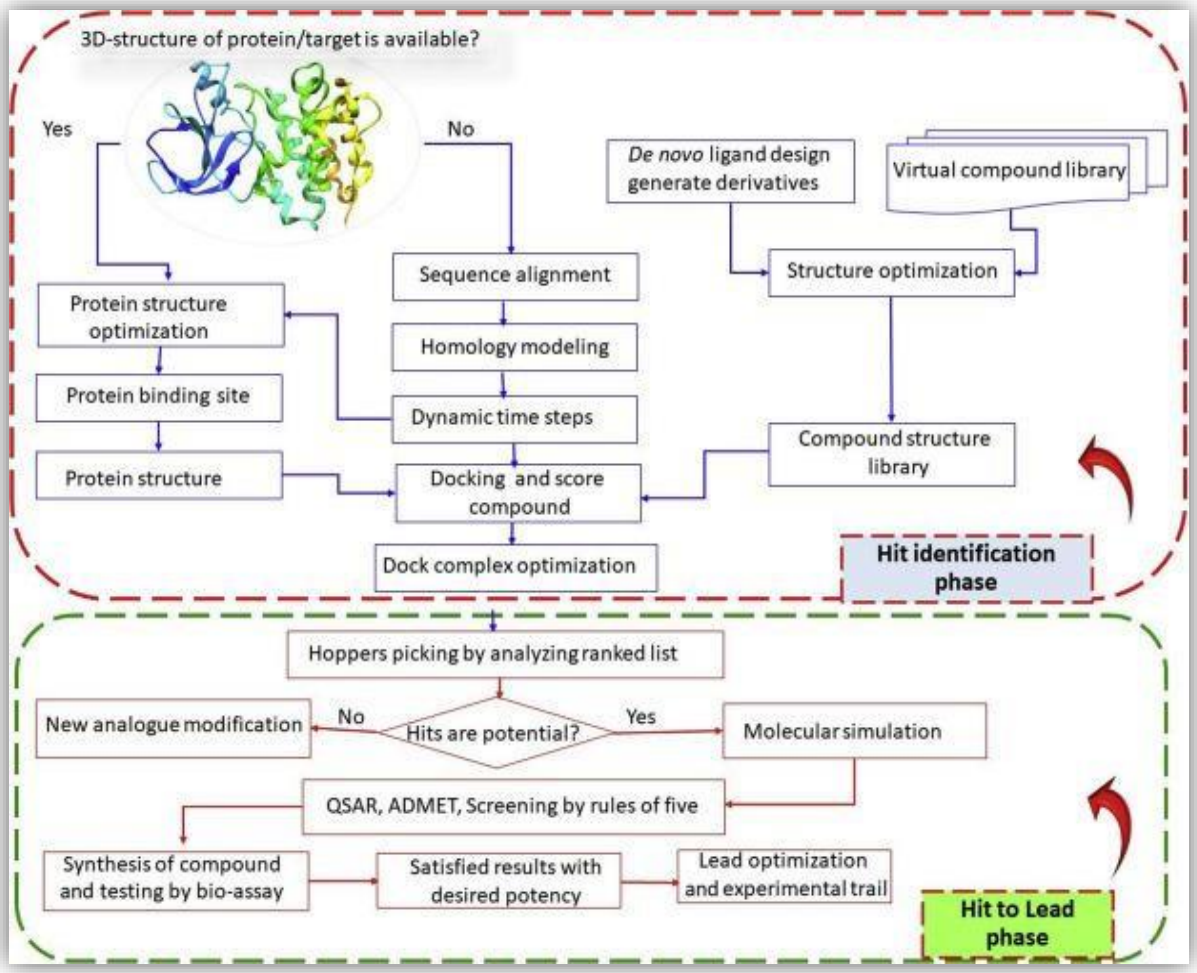


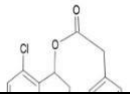
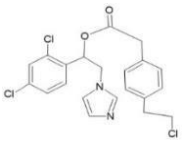
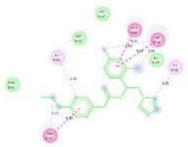
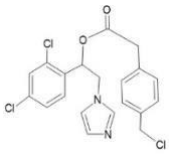
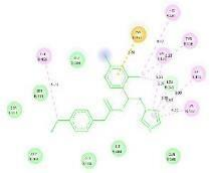
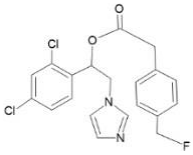
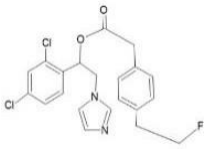
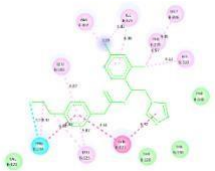
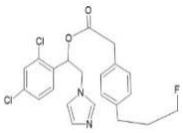
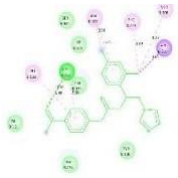
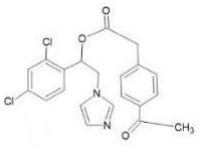
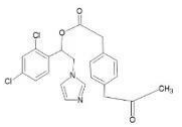
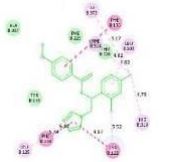
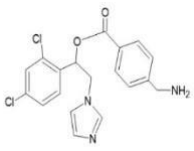
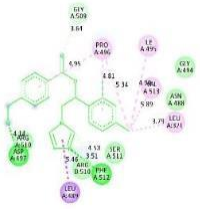
Figure 4: Stepwise procedure for Autodock 1.5.7

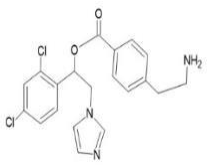
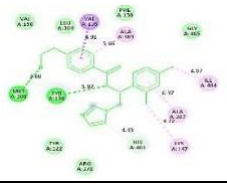
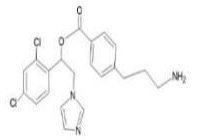
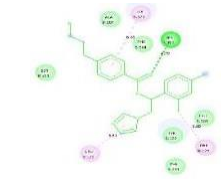
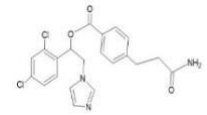
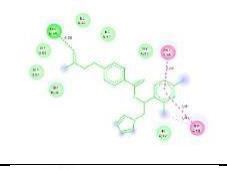
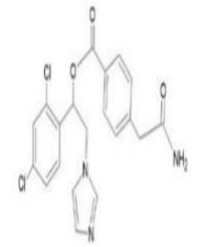
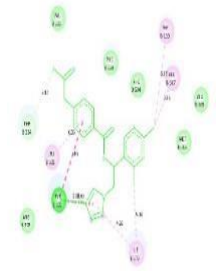
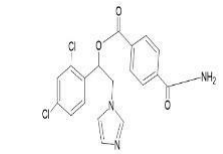
Results and Discussion

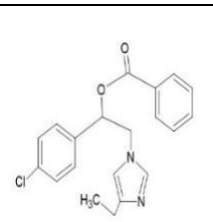
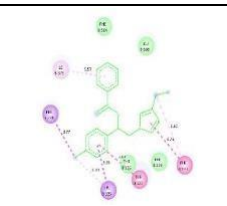
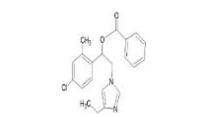
Using AutoDock Tools and ArgusLab, the minimum energy of these derivatives was compared to that of standard miconazole. Some derivatives exhibited lower minimum energy than miconazole, indicating greater stability, while others had higher minimum energy, suggesting lower stability. Binding affinity of the given azole derivatives with antifungal proteins (8VLK&4UYL) were listed in table 2.

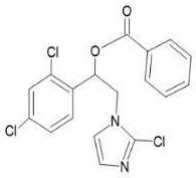
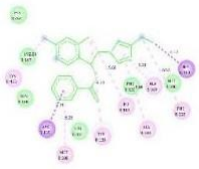
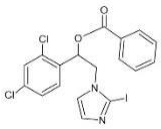
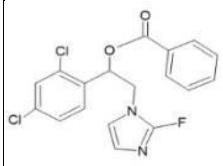
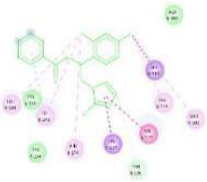
Table 2: Binding affinities of given Azole derivatives with anti-fungal proteins(8VLK&4UYL)

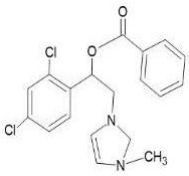
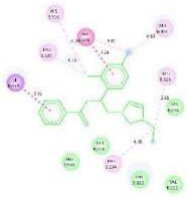
S. No.	Protein Name	Chemical Name	Structure	Capture	Result	
					AUTODOCK (kcal/mol)	ARGUS LAB (kcal/mol)
01.	8VLK	1-(2,4dichlorophen yl)-2-(1*H*imidazol-			-3.86	-12.84

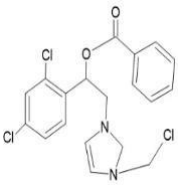
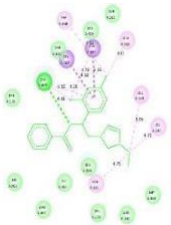
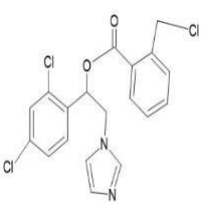
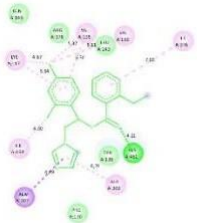
	4UYL	1yl)ethyl [4-(3chloropropyl)phenyl]aceta			-5.75	-14.61
02.	8VLK	1-(2,4dichlorophe n yl)-2-(1*H*imidazol-1yl)ethyl [4-(2chloroethyl)p			-3.43	-12.47
	4UYL				-5.25	-15.27
03.	8VLK	1-(2,4dichlorophe nyl)-2-(1*H*imidazol-1yl)ethyl [4(chloromethy l)phenyl]acet ate			-3.82	-10.94
	4UYL				-6.46	-14.48
04	8VLK	1-(2,4dichlorophe nyl)-2-(1*H*imidazol-1yl)ethyl [4(fluoromethy l)phenyl]acetate			-3.31	-11.82
	4UYL				-6.00	-14.07
05	8VLK	1-(2,4dichloroph enyl)-2-(1*H*imidazol-1yl)ethyl [4-(2fluoroethyl)p henyl]acetate			-2.94	-10.72
	4UYL				-5.65	-14.78
06.	8VLK	1-(2,4dichloroph enyl)-2-(1*H*imidazol-1yl)ethyl [4-(3fluoropropyl) phenyl]acetate			-3.27	-12.31
	4UYL				-7.01	14.69
07.	8VLK	1-(2,4dichloroph enyl)-2-(1*H*imidazol-1yl)ethyl (4acetylphenyl) acetate			-4.57	-13.56
	4UYL				-5.97	-13.80
08.	8VLK	1-(2,4dichloroph enyl)-2-(1*H*imidazol-1yl)ethyl [4-(2oxopropyl)ph enyl]acetate			-3.72	-12.20
	4UYL				-5.63	-14.86
09.	8VLK	1-(2,4dichloroph enyl)-2-(1*H*imidazol-1yl)ethyl 4-(aminomethy l)benzoate			-3.98	-11.27
	4UYL				-6.38	-12.79

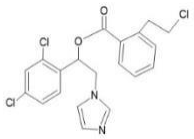
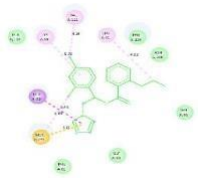
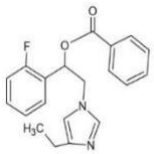
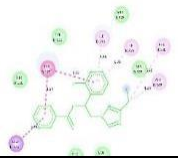
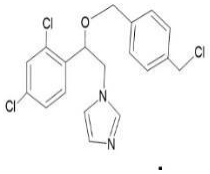
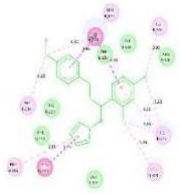
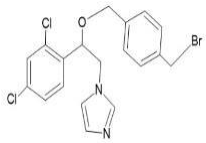
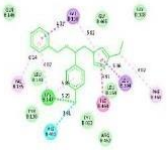
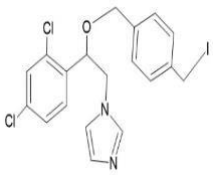
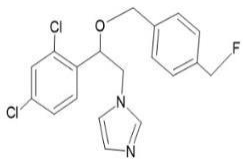
10.	8VLK	1-(2,4dichlorophenyl)-2-(1*H*imidazol-1yl)ethyl 4-(2aminoethyl)benzoate			-4.12	-9.29
	4UYL				-4.66	-13.26
11.	8VLK	1-(2,4dichlorophenyl)-2-(1*H*imidazol-1yl)ethyl 4-(3aminopropyl) benzoate			-4.26	-9.51
	4UYL				-5.55	-14.30
12.	8VLK	1-(2,4dichlorophenyl)-2-(1*H*imidazol-1yl)ethyl 4-(3amino-3-oxopropyl)be			-4.28	-9.51
	4UYL				-5.80	-13.43
13.	8VLK	1-(2,4dichlorophenyl)-2-(1*H*imidazol-1yl)ethyl4-(2amino-2oxoethyl)benzoate			-4.56	-9.53
	4UYL				-5.81	-13.68
14	8VLK	1-(2,4dichlorophenyl)-2-(1*H*imidazol-1yl)ethyl 4carbamoylbenzoate			-4.13	-11.09
	4UYL				-6.93	-12.72

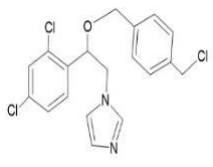
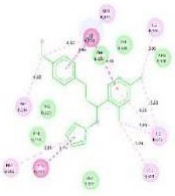
15.	8VLK	1-(4chlorophenyl)-2-(4-ethyl1*H*-imidazol1- yl)ethyl benzoate			-4.23	-12.12
	4UYL				-6.31	-13.42
16.	8VLK	1-(4-chloro-2methylpheny l)-2-(4-ethyl1*H*-imidazol1-yl)ethylbenzoate			-4.23	-10.44
	4UYL				-7.04	-13.53

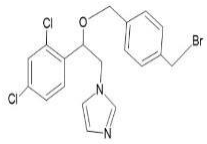
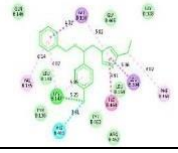
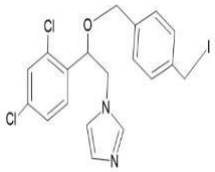
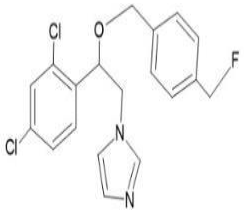
17.	8VLK	2-(2-chloro1*H*-imidazol1-yl)-1-(2,4dichlorophen yl)ethyl benzoate			-4.77	-12.14
	4UYL				-5.85	-13.74
18.	8VLK	1-(2,4dichlorophenyl)-2-(2iodo-1*H*imidazol-1yl)ethyl benzoate			-4.37	-12.33
	4UYL				-5.92	-13.73
19.	8VLK	1-(2,4dichlorophenyl)-2-(2fluoro-1*H*imidazol-1yl)ethyl benzoate			-4.54	-11.72
	4UYL				-5.74	-13.42

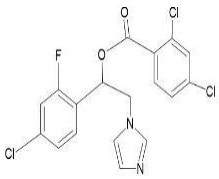
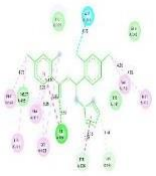
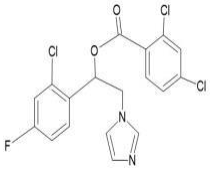
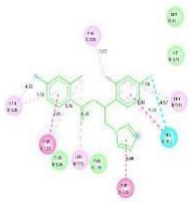
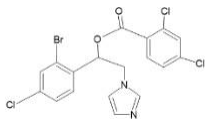
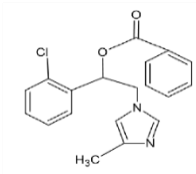
20.	8VLK	1-(2,4dichlorophenyl)-2-(3methyl-2,3dihydro-1*H*imidazol-1yl)ethyl benzoate			-5.20	-14.76
	4UYL				-6.13	-13.20

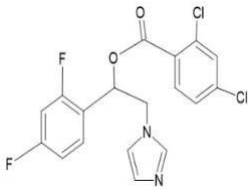
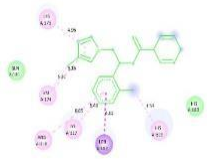
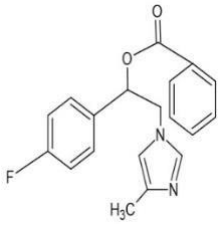
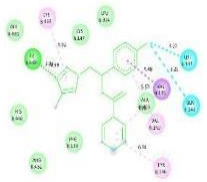
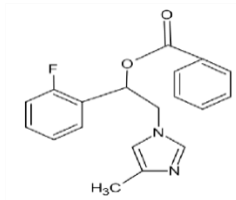
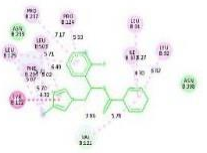
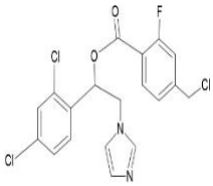
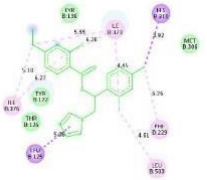
21.	8VLK	2-[3-(chloromethyl)-2,3dihydro-1*H*imidazol-1yl]-1-(2,4dichlorophenyl)ethyl benzoate			-3.96	-12.65
	4UYL				-5.74	-13.74
22.	8VLK	1-(2,4dichlorophenyl)-2-(1*H*imidazol-1yl)ethyl 2-(chloromethyl)benzoate			-3.71	- 12.65
	4UYL				-5.74	-13.41

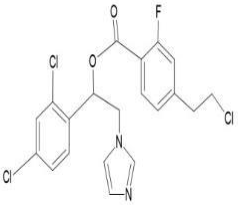
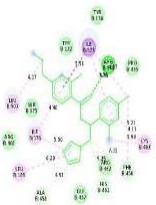
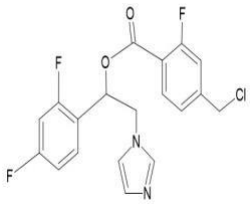
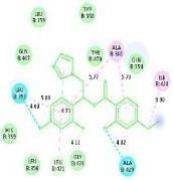
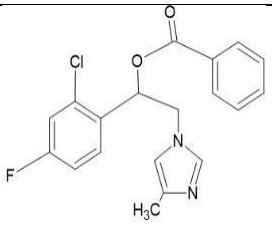
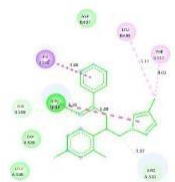
23.	8VLK	1-(2,4dichlorophenyl)-2-(1*H*imidazol-1yl)ethyl 2-(2chloroethyl)benzoate			-3.18	-12.84
	4UYL				-5.00	-14.16
24.	8VLK	1-(2,4dichlorophenyl)-2-(1*H*imidazol-1yl)ethyl 2-(bromomethyl)benzoate			-4.25	-12.68
	4UYL				-5.80	-14.99
25.	8VLK	1-[2-{[4(chloromethyl)phenyl]methoxy}-2(2,4dichlorophenyl)ethyl]-1*H*imidazole			-4.31	-11.40
	4UYL				-7.75	-14.77
26.	8VLK	2-(4-ethyl1*H*-imidazol1-yl)-1-(4fluorophenyl)ethyl benzoate			-3.90	-11.69
	4UYL				-5.76	-14.30
27.	8VLK	1-[2-(2,4dichlorophenyl)-2-{[4(iodomethyl) phenyl]methoxy}ethyl]1*H*-imidazole			-5.11	-11.43
	4UYL				-5.82	-13.11
28.	8VLK	1-[2-(2,4dichlorophenyl)-2-{[4(fluoromethyl)phenyl]methoxy}ethyl]1*H*-imidazole			-3.99	- 7.09
	4UYL				-5.51	-14.30

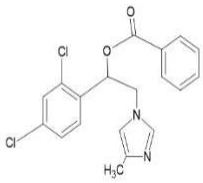
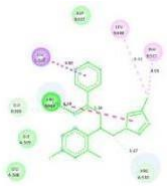
25.	8VLK	1-[2-{[4(chloromethyl)phenyl]methoxy}-2(2,4dichlorophenyl)ethyl]-1*H*imidazole			-4.31	-11.40
	4UYL				-7.75	-14.77

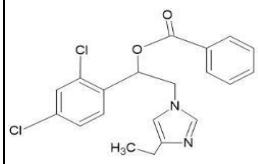
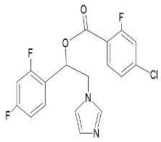
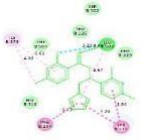
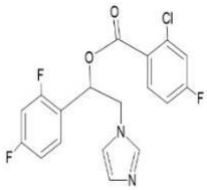
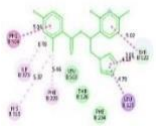
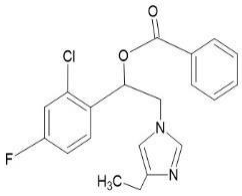
26.	8VLK	2-(4-ethyl1*H*-imidazol1-yl)-1-(4fluorophenyl)ethyl benzoate			-3.90	-11.69
	4UYL				-5.76	-14.30
27.	8VLK	1-[2-(2,4dichlorophenyl)-2-{[4(iodomethyl) phenyl]methoxy}ethyl]1*H*-imidazole			-5.11	-11.43
	4UYL				-5.82	-13.11
.28.	8VLK	1-[2-(2,4dichlorophenyl)-2-{[4(fluoromethyl)phenyl]methoxy}ethyl]1*H*-imidazole			-3.99	- 7.09
	4UYL				-5.51	-14.30

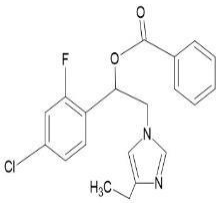
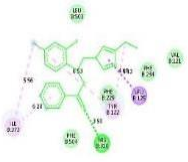
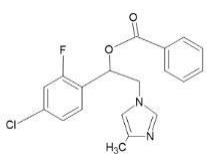
29.	8VLK	1-(4-chloro- 2-fluorophenyl)-2-(1*H*imidazol-1yl)ethyl 2,4dichlorobenzoate			-4.15	-13.89
	4UYL				-6.26	-12.77
30.	8VLK	1-(2-chloro- 4-fluorophenyl)-2-(1*H*imidazol-1yl)ethyl 2,4dichlorobenzoate			-4.55	-14.21
	4UYL				-6.86	-13.11
31.	8VLK	1-(4chlorophenyl)-2-(4methyl-1*H*imidazol-1yl)ethyl benzoate			-5.05	-9.82
	4UYL				-7.02	-8.05
32.	8VLK	1-(2chlorophenyl)-2-(4methyl-1*H*imidazol-1yl)ethyl benzoate			-3.94	-15.85
	4UYL				-6.37	-12.73

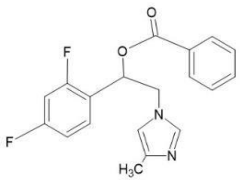
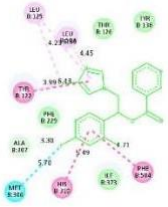
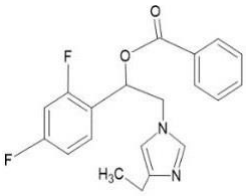
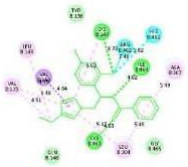
33.	8VLK	1-(2,4difluorophenyl)-2-(1*H*imidazol-1yl)ethyl 2,4dichlorobenzoate			-4.56	-9.00
	4UYL				-7.02	- 11.94
34.	8VLK	1-(4fluorophenyl)-2-(4methyl-1*H*imidazol-1yl)ethyl benzoate			-4.46	-9.41
	4UYL				-6.50	-11.69
35.	8VLK	1-(2fluorophenyl)-2-(4methyl-1*H*imidazol-1yl)ethyl benzoate			-4.28	-9.89
	4UYL				-6.96	-12.42
36.	8VLK	1-(2,4dichlorophenyl)-2-(1*H*imidazol-1yl)ethyl 4-(chloromethyl)-2-fluorobenzoate			-3.91	-9.65
	4UYL				-6.03	-13.72

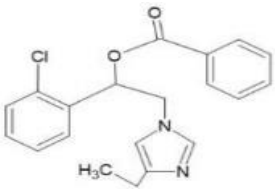
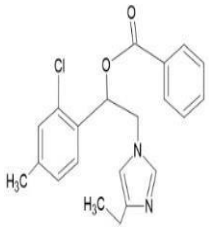
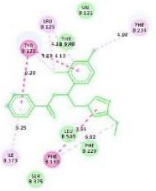
37.	8VLK	1-(2,4dichlorophenyl)-2-(1*H*imidazol-1yl)ethyl 4-(2chloroethyl)-2fluorobenzoate			-4.03	-9.52
	4UYL				-7.42	-13.72
38.	8VLK	1-(2,4difluorophenyl)-2-(1*H*imidazol-1yl)ethyl 4-(chloromethyl)-2fluorobenzoate			-3.69	-8.89
	4UYL				-5.23	-11.91
39.	8VLK	1-(2-chloro-4-fluorophenyl)-2-(4methyl-1*H*imidazol-1yl)ethyl benzoate			-3.78	-8.66
	4UYL				-6.69	-12.82

40.	8VLK	1-(2,4dichlorophenyl)-2-(4methyl-1*H*imidazol-1yl)ethyl benzoate			-4.32	-13.99
	4UYL				-6.79	-13.70

41.	8VLK	1-(2,4dichlorophenyl)-2-(4ethyl-1*H*imidazol-1yl)ethyl benzoate			-4.70	-8.09
	4UYL				-5.95	-13.59
42.	8VLK	1-(2,4difluorophenyl)-2-(1*H*imidazol-1yl)ethyl 4chloro-2fluorobenzoate			-4.36	-7.28
	4UYL				-6.33	-13.70
43.	8VLK	1-(2,4difluorophenyl)-2-(1*H*imidazol-1yl)ethyl 2chloro-4fluorobenzoate			-3.47	-9.22
	4UYL				-5.50	-11.95
44.	8VLK	1-(2-chloro-4fluorophenyl)-2-(4-ethyl1*H*-imidazol1-yl)ethyl benzoate			-4.11	-8.09
	4UYL				-5.30	-13.29

45.	8VLK	1-(4-chloro-2fluorophenyl)-2-(4-ethyl1*H*-imidazol1-yl)ethyl benzoate			-3.63	-7.77
	4UYL				-6.19	-12.59
46.	8VLK	1-(4-chloro- 2-fluorophenyl)-2-(4methyl-1*H*imidazol-1yl)ethyl benzoate			-3.64	-9.01
	4UYL				-5.86	-13.12

47.	8VLK	1-(2,4difluorophenyl)-2-(4methyl-1*H*imidazol-1yl)ethyl benzoate			-3.83	-8.21
	4UYL				-5.18	-11.54
48.	8VLK	1-(2,4difluorophenyl)-2-(4ethyl-1*H*imidazol-1yl)ethyl benzoate			-3.66	-8.71
	4UYL				-5.69	-13.12

49	8VLK	1-(2chlorophenyl)-2-(4-ethyl1*H*-imidazol1-yl)ethyl benzoate			-4.52	-9.81
	4UYL				-6.87	-13.45
50.	8VLK	1-(2-chloro-4methylphenyl)-2-(4-ethyl1*H*-imidazol1-yl)ethyl benzoate			-4.19	-10.48-
	4UYL				-6.85	-11.54

Molecular Docking Analysis

A variety of useful techniques for drug design and analysis are provided by molecular docking. Using Argus lab 4.0.1 and Autodock tools 1.5.7, molecular docking was used to examine the binding capacity of given derivatives with Anti-fungal proteins(8VLK& 4UYL). Let's discuss which derivatives fall into each category. To analyze which derivatives have a lower or higher minimum energy than the standard miconazole drug using AutoDock Tools and ArgusLab, we need to compare the binding energy values obtained from molecular docking simulations.

For 8VLK

Argus lab predicts a significantly lower (more negative) binding energy, which suggests a stronger interaction of Miconazole with its target compared to Autodock. For Autodock, almost all clusters (except 20, 27, 31) fall under the lowest energy minimum, indicating a wide range of favorable poses. For Argus lab, the lowest energy clusters are limited to a specific set (28, 39, 41, 42, 44, 45, 47), while the majority of clusters are classified as higher energy minima.

Table 3: Comparative Analysis of Miconazole Docking Energies using Autodock and Argus Lab with Anti-fungal protein (8VLK).

S. No.	Docking Tools	Standard Miconazole	Highest Energy Minimum	Lowest Energy Minimum
1.	Autodoc k 1.5.7	-4.85kcal/mol	20,27,31	1,2,3,4,5,6,7,8,9,10,11, 12,13,14,15,16,17,18, 19,21,22,23,24,25,26, 28,29,30,32,33,34,35, 36,37,38,39,40,41,42, 43,44,45,46,47,48,49, 50
2.	Argus lab	-8.69kcal/mol	1,2,3,4,5,6,7,8,9,10,11 ,12,13,14,15,16,17,18, 19,20,21,22,23,24,25, 26,27,29,30,31,32,33, 34,35,36,37,38,40,43, 46, 48,49,50	28,39,41,42,44,45,47

For 4UYL

A more negative binding energy indicates a stronger predicted interaction. Therefore, ArgusLab suggests a stronger binding affinity of Miconazole to the 4UYL protein compared to Autodock 1.5.7. Both tools identify different sets of residues contributing to the highest and lowest energy minima. Notably, residues 16, 25, 37, 40, and 49 appear in the highest energy minimum lists of both tools, suggesting these residues may play a significant role in Miconazole binding

.

Table 4: Comparative Analysis of Miconazole Docking Energies using Autodock and Argus Lab with Anti-fungal protein (4UYL).

S. No.	Docking Tools	Standard Miconazole	Highest Energy Minimum	Lowest Energy Minimum
1.	Autodock 1.5.7	-6.79kcal/Mol	6,9,14,16,25,30,31,33, 35,37,40,49,50	1,2,3,4,5,7,8,10,11,12, 13,15,17,18,19,20,21,2 2,23,24,26,27,28,29,32 ,33,34,36,38,39,41,42, 43,44,45,46,47,48
2.	Argus Lab	-13.428kcal/Mol	1,2,3,4,5,6,7,8,11,12,1 3,16,17,18,21,23,24,25 ,26,28,36,37,40,41,42, 44,49	9,10,14,15,19,20,22,27 ,29,30,31,32,33,34,35, 38,39,43,45,46,47,48, 50

Determination of Interaction

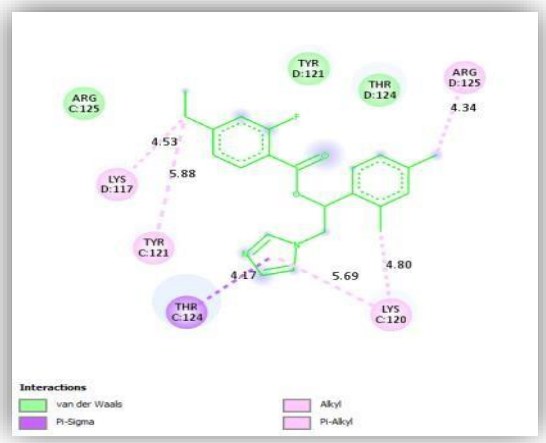


Figure 5: 2D diagram of miconazole with antifungal protein 8VLK.

Figure 6: Crystal structure of 8VLK.

Summary and Conclusion

Based on the findings of these studies, novel lead structures for Azole derivatives have been identified, providing a foundation for rational drug design. These modifications through molecular modelling potentially yield clinically useful Antifungal agents. Azole derivatives exhibit desirable molecular properties, making them biologically important molecules. The bioactivity score of these derivatives indicates a greater Antifungal activity. These derivatives with enhanced efficacy has more potent antifungal activity. Furthermore, these optimized Azole derivatives hold great promise for development into effective antifungal drugs, offering a potential solution for treating various fungal infections.

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Conflict of Interest

The authors declare no conflict of interest.

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