

Design and *In Silico* Evaluation of Novel 1,3,4-Oxadiazole Derivatives as Potential CYP51B Inhibitors Against *Aspergillus fumigatus*

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Abstract:

Antifungal resistance and invasive fungal infections remain the major therapeutic issues, especially in patients with impaired immune systems. *Aspergillus fumigatus* is the main cause of invasive aspergillosis and sterol 14- α -demethylase (CYP51B), a key enzyme in the biosynthetic pathway of ergosterol, is an important target for antifungal therapy. In the present study, four new 1,3,4-oxadiazole derivatives (SH1–SH4) were designed and assessed as possible inhibitors of *A. fumigatus* CYP51B (PDB ID: 6CR2) by an integrated *in silico* approach. Binding affinity and interaction patterns within the active site were investigated using the Glide module of the Schrödinger suite. The docking scores of designed compounds ranged from -7.52 to -9.61 kcal/mol. SH4 exhibited the highest docking score (-9.61 kcal/mol), which was very close to Econazole (-9.599 kcal/mol) and better than Clotrimazole and Ketoconazole. SwissADME showed good drug-like property, high gastrointestinal absorption and follow Lipinski's rule of five. The stability of the SH4–CYP51B complex was also confirmed by 200 ns molecular dynamics simulation in which the protein–ligand interactions remained consistent throughout the simulation. These results indicate that SH4 is a promising oxadiazole-based lead compound for further development of antifungal drugs targeting *A. fumigatus* CYP51B.

Keywords: 1,3,4-Oxadiazole; Molecular docking; Molecular dynamics simulation; ADME prediction.

1. Introduction

Among immunocompromised people, transplant recipients, chemotherapy patients, and critically sick patients admitted to

intensive care units, fungal infections have become a big worldwide health problem [1]. Despite advances in antifungal therapy, invasive fungal infections are still associated



with significant morbidity and mortality [2]. There is an urgent need to identify new and effective antifungal drugs. Invasive aspergillosis (IA) is a fatal fungal disease of the lungs and other parts of the body. It is caused by the opportunistic fungus *Aspergillus fumigatus* and affects the most persons with weak immune systems [3,4]. The pathogenic success of *A. fumigatus* is attributed to its ability to evade host immune responses and adapt to diverse settings [5]. Itraconazole, voriconazole, posaconazole and isavuconazole are triazole antifungal medications that are currently first line treatment for aspergillosis. These drugs have good pharmacokinetic profiles and wide range antifungal activity [6,7]. These compounds act by inhibiting the enzyme sterol 14- α -demethylase (CYP51) involved in the synthesis of ergosterol and exert their antifungal activity [8]. Because CYP51 is crucial for fungal survival and membrane integrity, it has become a prospective target for antifungal medicines development [9]. The emergence of azole-resistant strains of *Acinetobacter fumigatus* is an emerging global therapeutic problem, even if azole antifungal medications are of great clinical efficacy [10].

Common causes of resistance to antifungal therapy include CYP51 gene mutations, overexpression of target enzymes, increased efflux pump activity, and adaptive cellular responses. The need for new CYP51 inhibitors with better effectiveness and unique structural features that may overcome resistance mechanisms has been highlighted by the increasing number of resistant isolates, which has worsened treatment failures and clinical outcomes [11,12]. The sterol 14- α -demethylase target has been verified in antifungal drug research more than any other molecular target since it is essential for fungal survival and membrane biosynthesis [13].

Ergosterol production is catalyzed by two isoenzymes of CYP51, CYP51A and CYP51B, which are essential for fungal growth and viability maintenance in *A. fumigatus*. Reasonable antifungal medication design should benefit from CYP51B since structural investigations have shown that its catalytic architecture is highly preserved [14]. In addition, crystal structures of *A. fumigatus* CYP51B at high resolution have opened the door to new antifungal candidates through structure-based drug development [15].

Heterocyclic compounds are one of the most important classes of bioactive molecules in medicinal chemistry due to their broad spectrum of pharmacological action and unique structural diversity. One kind of scaffold that has attracted much attention is the 1,3,4-oxadiazole derivatives because of its numerous desired physicochemical properties, metabolic stability, synthetic accessibility and biological activity variety [16]. The 1,3,4-oxadiazole ring is a well-accepted bioisostere that maintains biological activity with increased lipophilicity, membrane permeability and pharmacokinetic properties [17,18].

Studies have shown that oxadiazole compounds may be potent against a broad spectrum of pathogenic fungi. Structural modifications such as the addition of electron-donating and electron-withdrawing groups leading to increased biological activity may induce significant changes in the molecular shape, electronic distribution, lipophilicity and target binding affinity. For aromatic oxadiazole derivatives containing halogen, nitro, methoxy and methyl substituents, the interactions with enzyme active sites may be strengthened via hydrophobic contacts, π - π stacking interactions and electronic stabilizing effects [19]. The oxadiazole scaffold appears to be a promising starting point for the development



of novel antifungal agents targeting CYP51, according to these results [20].

Computer-aided drug design (CADD) has become a key component of modern drug development, enabling the rapid discovery and optimization of prospective lead compounds while greatly reducing the time, effort and cost of experiments.

Molecular docking approaches are routinely used to understand biological targets, to anticipate modes of attachment of ligands and proteins, and to compute binding affinities [21]. Furthermore, molecular dynamics (MD) simulations under simulated physiological conditions provide insights into the conformational flexibility, dynamic stability and persistence of protein-ligand interactions [22,23]. *In silico* ADME property prediction also provides early assessment of pharmacokinetic suitability and drug-likeness that may aid in the selection of compounds with intriguing therapeutic potentials before experimental validation [24].

2. Computational methods

In the present computational study possible inhibitory effect of designed derivatives of 1,3,4-oxadiazole (SH1–SH4) against *Aspergillus fumigatus* sterol 14- α -demethylase (CYP51B) was evaluated by molecular docking, ADMET prediction approaches and molecular dynamics simulation. The chemical structures of the investigated compounds were first drawn using Chemdraw Professional (version 22.0, PerkinElmer, USA) and then transformed into three-dimensional structures by using Chem3D Ultra software. All ligands were geometry optimized and energy minimized to get stable conformations which can be used for molecular docking studies before computational analysis.

The Protein Data Bank was consulted in order to acquire the *Aspergillus fumigatus* sterol 14- α -demethylase (CYP51B) crystal

structure (PDB ID: 6CR2). Protein preparation was carried out through the Protein Preparation Wizard in Maestro prior to docking calculations comprising addition of hydrogen atoms, assignment of bond orders, optimization of ionization states, correction of missing side chains and removal of redundant crystallographic water molecules apart from those involved in essential ligand–protein interactions in the active site. The co-crystallized prosthetic group was retained in the active site during the protein preparation process. We computed the pharmacokinetic and drug-likeness characteristics of the designed derivatives by using the SwissADME online server.

2.1 Study of molecular docking

The Glide docking module from the Schrödinger Maestro molecular modeling software suite (Schrödinger Release 2018-1, Maestro version 11.4) was used to conduct molecular docking research. Docking calculations were carried out using a Windows workstation equipped with an Intel® Core™ i7 CPU operating at 3.4 GHz, 32 GB of RAM, and 1 TB of hard drive storage. The ligand binding area of the co-crystallized ligand of CYP51B (PDB ID: 6CR2) served as the foundation for the receptor grid.

Econazole, Clotrimazole, and Ketoconazole were chosen as reference drugs for comparative docking study against CYP51B. The most advantageous binding orientations and conformations within the receptor active pocket were then predicted using flexible ligand docking calculations. The top-ranked conformations were chosen for additional interaction investigation after the docking poses were ranked according to docking score values in kcal/mol. Using Maestro visualization tools and 2D and 3D visualization models, the interactions of amino acid residues of the CYP51B active



site, hydrophobic interactions, π - π stacking interactions and hydrogen bonding were investigated [25].

2.2 Molecular dynamics simulation

The Desmond program, which is integrated into the Maestro 11.4 (Schrödinger software package), was used to performed MD simulation. The Desmond package was used to perform classical molecular dynamics simulations for the chosen SH4–CYP51B complex in order to investigate the protein–ligand complex’s dynamic behavior and structural stability under physiological settings. The simulated system used the SH4–CYP51B complex with 21,499 water molecules and 72,251 atoms. The protein–ligand complex structure was simulated by MD in an orthorhombic simulation box with periodic boundary conditions using the SPC (single point charge) water model. The system’s net charge was neutralized by adding sodium ions.

Throughout the simulation process, the NPT ensemble maintained a constant temperature of 300 K and atmospheric pressure [26]. In order to investigate the conformational stability and interaction behavior of the SH4–CYP51B complex during the simulation trajectory, the entire simulation period was run for 200 ns.

Root mean square deviation (RMSD), root mean square fluctuation (RMSF), secondary structure element (SSE), ligand torsional behavior, protein–ligand interaction mapping, ligand RMSF analysis, and ligand property analyses were used to assess the structural stability and dynamic fluctuations of the simulated complex over the course of

the simulation [27]. In order to investigate the hydrogen bonding, hydrophobic interactions, ionic contacts, halogen interactions, and water bridge interactions involved in the stabilization of the SH4–CYP51B complex, an investigation of protein–ligand interactions were also conducted.

2.3 Drug-Likeness and ADME Prediction

The online server SwissADME was used to predict pharmacokinetic and drug likeness properties of the designed oxadiazole derivatives [28]. Chemical structures of SH1–SH4 were first converted into canonical SMILES format for computational evaluation. Various physicochemical and pharmacokinetic parameters were predicted such as molecular weight, blood-brain barrier permeability, water solubility, gastrointestinal absorption, lipophilicity (LogP), number of hydrogen bond acceptors and donors, topological polar surface area (TPSA), P-glycoprotein substrate prediction, and Lipinski’s rule of five compliance.

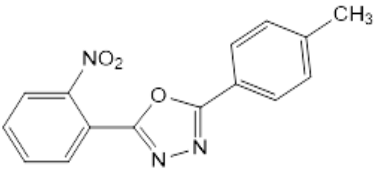
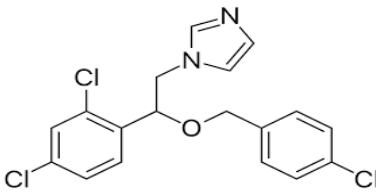
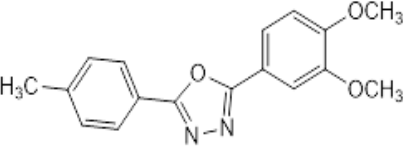
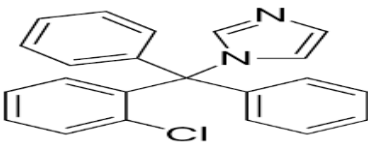
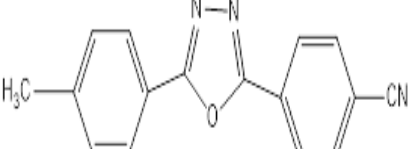
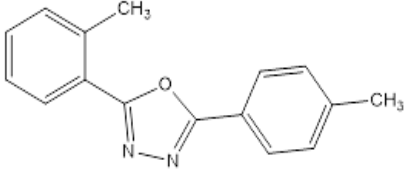
3. Results

3.1 Molecular docking analysis

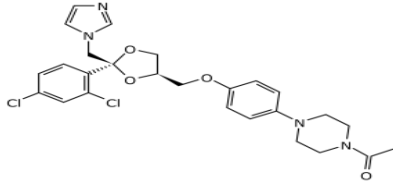
The proposed 1,3,4-oxadiazole derivatives (SH1–SH4) were tested for their binding affinity and interaction behavior with the active site of the *Aspergillus fumigatus* sterol 14- α -demethylase (CYP51B) using molecular docking experiments. As shown in Table 1, the docking profiles of the compounds under investigation and the reference antifungal medications are shown.



Table 1. Molecular docking characteristics of the reference antifungal medications and the proposed oxadiazole derivatives (SH1-SH4) against *Aspergillus fumigatus* CYP51B.

Rank	Compound	Structure	Docking Profile (Score · Interaction · Residues)
1	SH4 (Designed)		Docking score: −9.61 kcal/mol Interaction: π - π stacking, hydrophobic interactions Key residues: Tyr122, Val121, Leu125, Thr126, Phe234, Phe130, Tyr136, Phe229, Leu503, Phe504, Ile373, Ala307
2	Econazole (Reference)		Docking score: −9.599 kcal/mol
3	SH2 (Designed)		Docking score: −7.96 kcal/mol Interaction: π - π stacking, hydrophobic interactions Key residues: Phe130, Tyr122, Val121, Pro124, Leu125, Phe229, Phe234, Phe504, Leu503, Ile377, Met306, Ala307
4	Clotrimazole (Reference)		Docking score: −7.901 kcal/mol
5	SH1 (Designed)		Docking score: −7.86 kcal/mol Interaction: Hydrogen bond, π - π stacking, hydrophobic interactions Key residues: Trp238, Phe234, Tyr122, Val121, Pro124, Leu125, Met235, Phe229, Phe130
6	SH3 (Designed)		Docking score: −7.52 kcal/mol Interaction: π - π stacking, hydrophobic interactions Key residues: Tyr122, Leu125, Thr126, Phe234, Phe229, Phe130, Tyr136, Leu503, Phe504, Ile373, Ala307



Rank	Compound	Structure	Docking Profile (Score · Interaction · Residues)
7	Ketoconazole (Reference)		Docking score: -7.385 kcal/mol

According to Table 1, SH4 had a docking score of -9.61 kcal/mol for CYP51B, which was somewhat higher than the reference antifungal medication Econazole's value of -9.599 kcal/mol. SH2 had a docking score of -7.96 kcal/mol and SH1 -7.86 kcal/mol, while SH3 had the lowest affinity of all the developed derivatives at -7.52 kcal/mol. But all the tested chemicals fit into the active-site cavity and formed favorable interactions with key amino acid residues. As illustrated in Table 1, the designed compounds formed a combination of π - π stacking, hydrogen-

bonding and hydrophobic interactions that are responsible for complex stabilization. Among them, SH4 demonstrated the most favorable interaction profile, which was reflected in its superior docking score and predicted binding affinity toward CYP51B. The two-dimensional interaction diagrams of the designed compounds within the CYP51B binding pocket are presented in Figure 1. Based on the docking results, SH4 was selected for further molecular dynamics simulation studies.

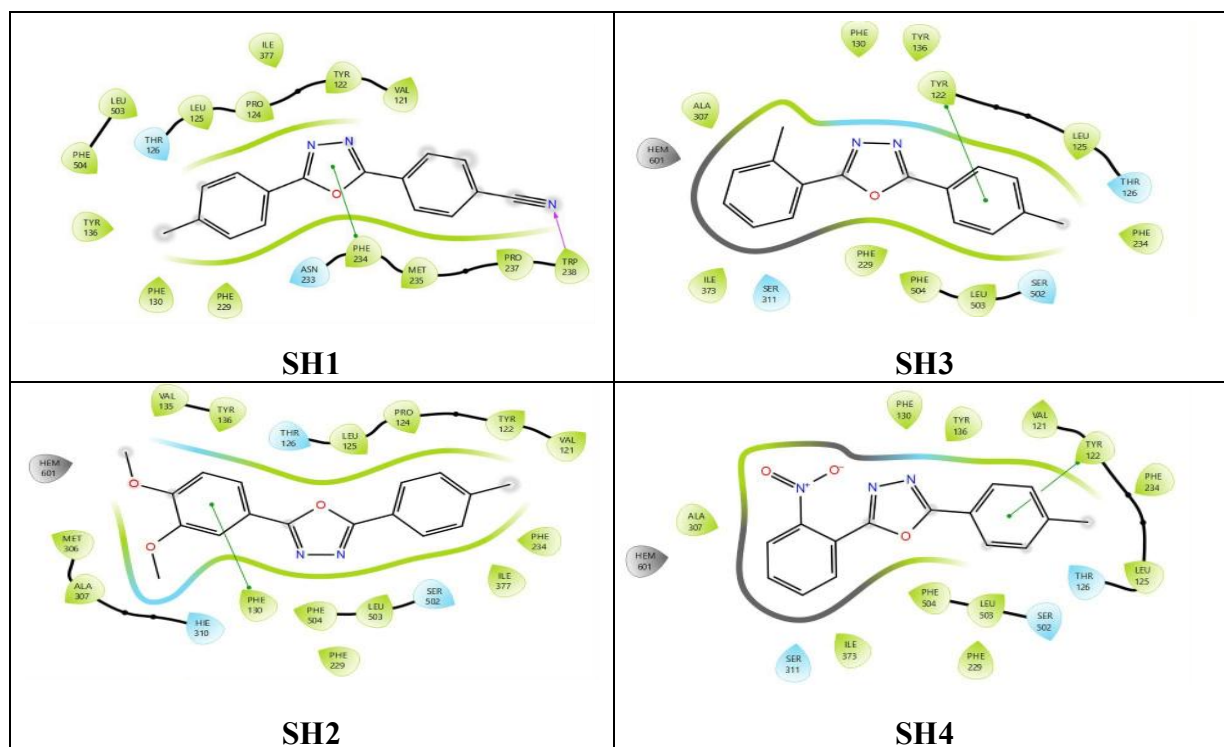


Figure 1. Docked SH1-SH4 interact with the *Aspergillus fumigatus* CYP51B active site (PDB ID: 6CR2) in two dimensions.

3.2 Molecular Dynamics Simulation

The most active compound, SH4, was chosen for molecular dynamics simulation research to further analyze the thermodynamic stability and dynamic behavior of the ligand–receptor complex. Afterwards, an MD simulation of 200.398 ns was applied on the SH4–CYP51B complex to study its conformational stability, residue flexibility, secondary structural integrity as well as persistence of protein–ligand interactions throughout the trajectory.

Root mean square deviation (RMSD) analysis was used to evaluate the structural stability of the SH4–CYP51B complex (Figure 2). The protein C α backbone exhibited moderate fluctuations during the simulation and remained within an acceptable range of approximately 1.5–3.0 Å after the equilibration phase, indicating that

the overall structure of CYP51B maintained a stable conformation throughout the 200 ns trajectory. The range of the ligand RMSD (Lig fit Prot) was around 2.5 to 5.6 Å. Although the ligand was more mobile than the protein backbone, there was no sign of the ligand dissociating from the binding pocket. The simulation results that SH4 remains consistently positioned within the active region are supported by the continuance of key protein–ligand interactions. In addition, the fact that the receptor's secondary structure parts were preserved throughout the simulation provides further evidence of its structural stability. This suggests that conformational flexibility inside the binding pocket, rather than complex instability, may be responsible for the observed ligand fluctuations.

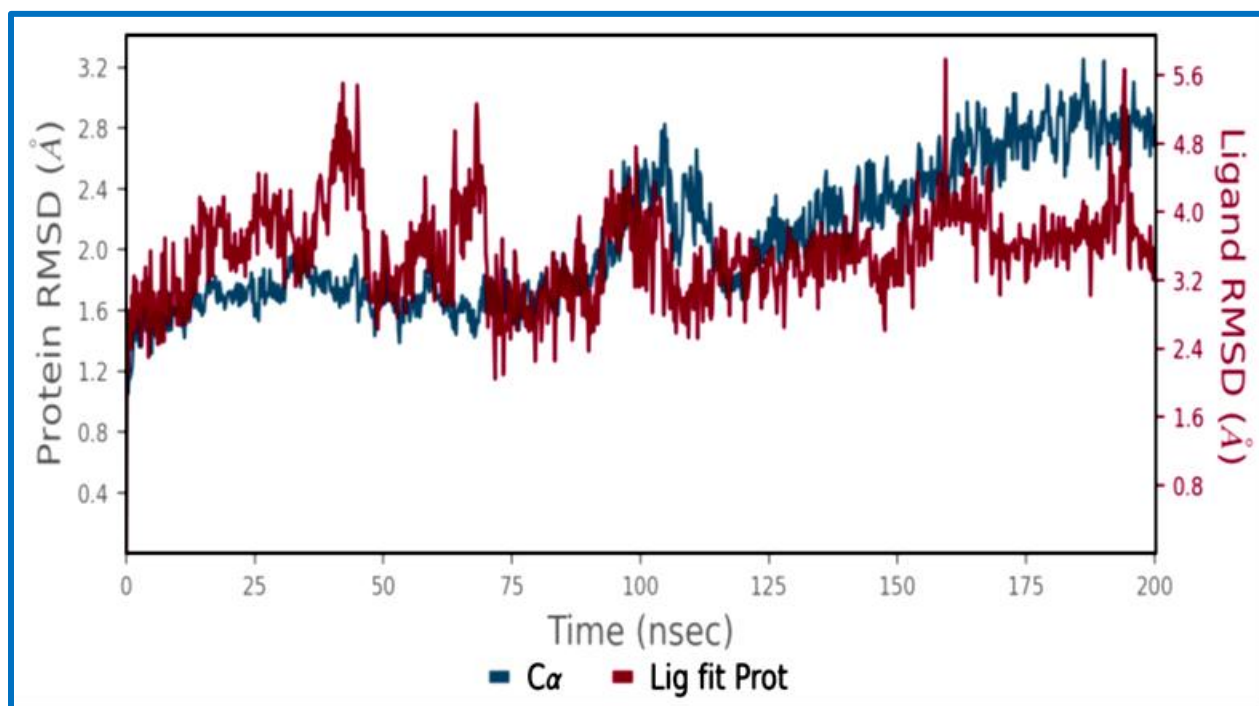


Figure 2. Protein-ligand RMSD plot of the CYP51B-SH4 complex during 200 ns molecular dynamics simulation.

Figure 3 shows the results of the RMSF study that looked at the residue-level flexibility of CYP51B during the simulation. The protein core was noticeably stiff because most amino acid residues had poor RMSF values. As is typical in molecular dynamics simulations, the majority of the increased fluctuations

were contained in the terminal and loop regions. It is worth noting that the residues involved in binding the ligand showed a fair amount of stability, which indicates that the receptor was not structurally significantly disturbed by the ligand contact.

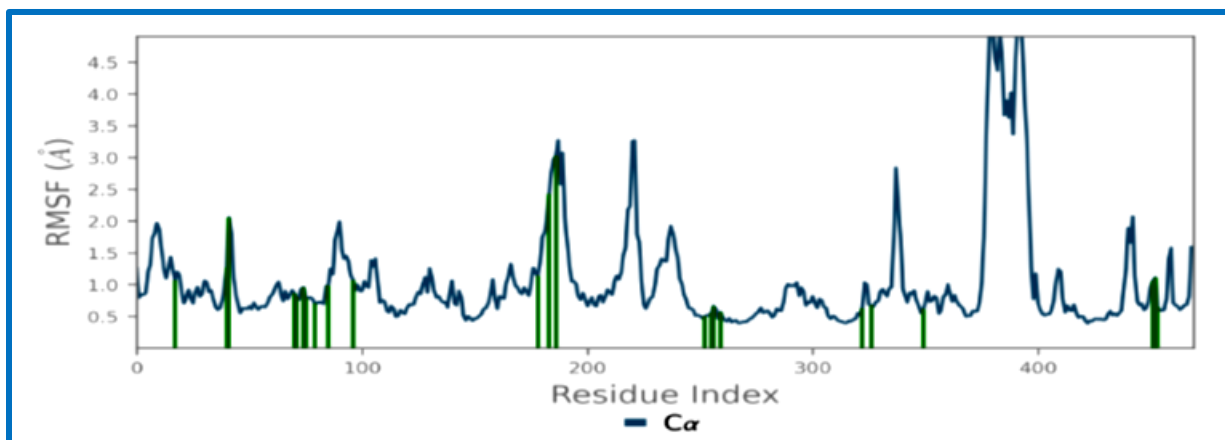


Figure 3. RMSF analysis of the amino acid residues of CYP51B in the 200 ns molecular dynamics simulation.

The simulation successfully maintained CYP51B's secondary structural architecture, as seen in Figure 4's investigation of secondary structure elements. The percentage of secondary structures, which included α -helices at 42.29% and β -strands at 9.83%, was 52.12%. It seems that SH4 binding had

no detrimental effect on the receptor's structural organization, since the constant SSE profile throughout the simulation trajectory provides additional evidence of the protein-ligand complex's conformational stability.

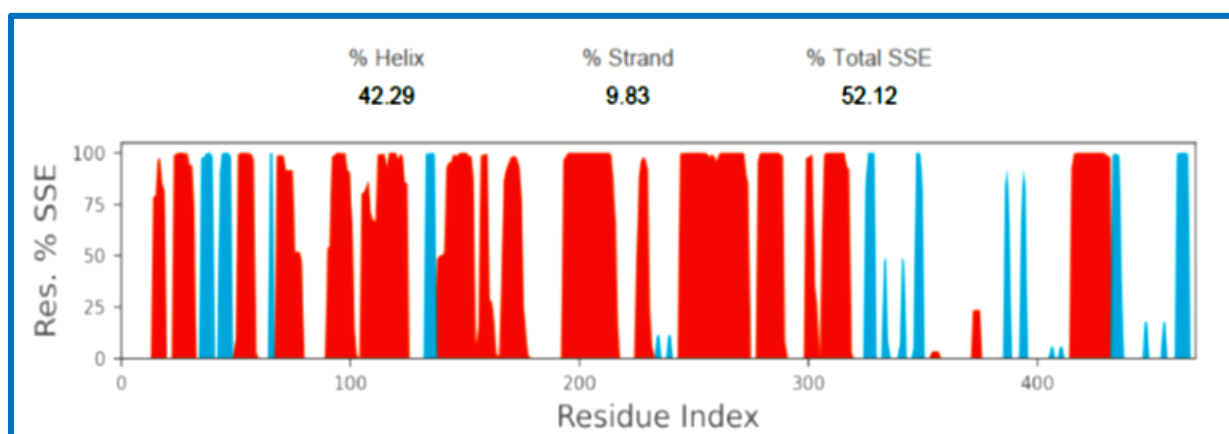


Figure 4. Secondary structure elements analysis of CYP51B during the molecular dynamics simulation.

An in-depth examination of protein–ligand interactions indicated that hydrophobic interactions were the primary stabilizing factor in the SH4–CYP51B complex (Figures 5 and 7). Of all residues, TYR122 had the most enduring contact, sustained for nearly 78% of the simulation duration. PHE504 demonstrated a notable hydrophobic/ π -interaction that lasted for roughly 48% of the

simulation duration. Further contributions from residues such as VAL121, PHE229, ILE373, ILE377, and LEU503 were noted along the simulation trajectory. The interaction timeline analysis (Figure 6) demonstrated that these connections were maintained during a significant duration of the 200 ns simulation, underscoring the robustness of the binding mode.

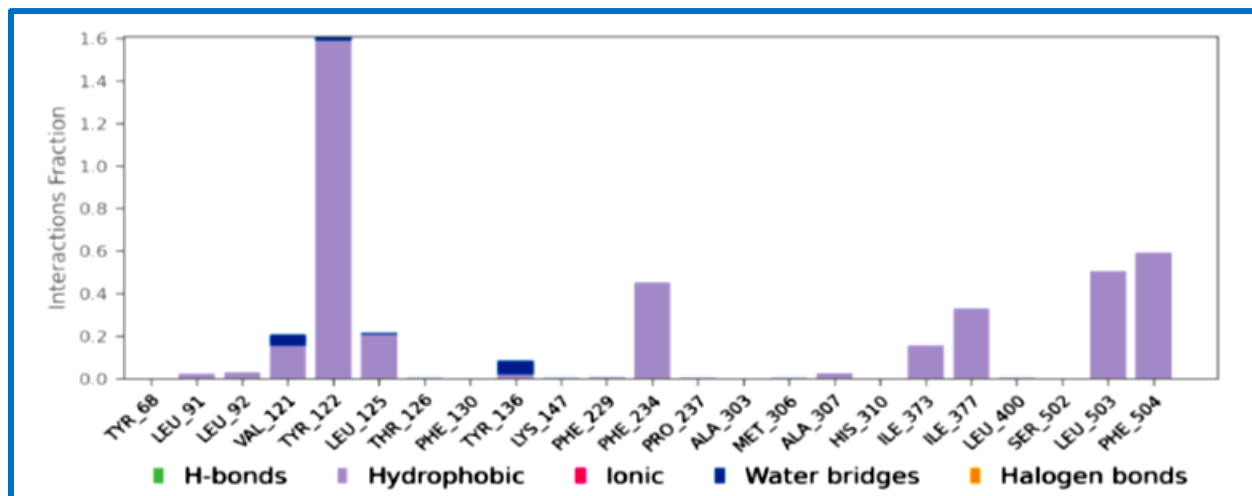


Figure 5. Protein–ligand interaction analysis of CYP51B–SH4 complex during the molecular dynamics simulation.

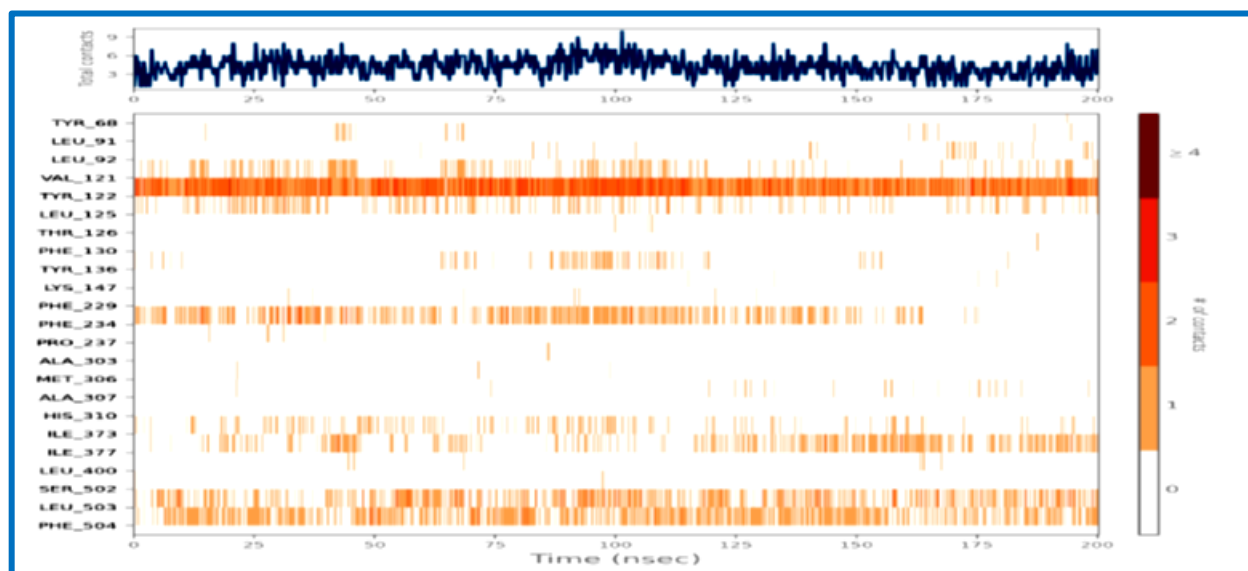


Figure 6. Time-course analysis of protein–ligand contacts during the 200 ns molecular dynamics simulation.

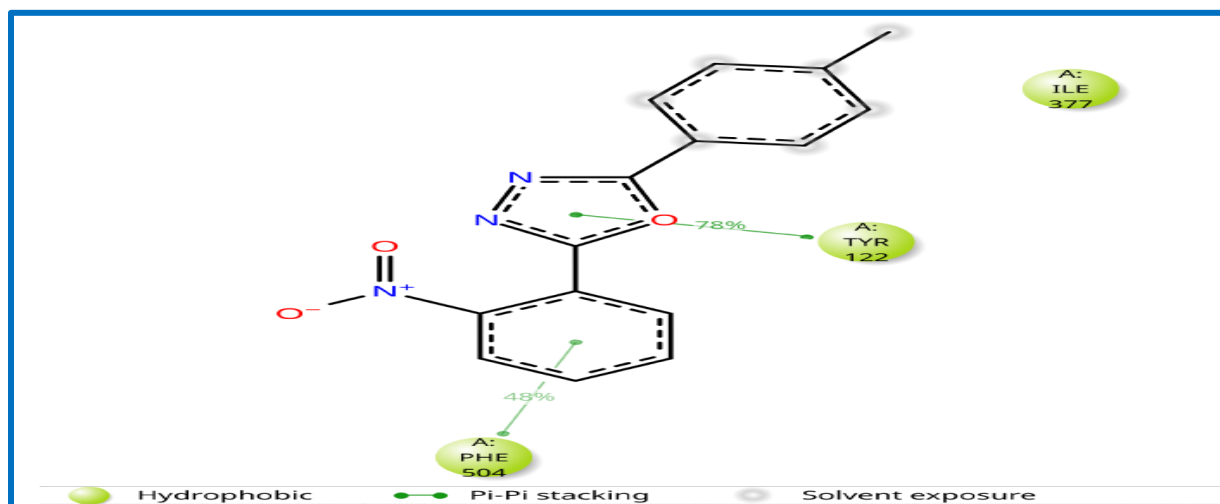


Figure 7. Detailed ligand–protein interaction diagram of SH4 within the CYP51B binding pocket.

3.3 Analysis of ADME and Drug-Likeness

The SwissADME web server was used to forecast the pharmacokinetic characteristics

of the designed compounds. Table 2 summarizes the computed physicochemical and pharmacokinetic characteristics.

Table 2: Predicted ADME and drug-likeness parameters of SH1–SH4 compounds.

Property	SH1	SH2	SH3	SH4
Molecular Formula	C ₁₆ H ₁₁ N ₃ O	C ₁₇ H ₁₆ N ₂ O ₃	C ₁₆ H ₁₄ N ₂ O	C ₁₅ H ₁₁ N ₃ O ₃
M. Wt. (g/mol)	261.28	296.32	250.30	281.27
H-Bond Acceptors	4	5	3	5
H-Bond Donors	0	0	0	0
Lipophilicity (Log P)	3.25	3.44	3.80	2.68
Water Solubility	Moderately soluble	Moderately soluble	Moderately soluble	Moderately soluble
GI Absorption	High	High	High	High
BBB Permeant	Yes	Yes	Yes	No
P-gp Substrate	No	No	No	No
Lipinski (Rule of Five)	Yes (0 violations)	Yes (0 violations)	Yes (0 violations)	Yes (0 violations)

There were no infractions of Lipinski's rule of five by any of the four compounds that were developed (SH1–SH4), suggesting that they have promising drug-like properties and are suitable for oral administration. The compounds' molecular weights were between 250.30 and 296.32 g/mol, and their computed Log P values (2.68–3.80) were within the permissible range for potential orally active drugs. In addition, when being taken orally, all of the substances showed very effective intestinal uptake, indicating high gastrointestinal (GI) absorption.

There was less chance of active efflux and maybe better bioavailability as none of the studied derivatives were projected to be P-glycoprotein (P-gp) substrates. It was anticipated that SH1, SH2, and SH3 would be able to cross the blood-brain barrier (BBB), but SH4 would not be able to do so. This

second feature may be useful for antifungal treatment as it reduces the risk of adverse effects on the central nervous system without sacrificing systemic efficacy.

The drugs' gastrointestinal absorption and brain penetration characteristics were visualized using the BOILED-Egg model. The compounds' good oral bioavailability characteristics were confirmed by their placement inside the area associated with high intestine absorption, as illustrated in Figure 8. All of the oxadiazole derivatives that were created showed good pharmacokinetic behavior, acceptable physicochemical features, and promising drug-likeness characteristics in the ADME study. This suggests that they might be good candidates for orally active antifungal treatments.

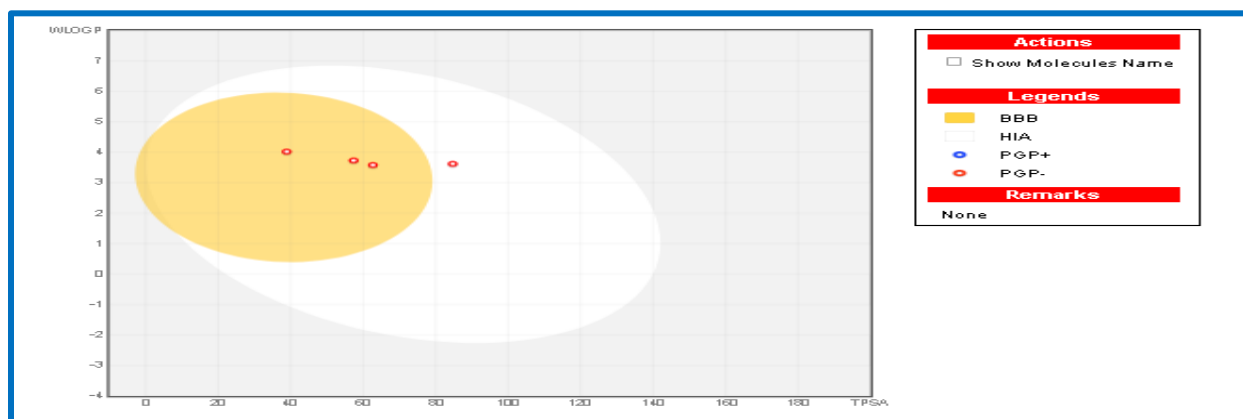


Figure 8. The estimated gastrointestinal absorption and blood–brain barrier permeability profiles of SH1–SH4 were created using SwissADME in a BOILED-Egg plot.

4. Discussion

The development of novel antifungal medicines targeting sterol 14- α -demethylase (CYP51B) is a major strategy in the battle against invasive fungal infections and the emerging issue of azole resistance. The 1,3,4-oxadiazole derivatives obtained in this study exhibited a promising interaction with the active site of CYP51B. This shows that the

oxadiazole scaffold may be employed to develop antifungal medicines.

The different binding affinities of the investigated compounds suggest that differences in the structure of the aromatic substituents are of great importance for the accommodation of the ligands and the patterns of their interactions with the binding cavity. In particular, the enhancement of

SH4's performance highlights the need of the correct electrical and hydrophobic characteristics to promote excellent protein-ligand interactions. Molecular docking studies are useful for understanding the ligand binding however the behavior of proteins and ligands under physiological conditions may be better predicted using molecular dynamics modeling. Based on the molecular dynamics data across the 200 ns simulation, the CYP51B-SH4 complex was stable and maintained its structure and interaction with its ligand. Hydrophobic and aromatic interactions were present throughout the simulation, consistent with the predicted binding mechanism and suggesting that SH4 can stabilize its accommodation at the active site.

The docking and molecular dynamics findings are congruent, therefore there is additional reason to trust in the computational predictions and to consider SH4 as a potential effective inhibitor of CYP51B. For a drug to be effectively created, it must have good pharmacokinetic properties, target affinity and complex stability. The ADME analysis indicated that all the produced compounds complied with Lipinski's rule of five and had favorable gastrointestinal absorption profiles, indicating excellent oral administration prospects. Moreover, the expected physicochemical properties were in agreement with the commonly accepted criteria for medications. One possible advantage of systemic antifungal therapy is that SH4 is not predicted to penetrate the blood-brain barrier, which may reduce the risk of inadvertent exposure to the central nervous system. From all substances studied, SH4 was shown to be the most promising derivative based on the combination of molecular docking, molecular dynamics modeling and ADME evaluation. The oxadiazole derivative showed strong pharmacokinetic features, steady interaction

profile and high binding affinity, which make it a viable candidate as a new antifungal medication against CYP51B.

5. Conclusion

In this study, four novel 1,3,4-oxadiazole derivatives (SH1-SH4) were designed and in silico evaluated as potential antifungal agents against the *Aspergillus fumigatus* sterol 14- α -demethylase (CYP51B). Molecular docking tests suggested high binding affinities for all tested compounds. In the produced derivatives, SH4 presented the best binding profile. Moreover, MD simulations also confirmed the stability of the CYP51B-SH4 complex in the whole 200 ns simulation time, which confirmed the reliability of the predicted binding mode and indicated that the favorable protein-ligand interactions can be maintained even in changing environments. The produced compounds also exhibited promising pharmacokinetic properties and acceptable drug-like qualities in the ADME investigation, including the fulfillment of all five conditions of Lipinski's rule and high gastrointestinal absorption as predicted. In summary, the findings suggest that SH4 is the most promising of the oxadiazole derivatives tested and that the 1,3,4-oxadiazole scaffold is a very promising platform for the development of novel antifungal medicines against CYP51B. However, more in vitro, in vivo and toxicity studies are essential to validate the computational data and evaluate the therapeutic potential of SH4 as a potential antifungal lead compound.

6. Acknowledgements

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