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Original Research Article

Computational Design of Novel Triazole Derivatives of Para-Aminobenzoic Acid as Potential Inhibitors of Fungal Lanosterol 14-Alpha Demethylase Enzyme.

Article History:

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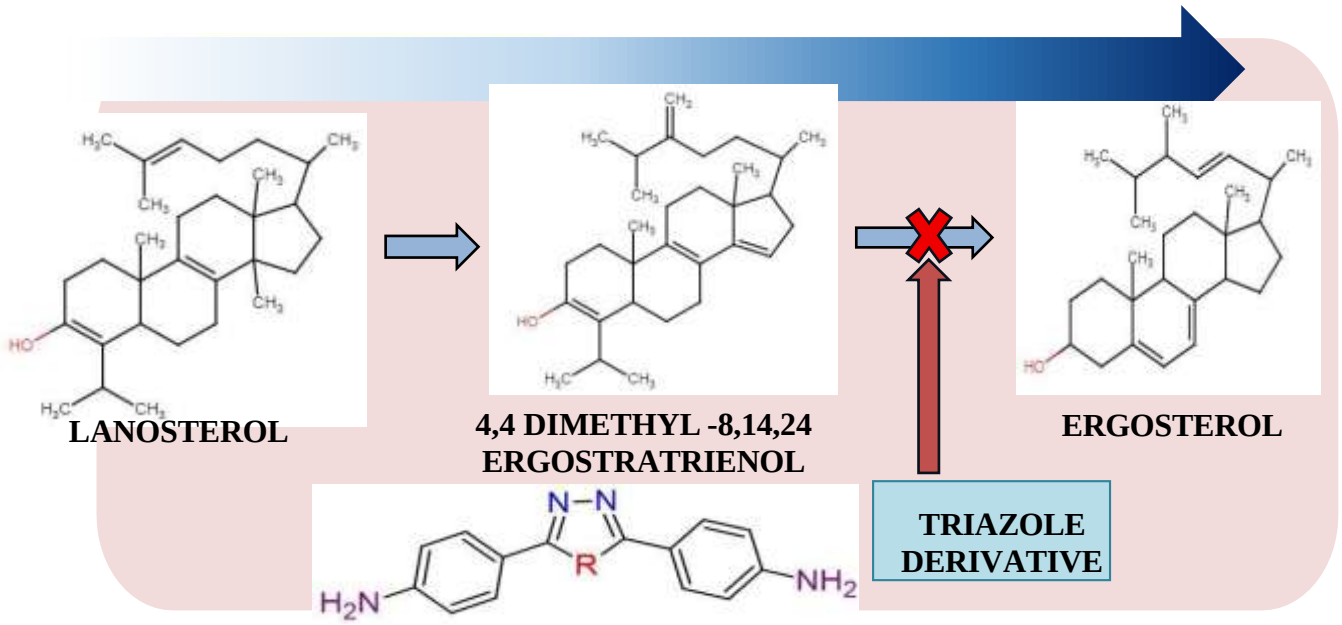
Abstract: The limited availability of anti-fungal drug, emergence of resistance and also growing population there is a need for novel antifungal agents. The aim of the present study is to design and synthesis novel triazole lead moieties against Lanosterol 14-Alpha Demethylase enzyme (LDM) with potential antifungal activity using computational methods. A total of eight newly compounds were designed from Para-aminobenzoic acid (PABA) and evaluated for antifungal activity against PDB ID: 5EQB. As a result, the compound CT 6, CT 2, and CT 5 had shown potent inhibitory activity when compared to the standard drug fluconazole. In conclusion the lead compound CT 6 exhibited potential antifungal activity and its newer derivatives may be synthesized and studied further.

Keywords: Triazole, Para amino benzoic acid, Fluconazole, LDM.

GRAPHICAL ABSTRACT:



INTRODUCTION

Some Saccharomyces species and Candida albicans are common fungal species present in the oral cavity, Gastro intestinal tract and Vaginal flora. Under certain conditions, such as the use of broad-spectrum antibiotics, malnutrition and immunosuppression these fungi can become pathogenic agents leading harmful infections to the humans. The global estimation says that fungal infections cause over 3.8 million death per year with 2.5 million of those deaths being directly attribute to fungal diseases. [1,2]

Recently, azole group drugs such as Fluconazole and Ketoconazole are frequently used to treat fungal infections. However, new antifungal agents are needed because fungal infections produce resistance to these drugs. The azole drugs act by halting the synthesis of ergosterol through the inhibition of the 14-Alpha Lanosterol Demethylase enzyme (CYP 51). Because, the absence of ergosterol will lead to disappear fungi as they play crucial role on the fungal cell membrane. The binding site of HEM co-factor which interacts with imidazole and triazole rings. [3,4,5] The studies says that the triazole ring system are still subjected to many biological activities because they are electron rich due to presence of three nitrogen atoms and they are aromatic heterocyclic compounds. They exist in 2 isomeric forms (1,2,3- triazole and 1,2,4- triazole) both of which are key structural motifs in drugs

antifungal, anticancer, antiviral and anti-inflammatory properties. Their broad activity produces several advantages and act as a major scaffold inn modern drug discovery, particularly against fungal infections. [5] The triazole ring shows better antifungal property with its positive pharmacokinetic character, lower toxicity when compared to other heterocyclic compounds and various pharmacological actions because they produce better co=ordination

with the Fe2+ ion.

Based on this data, nearly eight triazole derivatives were designed from para-amino benzoic acid as a precursor and evaluated for their antifungal activity. Molecular docking studies were performed to elucidate the mechanism of action. The designed compounds will be synthesized based on the scheme 1 in future using classical methods of organic synthesis.

MATERIAL AND METHODS

1. Computational Study:

A) Target Selection:

This study focuses on the antifungal potential of triazole derivatives targeting the protein with PDB ID: 5EQB CHAIN A (Crystal structure of lanosterol 14-alpha demethylase with intact transmembrane domain bound to itraconazole) for inhibiting the key enzyme LDM in the ergosterol biosynthesis pathway. Through target prediction and molecular docking studies, the interaction of these compounds with PDB ID: 5EQB was evaluated to identify effective inhibitors. [6]

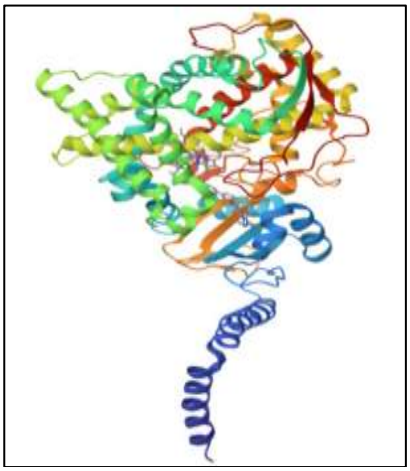


Fig 1: Ribbon structure of PDB ID: 5EQB

B) Ligand preparation:

Eight novel triazole derivatives were synthesized starting from para-aminobenzoic acid by fusing it with triazole and various amine derivatives. The synthesis was carried out using the Schiff base principle, which enabled the formation of the desired compounds through condensation reactions. These newly prepared ligands were characterized and then used for further molecular docking studies targeting the antifungal protein PDB ID: 5EQB.

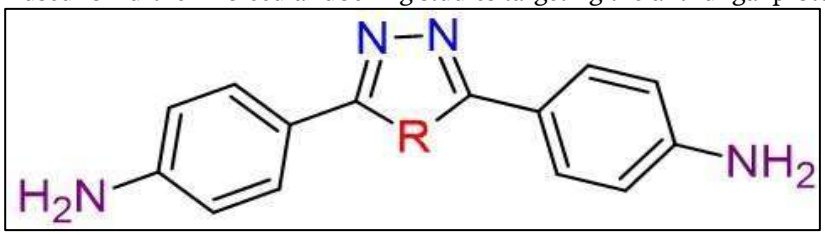


Fig 2. 4-R-3,5-bis(4-aminophenyl) -4H-1,2,4-triazole, general structure of novel triazole derivatives.

C) Molecular Docking:

Molecular docking analysis has been performed on different derivatives of triazole compounds designed from para-amino benzoic acid. The software used for molecular docking studies Schrödinger v.1.3 to estimate the binding para of ligand interacting with (PDB ID 5EQB) a micro molecular such as protein and other associated quantities to produce binding affinity. The PDB ID: 5EQB is used for interaction with different derivatives of triazole compounds.

D) Synthesis of Lead compounds:

In this study, eight novel triazole derivatives were synthesized using para-aminobenzoic acid as the starting compound. These derivatives were prepared by incorporating the triazole moiety and various amine derivatives through a Schiff base reaction, a well-established condensation method involving the reaction of aldehydes or ketones with primary amines. This approach enabled the formation of imine (–C=N–) linkages, leading to structurally diverse and potentially bioactive novel ligands. The Schiff base principle was employed due to its efficiency in generating stable heterocyclic compounds with potential antifungal properties. Each derivative was carefully designed to explore the influence of different amine substitutions on biological activity. These designed ligands were then characterized using *In-silico* molecular docking studies against the antifungal target 5EQB

involved in the ergosterol biosynthesis pathway.

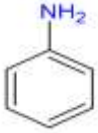
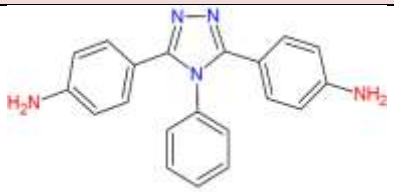
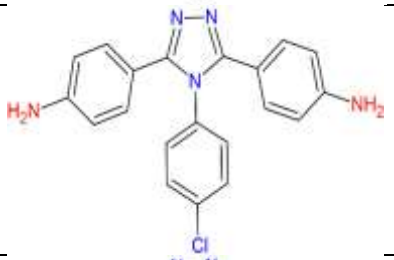
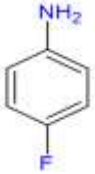
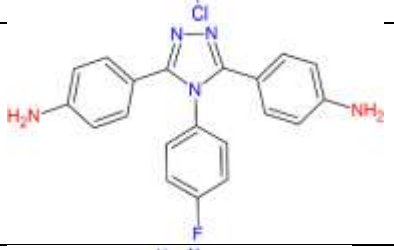
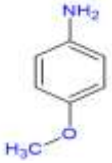
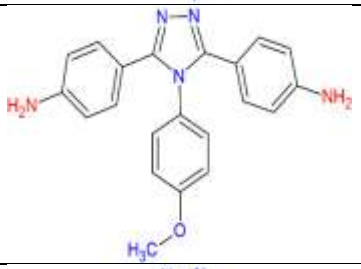
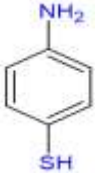
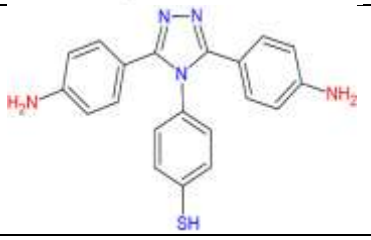
Results and Discussion:

A) Target Selection:

Based on the several studies PDB ID: 5EQB is selected as a target protein (Chain A) and refined using Schrödinger software.

B) Ligand Preparation:

Eight new triazole derivatives were designed from para-aminobenzoic acid via Schiff base reactions with different amines. The structure was designed using Chem sketch software.

S. NO	DERIVATIVE CODE	AMINE DERIVATIVES	STRUCTURE OF DESIGNED TRIAZOLE DERIVATIVE	IUPAC NAME OF TRIAZOLE DERIVATIVE
1	CT 1	 Aniline		4,4'-(4-phenyl-4*H*-1,2,4-triazole-3,5-diyl)dianiline
2	CT 2	 Chloro aniline		4,4'-[4-(4-chlorophenyl)-4*H*-1,2,4-triazole-3,5-diyl]dianiline
3	CT 3	 Fluro aniline		4,4'-[4-(4-fluorophenyl)-4*H*-1,2,4-triazole-3,5-diyl]dianiline
4	CT 4	 Methoxy aniline		4,4'-[4-(4-methoxyphenyl)-4*H*-1,2,4-triazole-3,5-diyl]dianiline
5	CT 5	 Benzylamine		4,4'-(4-benzyl-4*H*-1,2,4-triazole-3,5-diyl)dianiline
6	CT 6	 Thio aniline		4-[3,5-bis(4-aminophenyl)-4*H*-1,2,4-triazol-4-yl]benzene-1-thiol

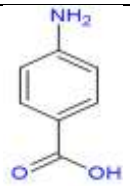
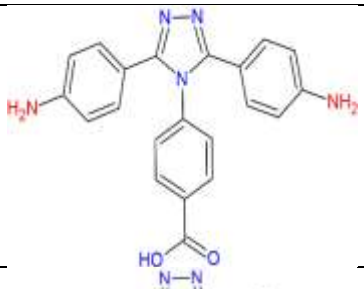
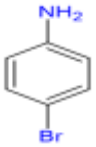
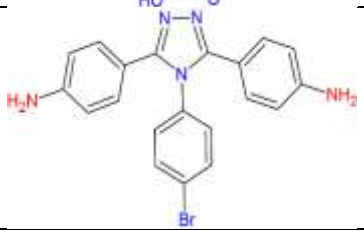
7	CT 7	 Para amino benzoic acid		4-[3,5-bis(4-aminophenyl)-4*H*-1,2,4-triazol-4-yl]benzoic acid
8	CT 8	 Bromo aniline		4,4'-[4-(4-bromophenyl)-4*H*-1,2,4-triazole-3,5-diyl]dianiline

Table 1: Novel triazole derivatives designed from para-amino benzoic acid

C) Molecular Docking:

The software predicts the intermolecular Vander Waals Interaction between the proteins and ligands (Table 2) represents different modes and affinity in Kcal/mol for the compounds from CT1 to CT8.

The Table 2 shows that compound has good binding affinity towards the triazole derivative CT1 to CT8 has produced good binding affinity towards the targeted protein.

From the data obtained, it clearly shows the compound CT 6 had produced better pharmacological activity when compared to the standard triazole drug Fluconazole.

CD CODE	MOL MW	DOCKING SCORE	GLIDE EMODEL	D.HB	A. HB	RULE OF FIVE	CNS	QPlog BB	QPlog KP	%HOA
STD	306.270	**-9.023**	-75.389	3	4	0	-2	-1.261	-3.016	**89.963**
CT 1	327.388	-8.148	-65.950	3	4	0	-2	-1.219	-3.049	87.139
CT 2	361.833	-8.751	-71.140	3	4	0	-2	-1.049	-3.214	90.417
CT 3	345.358	-8.480	-67.863	3	4	0	-2	-1.199	-3.187	88.538
CT 4	357.414	-7.943	-70.487	3	3.75	0	-2	-1.311	-3.257	87.809
CT 5	359.448	-8.549	-73.337	3	4	0	-2	-1.145	-3.009	88.548
CT 6	341.415	**-9.472**	-76.089	3	4	0	-2	-1.281	-2.856	**90.869**
CT 7	373.413	-7.995	-34.953	3	3.7	0	-2	-2.53	-4.64	48.678
CT 8	406.286	-8.184	-71.769	3	4	0	-2	-1.06	-3.210	87.560

Table 2: Docking score and QikProp properties of designed triazole derivative from CT 1 to CT 8 with the target protein PDB ID: 5EQB with standard drug Fluconazole.

D) SYNTHESIS:

Eight new triazole derivatives will be synthesized in future using the below scheme from para-aminobenzoic acid via Schiff base reactions with different amines [6,7]. The ligands were characterized and showed favourable docking interactions against the fungal target PDB ID: 5EQB, supporting their potential as antifungal agents.

The synthesis of 4-alkyl-3,5-bis(4-aminophenyl) -4H-1,2,4-triazole was carried out through a three-step process beginning from *p-aminobenzoic acid*. In the first step, *p-aminobenzoic acid* was treated with phosphorus pentachloride (PCl_5) to form *4-aminobenzoyl chloride*, which was subsequently condensed with hydrazine hydrate in the presence of triethanolamine and chloroform to yield *N, N'-bis(4-aminobenzoyl) hydrazine* [10,11]. In the second step, this

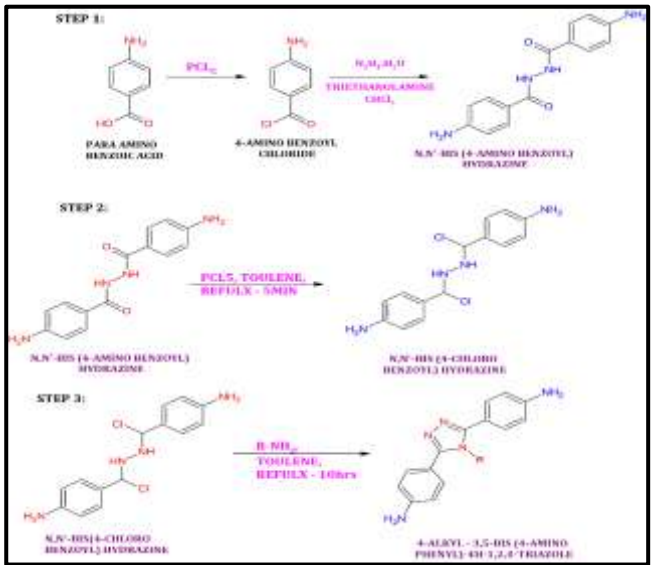
intermediate was refluxed with PCl_5 in toluene for five minutes to produce *N, N'-bis(4-chlorobenzoyl) hydrazine* through chlorination of the amide group. In the final step, the obtained bis(4-chlorobenzoyl) hydrazine was reacted with various amine or aniline derivatives under reflux in toluene for ten hours to afford the target *4-alkyl-3,5-bis(4-aminophenyl) -4H-1,2,4-triazole* derivatives. The formation of the triazole ring occurred through condensation followed by intramolecular cyclization and dehydrogenation, yielding stable heterocyclic systems potentially possessing antifungal activity [12,13,14]

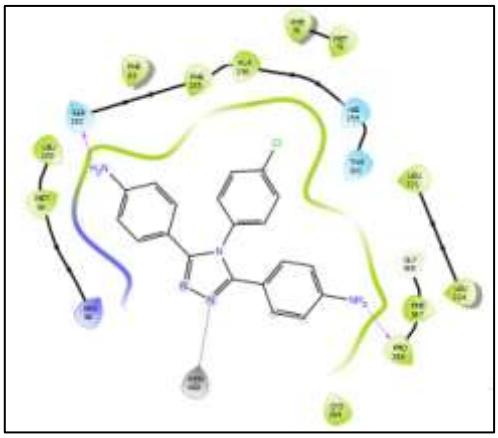
(**Reaction conditions**

Step 1: Triethanolamine acts as a mild base to neutralize HCl and stabilize intermediates; Chloroform serves as an inert, nonpolar solvent maintaining reaction homogeneity; Moderate temperature (50–60 °C) ensures complete substitution without acid chloride hydrolysis.

Step 2: Toluene serves as a non-polar inert medium enabling chlorination under anhydrous conditions.; PCl_5 is both a chlorinating and dehydrating agent, promoting substitution at nitrogen and electrophilic aromatic sites; Mild heating (50–70 °C) under reflux typically ensures full conversion without decomposing the hydrazide backbone.

Step 3: Solvent: Toluene (dehydrating, non-polar medium); Temperature: 80–100 °C (reflux); Catalyst: Often none required; aromatic amines act as both reactants and mild bases; Duration: 6–8 h until evolution of HCl ceases [10 – 14])





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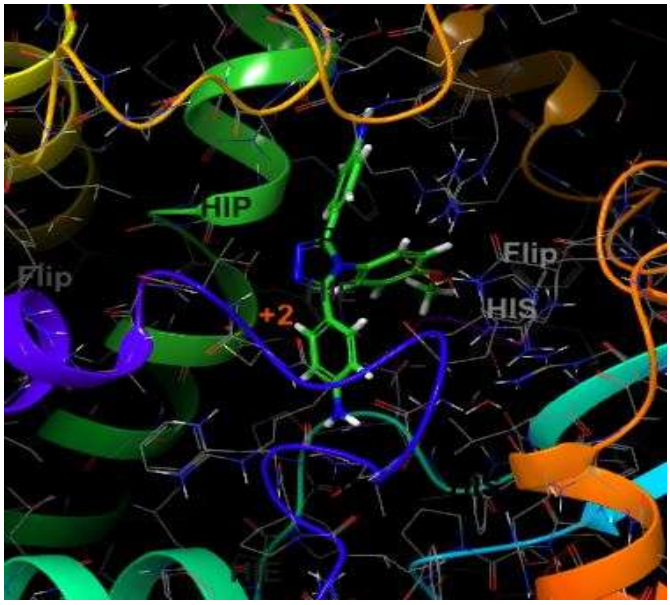
Scheme 1: Synthesis of designed novel triazole derivatives.

Fig 3. 2D AND 3D INTERACTION OF CT 1 (4,4'-(4-phenyl-4*H*-1,2,4-triazole-3,5-diyl)dianiline). The derivative is interacted with LEU 100 amino acids and HEM 460.



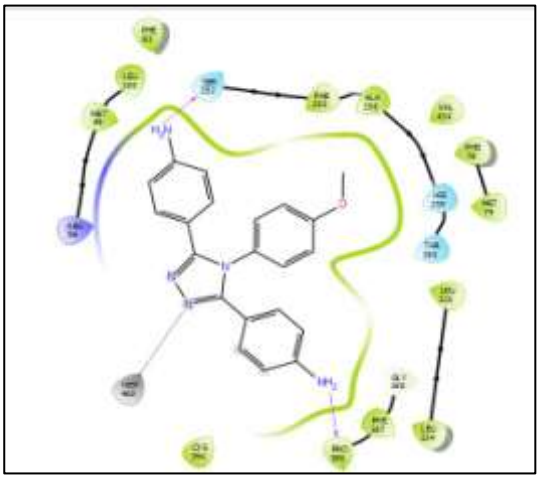
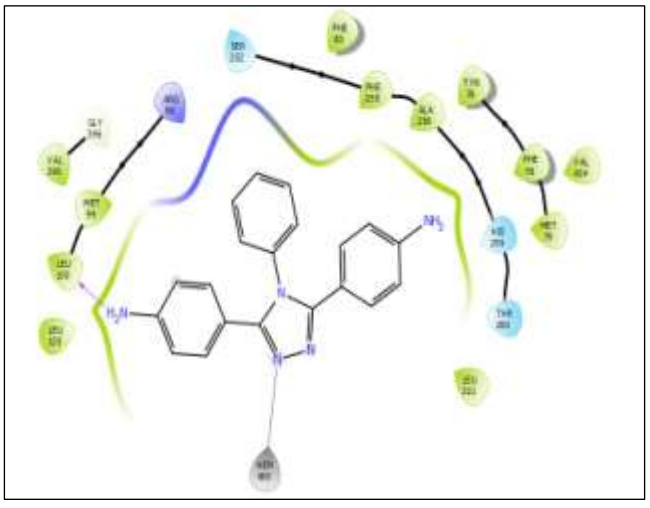
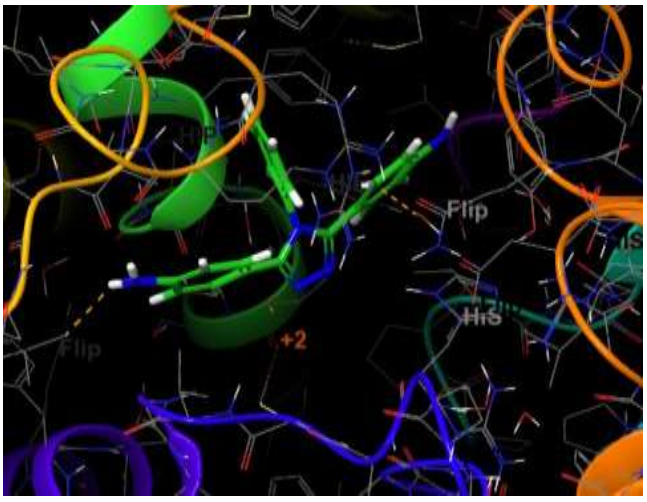
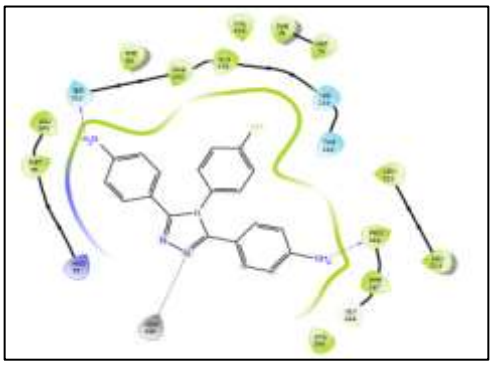


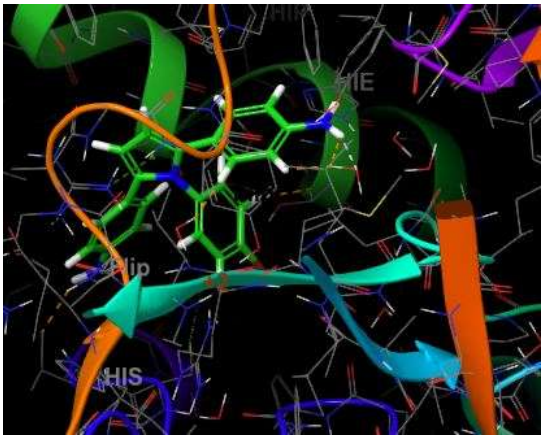
Fig 4. 2D AND 3D INTERACTION OF CT 2 (4,4'-(4-Chlorophenyl-4*H*-1,2,4-triazole-3,5-diyl)dianiline). The derivative is interacted with SER 252, PRO 386 amino acids and HEM 460.

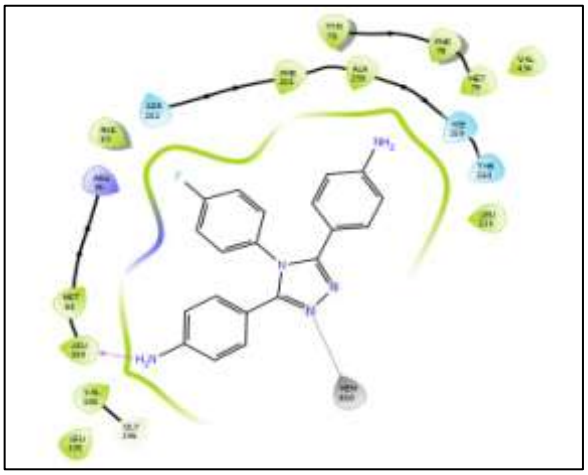
Fig 5. 2D AND 3D INTERACTION OF CT 3 (4,4'-(4-Flurophenyl-4*H*-1,2,4-triazole-3,5-diyl)dianiline). The derivative is interacted with LEU 100 amino acids and HEM 460.











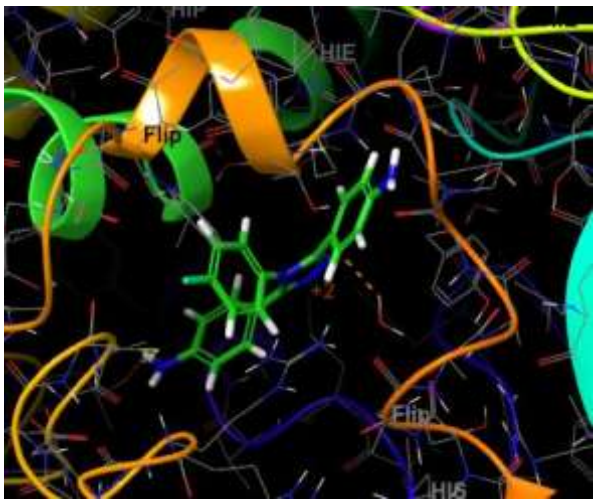
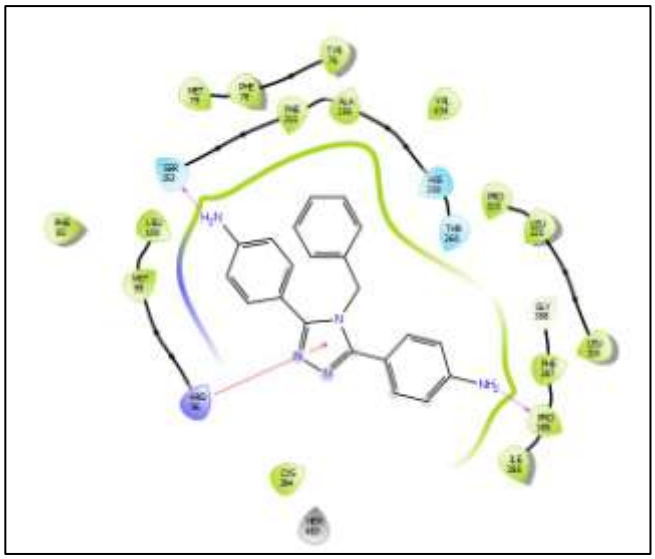


Fig 6. 2D AND 3D INTERACTION OF CT 4 (4,4'-(4-methoxyphenyl-4*H*-1,2,4-triazole-3,5-diyl)dianiline). The derivative is interacted with SER 252, PRO 386 amino acids and HEM 460



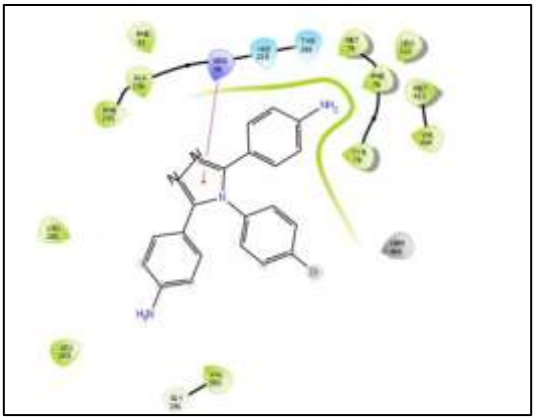
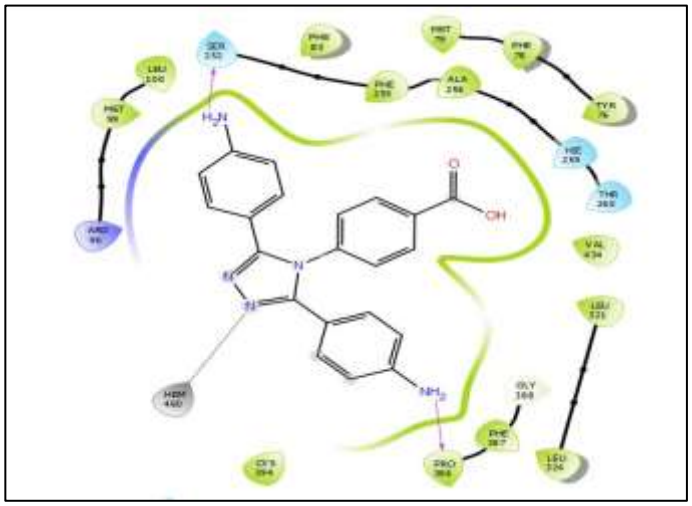
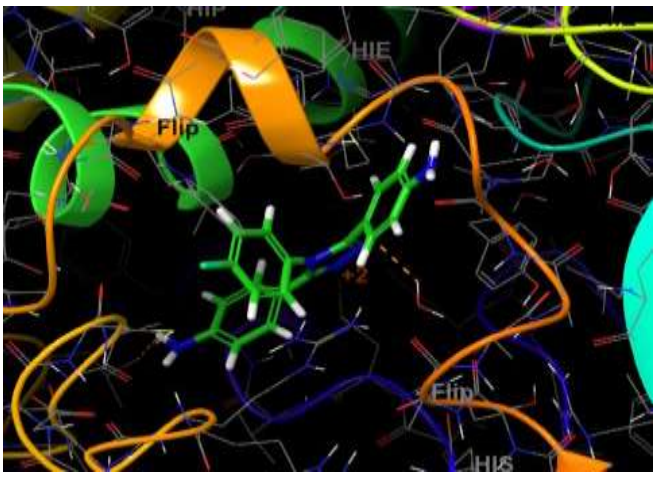
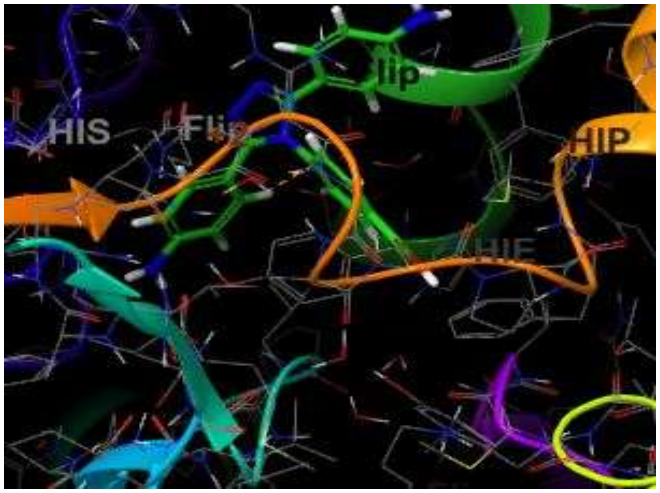
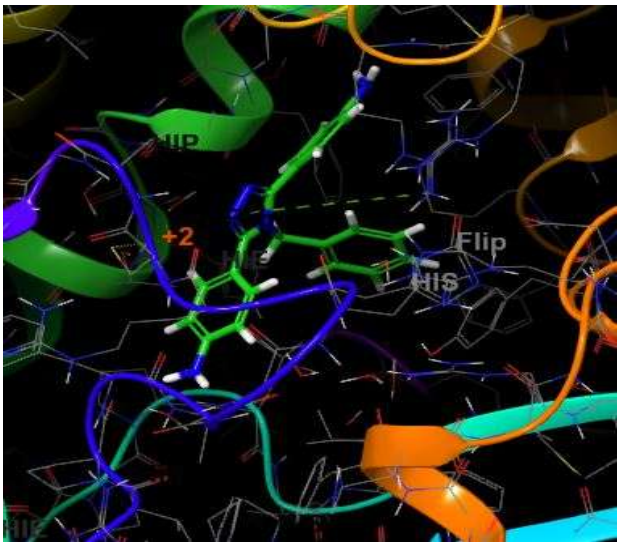


Fig 7. 2D AND 3D INTERACTION OF CT 5 (4,4'-(4-benzyl-4*H*-1,2,4-triazole-3,5-diyl)dianiline).

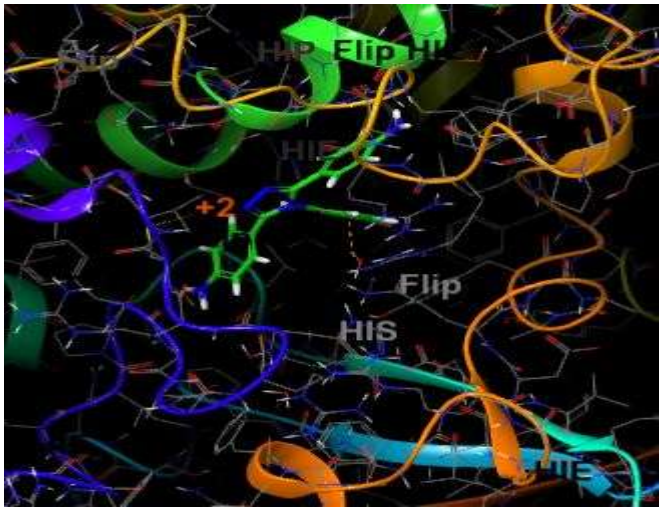








The derivative is interacted with ARG 96, SER 252, and PRO 386 amino acids.



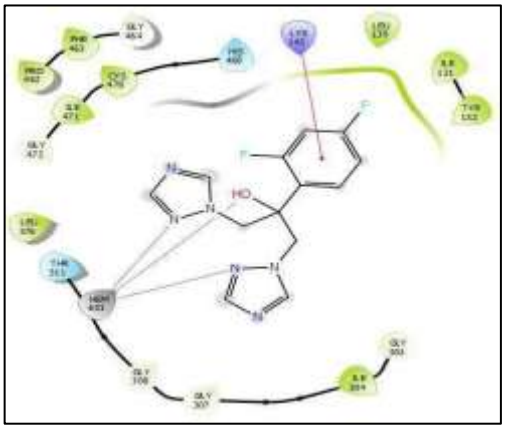


Fig 8. 2D AND 3D INTERACTION OF CT 6 (4-[3,5-bis(4-aminophenyl)-4*H*-1,2,4-triazol-4-yl]benzene-1-thiol). The derivative is interacted with PRO 386 amino acid and HEM 460.

Fig 9. 2D AND 3D INTERACTION OF CT 7 (4-[3,5-bis(4-aminophenyl)-4*H*-1,2,4-triazol-4-yl]benzoic acid).

The derivative is interacted with SER 252, PRO 386 amino acid and HEM 460.

Fig 10. 2D AND 3D INTERACTION OF CT 8 (4,4'-[4-(4-bromophenyl)-4*H*-1,2,4-triazole-3,5-diyl]dianiline). The derivative is interacted with ARG 96 amino acid.

Fig 11. 2D AND 3D INTERACTION OF FLUCONAZOLE (STD). The derivative is interacted with LYS 243 amino acid and HEM 601

CONCLUSION

In conclusion, this study successfully addressed the urgent need for novel antifungal agents by designing and synthesizing eight triazole derivatives from para-aminobenzoic acid as lead compounds targeting the Lanosterol 14-Alpha Demethylase enzyme. The computational evaluation against PDB ID: 5EQB revealed that compounds CT 6, CT 2, and CT 5 demonstrated superior inhibitory activity compared to the standard drug fluconazole, with CT 6 emerging as the most promising lead compound. These findings suggest that the designed triazole derivatives represent a viable approach to overcome the limitations of current antifungal therapeutics, including drug resistance and limited availability. The superior binding affinity and antifungal potential exhibited by CT 6 warrant further investigation through synthesis of its newer derivatives and comprehensive biological evaluation. This research contributes valuable insights into the development of next-generation antifungal agents that could potentially address the growing challenge of fungal resistance and improve therapeutic outcomes in antifungal therapy.

Future Scope

Further mechanistic studies, in vitro and in vivo validation, and structural optimization of these promising triazole leads, particularly CT 6 and its derivatives, are recommended to advance their clinical development as effective antifungal agents.

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