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Molecular Designing and Simulation Studies for 14-Alpha Demethylase (CYP51) Inhibitors

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Abstract: Inhibitors of 14α-Demethylase (CYP51) are often used as antifungal therapies. This work included molecular docking of several imidazole-based compounds with CYP51 inhibitory capabilities, followed by QSAR analysis to determine the optimal physicochemical characteristics of potential CYP51 inhibitors. 1. Imidazoles of interest were constructed using HyperChem, thereafter undergoing conformational analysis using a semiempirical approach, followed by the use of the PM3 technique. "Docking was conducted with all compounds with AutoDock. CYP51 represents a compelling class of P450 enzymes for fundamental study and serves as a pivotal mechanism for several useful pharmaceuticals.'' This study will provide an update on the CYP51 family members, their physiological functions, natural substrates, substrate preferences, and potential manipulation in laboratory experiments.

We have presented evidence that conserved CYP51 amino acid sequences serve as a hallmark of CYP51. Two key patterns in the evolution of CYP51 are examined, along with a synopsis of the significant efforts in CYP51 inhibition. [3, 4] The fungal cytochrome P450 enzyme sterol 14 alpha-demethylase (SDM) is an essential enzyme in the ergosterol biosynthesis pathway. The binding of azoles to the active site of SDM results in the depletion of ergosterol in cells [5].

Keywords: *14α-Demethylase, Molecular Docking, Thiadizoles Derivatives, Ligand-Target Interaction, ADME Prediction.*

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I. INTRODUCTION

The azole division's triumphant entry into the antifungal market goes back to the time when clotrimazole and miconazole were first used clinically in the late 1960s. At present, imidazoles as well as triazoles are recognized as the two major classes of azoles used in medicine. Imidazoles were the first, and triazoles were the second and third generations.

Triazole antifungals all have a five-membered di-unsaturated ring system that possesses a heterorcyclic core with three nitrogen atoms[6]. The first triazole application took place in the agricultural field in 1973, with a total of thirty-one total licenses. The triazole antifungal application in human health care began during the 1990s. Currently, there are five triazoles available for treating systemic mycotic infections, including fluconazole (FLC), itraconazole (ITC), voriconazole (VCZ), posaconazole (PCZ), and isavuconazole (IVU). The azole agents are favoured due to their considerably low costs compared to other antifungal drugs, along with their relatively broad spectrum of antimycotic efficacy.[7,8] The azoles are used in: (1) treatment and prophylaxis of animal infections (e.g., ringworm in cattle, aspergillosis in poultry, oomycete infections in aquaculture), (2) treatment in veterinary medicine (e.g., zoo animals and pets), (3) crop protection (e.g., mildews and rusts of grains, fruits, vegetables, flowers) , (4) Control of various plant-species diseases (e.g., leaf spot on flowers,scrubs and trees, including the timber industry), (5) Building protection (e.g., antifouling coatings), (6) cosmetic and hygiene products, and (7) prophylaxis and treatment in human medicine.[9]

The study by Santos and others estimated that fungal pathogens inflict yield losses of up to 30%, thus stressing the need for ecient food production and food security. Azoles fall into the best tolerated antifungal class with good biological activity that makes them the drug choice to be used in the initial empowerment in the treatment of fungal diseases in both human and animal medicine. This popularity and extensive utilization fortunately comes at a cost in the form of fierce selective pressure for azole-resistance in the fungous pathogens of plants, animals, and humans. The increased incidence of particularly intrinsically azole-resistant fungi and the emergence of azole-resistant types out of naturally susceptible fungi had disallowed consummation with massive food supply issues and therapeutic anomalies in veterinarian as well as human medicine. Many molds that are human

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pathogens are saprophytes-contributors to the decomposition of and are identified prevalent to argue for the environment which includes agricultural soils. An interface of similar mode of drug class between medicine and agriculture from similar structures of azole drugs has allowed azole resistance to develop in pathogenic fungi affecting humans in the environment. Besides the interface with nothing else is plant poison Fusarium spp. and Aspergillus spp. All things bridging species and that cause infections are confronting organs of plants, animals and humans.

The targets of antifungal agrochemicals (sterol demethylase inhibitors, SDI) and antifungal drugs are the cytochrome p450 enzyme sterol 14α-demethylase CYP51 (synonym in molds; e.g., Aspergillus), ERG11 (synonym in yeasts; e.g., Candida spp.), or sterol 14α-demethylase (SDM; general term), a key enzyme in the fungal-specific ergosterol biosynthesis pathway. This enzyme catalyzes the three-step conversion of lanosterol and eburicol to a 14α-demethylated product. [13, 14, 15] Azoles prevent demethylation of the substrate by occupying the binding site of the substrate, Heme iron, and other functions in a ligand binding groove. The increased specificity of the association of inactivated azoles by SDM leads to a reduced formation of ergosterol in the cell wall, which leads to decreased membrane fluidity and increased lipid layer integrity. Intoxicating intermediates and sterol precursors, such as 14-methyl-3,6-diols, accumulate. One event leads to the blockage of fungal growth. Azole fungicides usually halt the growth of fungi without killing them.

This feature of the fungus allows it to adjust to being treated with this antifungal drug. Chronic exposure, repeated cycles of exposure, over-exposure, or underexposure to azole drugs favor the onset of azole resistance[16]

Different mechanisms at the genetic and transcriptional levels allow fungi to become resistant to azole antifungals. The most common of these resistance mechanisms are: (1) amino acid (AA) substitutions in the SDM, affecting the active site of the enzyme, (2) overexpression of the SDM, and (3) overexpression of efflux pumps such as ATP-binding cassette (ABC) transporters and/or major facilitator superfamily (MFS) transporters. This review will look at the main amino acid changes that happen in the ligand-binding area of SDMs. We will summarize the known impact of these residues on resistance to short- and long-tailed azoles in pathogenic fungi of humans, animals, and plants. [17,18]

In designing molecular structures, the effect of 14-alpha demethylase inhibitors is determined; these studies are expected to use computational methods to predict and optimize the binding of small molecules to the active site of 14-alpha demethylase.

The enzyme is an essential antifungal target as such for antifungal drugs, for it is very important in the intermediate biosynthesis of ergosterol, which is the essential constituent of the fungal cell membrane.

The process of molecular designing and simulation study involves several steps, starting from the identification of possible drug candidates based on their structures and properties.

Docking or embedding these candidates into the active site of the 14-alpha demethylase enzyme demonstrated that their binding affinities along with enzyme interactions may be characterized under the action of molecular dynamics simulations and other computational methods.

The process helps improve the binding of a drug candidate to the enzyme. This yields increasing the drug's efficacy and interaction specificity toward the target.

Judicious selection of such molecular entities enables the generation of a set of antifungal agents with heightened potency and selectivity and a lower side effect profile than is currently seen.

- *Background Research*

Na Shi, Qingchuan Zheng, and Hongxing Zhang Molecular Dynamics Investigations of Binding Mechanism for Triazoles Inhibitors to CYP511,National centre biotechnology information. 2020 Sep 25.

We conducted 200 ns MD simulation of five systems, determining for CYP51 the RMSD values of protein backbone atoms, binding cavity residues, and heavy atoms of inhibitors, to probe structural stability.

Bibek Pati, Subhasis Banerjee Molecular Docking-Based Virtual Design of Polysubstituted Triazoles as an Inhibitor for CYP51 (Cytochrome P450 14-Alpha-Sterol Demethylase), Journal of PharmaSciTech 2012; 1(2):46-51. Docking-based drug design utilizing structural biology is undoubtedly one of the most pragmatic approaches used in the application of drug design.

An understanding of the specific binding interaction of the active site residues with specific groups of agonist or antagonist provides the ground for designing highly specific agents with higher probability of biological whne. "The most commonly utilization protocol for Structure-based CADD encompasses docking and molecular mechanics."

Rodolfo González-Chávez,a,b Roberto Martínez,c María Eugenia Torre-Bouscoulet,b Marco Gallo,b and Marco Martín González-Chávez**.** De Novo Design of Non-coordinating Indolones as Potential Inhibitors for Lanosterol 14-α-Demethylase (CYP51) Vol. 62, No. 1 2014

The new strategy, which used the same approach employed by azole drugs, relied upon the imidazole and the triazole group to act as an electron-donating pair and establish a coordinating bond to the iron atom of the heme group. "The azole drugs largely suffer from low selectivity toward different isoforms of the ubiquitous family of CYPS."

DAVOOD, ASGHAR and IMAN, MARYAM (2013**)** "Molecular docking and QSAR study on imidazole

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derivatives as 14 /alpha -demethylase inhibitors," Turkish Journal of Chemistry: Vol. 37: No. 1, Article 9.

The ADT program was used to analyze hydrogen bonding and the hydrophobic interactions between potent mimics and macromolecules that had been successfully docked. "The best result of docking was considered docked energy with a lower conformation.'

Jagdish K. Sahu1, *, Swastika Ganguly2 and Mohammad Yasir Synthesis, SAR and Molecular Docking Studies of Certain New Derivatives of 1,2,4-Triazolo. Thiadiazole as Potent Antimicrobial Agents 2018 Bentham Science Publishers

The primary target of azoles is found to be the heme protein that also cocatalyzes the cytochrome P-450-dependent 14α-demethylation of lanosterol. Thus, inhibition of 14α-demethylase reduces the levels of ergosterol and allows build-up of its precursors like 14α-methylated sterols-lanosterol, 4,14-dimethylzymosterol, and 24-methylenedihydrolanosterol-and results in the production of structurally and functionally altered plasma membranes.

Mahendrasinh M. Raj1*, Hemul V. Patel2, Lata M. Raj3 and Naynika K. Patel synthesis and biological evaluation of some new 1,3,4- thiadiazole derivatives for their antimicrobial activities international journal of pharmaceutical, chemical and biological sciences.

The novel thiadiazole derivatives were synthesized from the reaction of hydroxybenzoic acid and benzoic acid with thiosemicarbazide. 5-Phenyl-1,3,4-thiadiazol-2-amine were yielded from (A); similar products from (B) were 2-(5-amino-1,3,4-thiadiazole-2-yl) phenol. "These compounds (A and B) were subjected to various synthetic methodologies to produce derivatives of the 1,3,4-thiadiazole core.

- *Need of Research:*

A decrease in the fungal infection burden: Fungal infections like candidosis, aspergillosis, and cryptococcosis are a challenge that public health professionals or physicians must look upon, particularly among those with a deficient immune system. The increase in cases of fungal infection in the general population, especially over the past few years, warrants the need for better and novel antifungal drugs.

Restricted opportunities for treatment: The present antifungal agents are succumbed to the limitations of toxicity, drug resistance, and drug-drug interactions. Therefore, the demand to develop new improved antifungal agents with better efficacy, safety, and selectivity is high.

Computational Methods: An economical approach: The use of computational methods such as molecular designing and simulation studies has been identified as a time and money-saving option in drug discovery and optimisation of already known drugs. These methods could theoretically give the researcher adequate information to predict qualities and optimize potential drug candidates long before the compounds are synthesized and tested in the lab.

The significance of the enzyme 14-alpha-demethylase in antifungal treatment cannot be exaggerated, as the enzyme bears the most important place in the pathways of ergosterol biosynthesis, a lipid of the cell membrane of all fungi.

- *Plan of Work:*

Molecular designing and simulation studies of 14α-demethylase (CYP51) inhibitors are quite beneficial at present to mark the progress on development of some new and better antifungals. Under the summary of the significance, some of its main importance in the current status of molecular designing and simulation studies of inhibitors for CYP51 include:

Novel drug discovery: The molecular designing and simulation studies gave rise to identification of new chemical scaffolds that are highly potent in CYP51; such could be the foundation for further new antifungal drug development.

Optimization of existing inhibitors: These studies also removed certain drawbacks in the existing CYP51 inhibitors and thus led to optimization of their chemical and pharmacokinetic properties to eventually result in more effective antifungal agents that are less toxic.

Target representation or modeling for drug targeting: Computational methods are being widely employed in research to study the inhibition of CYP51 and have provided the molecular insight on the mode of binding of inhibitors and the interactions that are taking place between the drug species and the enzyme and that can be a guide to develop more selective and potent inhibitors.

Predictive capability for drug effectiveness: The same simulation studies from molecular dynamics, for example, were useful to check for the potency and stability of potential drugs for drugs laid out in the industry for further development.

Investigations for developing new drug therapies: The combination of molecular design and simulation work on CYP51 inhibitors has thus generated new antifungal therapies with more effective, selective, and pharmacokinetic properties, now leading to clinical prospects for treatment of fungal infections.

II. MATERIAL AND METHODS

Molecular docking software (eg. autodock, avagadro)

Molecular dynamics software (eg. Pyrx, BIOVIA discovery studio visualizer)

Protein crystal structure of 14 alpha demethylase

Ligand database of potential inhibitors

Computational resources (eg. High performance computing cluster)

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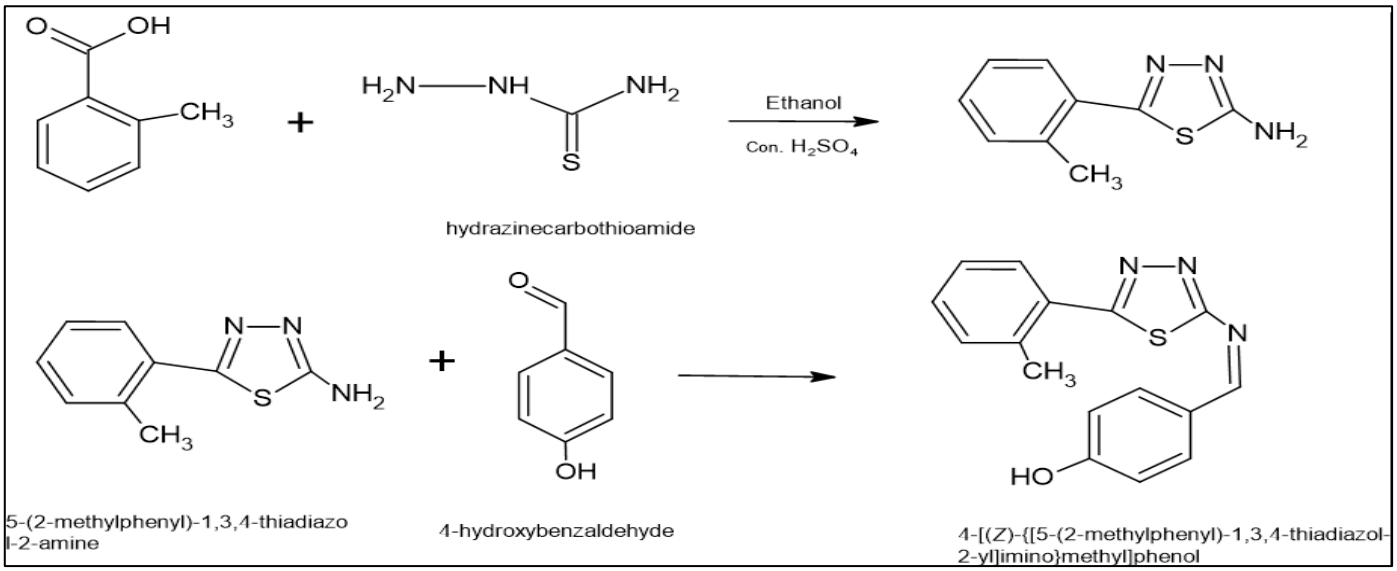
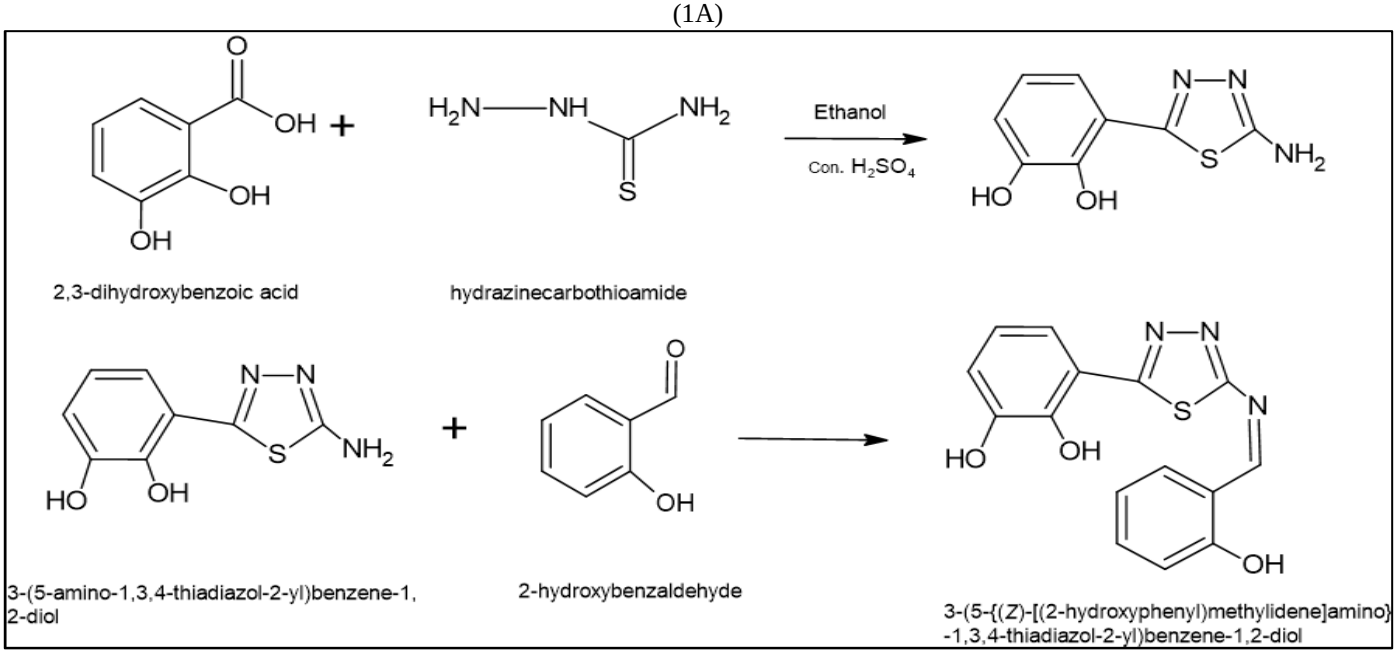
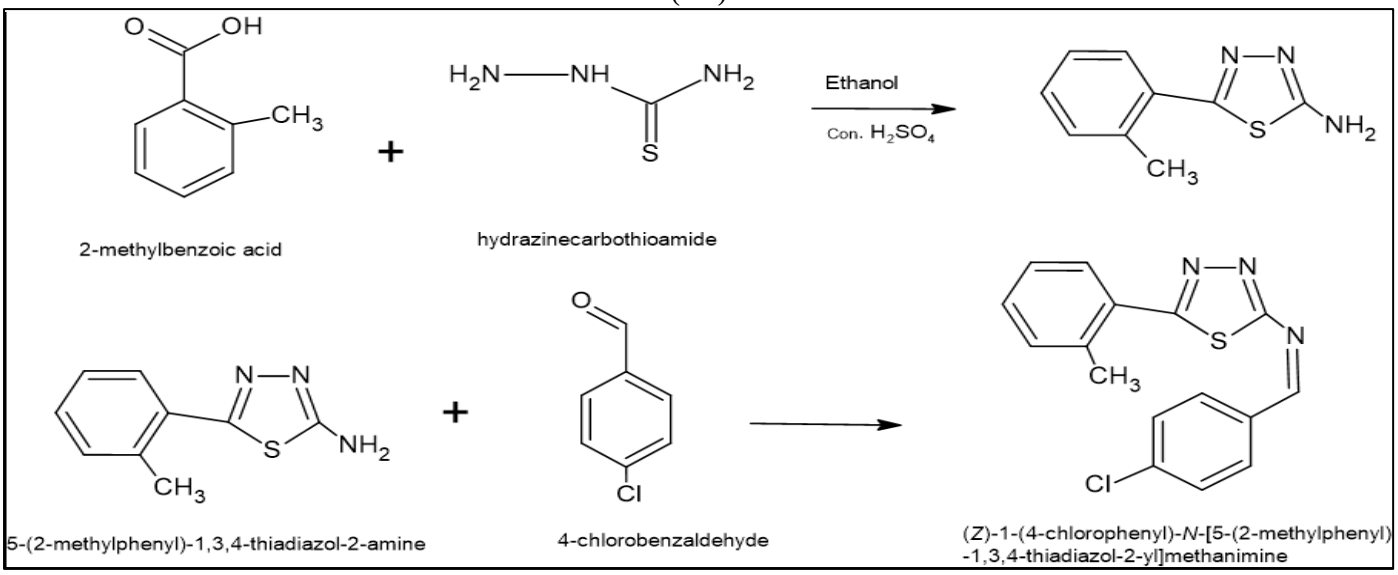


(1A)



(2 B)



(3 A)

Fig 1 Synthesis of Novel 1,2,3 Thiadiazole Derivatives for Their Antifungal Activities

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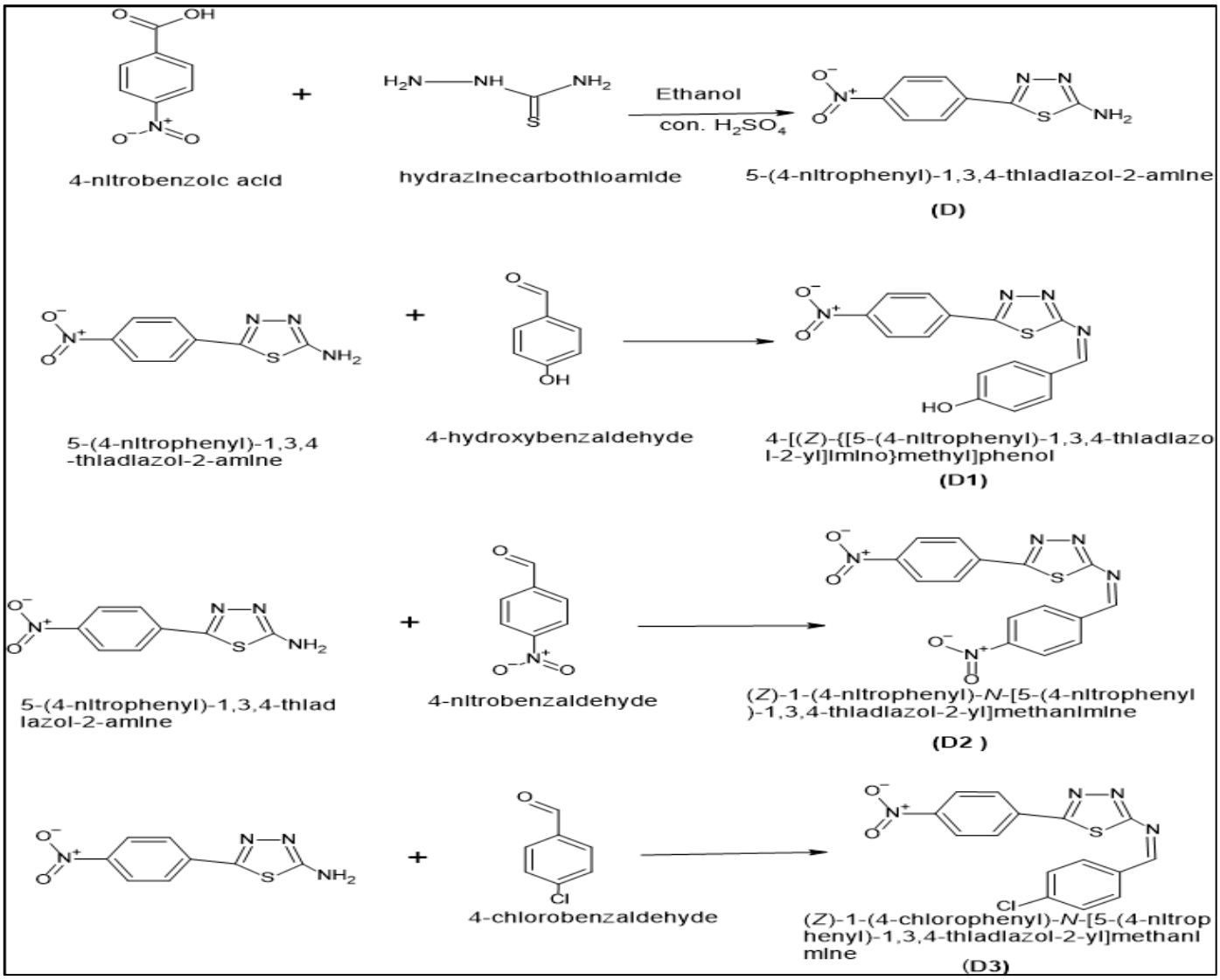

Fig 2 Synthesis of 5-(Substituted)-2- Amino-Thiadiazole for Their Antifungal Activity

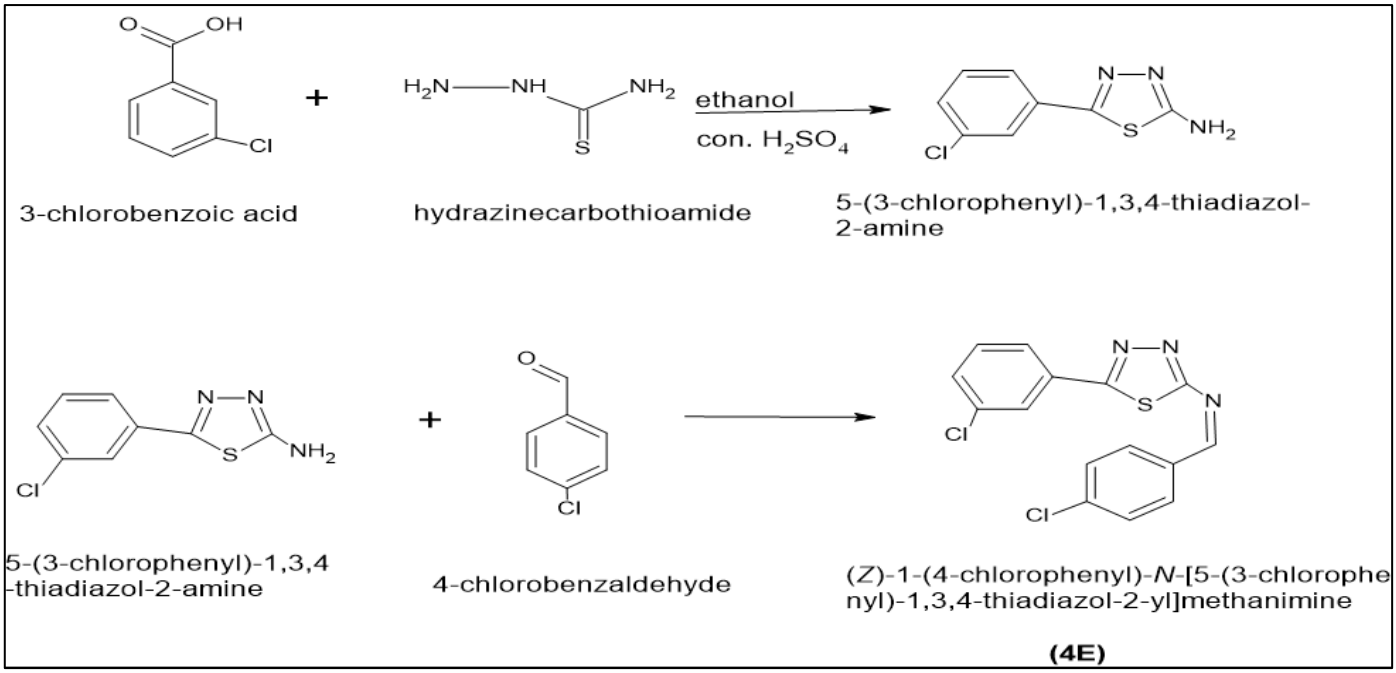

Fig 3 Synthesis of 5-(Substituted)-2-Amino-Thiadiazole for Antifungal Activity

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➢ *Computational Method*

- *Ligand Preparation*

The 3D model of compound 1A 2B 3C D1 D2 D3 4E where prepare using chem sketch tool of the ADR chemsketch software which are converted into 3D form in Avagadro.

- *Protein Preparation*

The 3D structure of 14-alpha demethylase (Cyp51) was retrieved from the protein data bank in excellent resolution. The Autodock tools were employed for receptor preparation for molecular docking purposes. [22]

Hydrogen atoms were assigned charges and bond orders, and were then added to the protein macro molecules. All remaining waters were deleted.

Hydrogen bonds were then assigned and neutralized at pH, while an energy minimization was also carried out.

- *Molecular Docking*

Use of a binary complex model was envisaged to try and test the docking simulation software itself. 'The necessary receptor grid will, therefore, need to be determined if the target ligand is to be accommodated into the active site.' Calculation of physiochemical and ADME properties [20,]

Swiss ADME model was calculated for molecular weight, pharmacokinetics, Lipophilicity, druglikeness, medicinal chemistry, pharmacokinetics.

III. RESULT AND DISCUSSION

Table 1 Docking Result of Selected Ligand Molecules

Ligand_ID	uff_E1	uff_E2	Affinity	RMSD_ub	RMSD_lb
4ck8_ (1)	518.53	536.62	-8.0	0.0	0.0
4ck8_ (1)	518.53	536.62	-8.0	22.022	21.101
4ck8_(1)	518.53	536.62	-7.7	32.292	30.487
4ck8_(1)	518.53	536.62	-7.4	22.195	21.294
4ck8_(1)	518.53	536.62	-7.4	25.449	23.857
4ck8_(1)	518.53	536.62	-7.1	60.268	58.844
4ck8_(1)	518.53	536.62	-7.0	23.656	22.405
4ck8_(1)	518.53	536.62	-7.0	39.572	37.219
4ck8_(1)	518.53	536.62	-6.9	24.35	23.267
4ck8_(1)	496.18	548.35	-8.4	0.0	0.0
4ck8_(1)	496.18	548.35	-8.4	55.158	53.506
4ck8_(1)	496.18	548.35	-8.2	25.553	23.86
4ck8_(1)	496.18	548.35	-8.1	34.698	33.369
4ck8_(1)	496.18	548.35	-7.7	23.595	22.072
4ck8_(1)	496.18	548.35	-7.6	34.856	33.464
4ck8_(1)	496.18	548.35	-7.5	33.766	32.318
4ck8_(1)	496.18	548.35	-7.4	3.457	2.695
4ck8_(1)	496.18	548.35	-7.4	53.943	52.294
4ck8_(1)	515.36	622.68	-9.1	0.0	0.0
4ck8_(1)	515.36	622.68	-8.8	6.594	5.358
4ck8_(1)	515.36	622.68	-8.2	41.337	38.737
4ck8_(1)	515.36	622.68	-8.2	2.624	1.524
4ck8_(1)	515.36	622.68	-8.2	40.973	38.533
4ck8_(1)	515.36	622.68	-8.1	5.451	4.446
4ck8_(1)	515.36	622.68	-8.1	9.349	6.97
4ck8_(1)	515.36	622.68	-8.0	6.847	5.576
4ck8_(1)	515.36	622.68	-7.8	42.006	39.447
4ck8_(1)	568.07	662.98	-9.4	0.0	0.0
4ck8_(1)	568.07	662.98	-9.0	9.544	2.267
4ck8_(1)	568.07	662.98	-8.6	33.992	31.146
4ck8_(1)	568.07	662.98	-8.4	32.004	30.802
4ck8_(1)	568.07	662.98	-8.4	39.353	38.384
4ck8_(1)	568.07	662.98	-8.2	40.946	37.264
4ck8_(1)	568.07	662.98	-8.2	38.834	38.182
4ck8_(1)	568.07	662.98	-8.2	2.953	2.267
4ck8_(1)	568.07	662.98	-8.1	33.912	32.124
4ck8_(1)	610.19	606.95	-8.6	0.0	0.0

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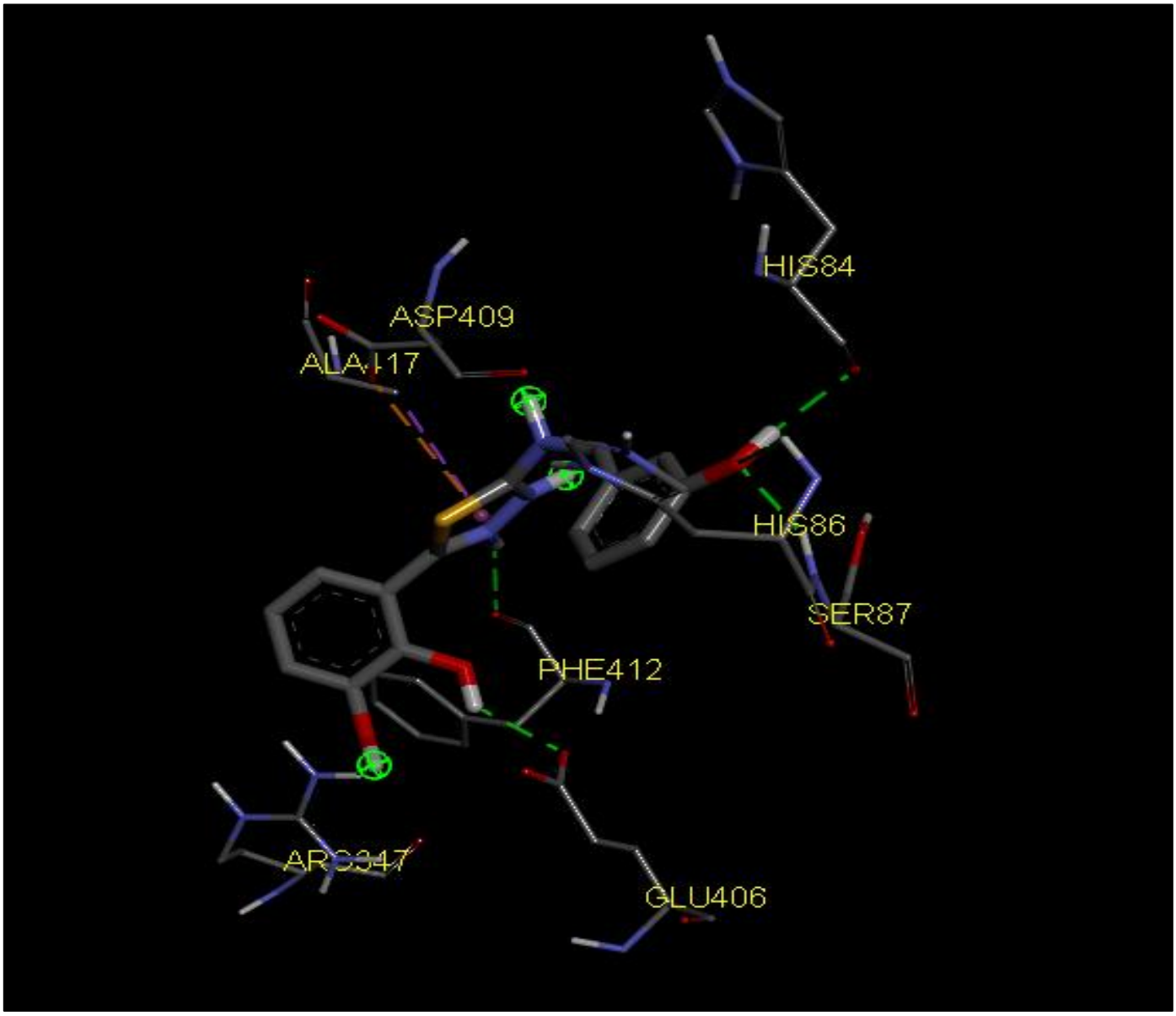
4ck8_(1)	610.19	606.95	-8.6	8.625	2.913
4ck8_(1)	610.19	606.95	-8.4	36.594	35.366
4ck8_(1)	610.19	606.95	-8.4	6.715	4.92
4ck8_(1)	610.19	606.95	-8.2	36.591	34.695
4ck8_(1)	610.19	606.95	-8.1	5.53	4.734
4ck8_(1)	610.19	606.95	-8.0	34.341	31.376
4ck8_(1)	610.19	606.95	-7.9	8.676	2.669
4ck8_(1)	610.19	606.95	-7.9	8.837	4.912
4ck8_(1)	603.43	663.64	-8.0	0.0	0.0
4ck8_(1)	603.43	663.64	-7.7	33.226	30.988
4ck8_(1)	603.43	663.64	-7.6	43.897	40.956
4ck8_(1)	603.43	663.64	-7.6	41.091	38.008
4ck8_(1)	603.43	663.64	-7.5	7.437	2.804
4ck8_(1)	603.43	663.64	-7.5	47.141	45.04
4ck8_(1)	603.43	663.64	-7.5	41.044	38.305
4ck8_(1)	603.43	663.64	-7.5	56.721	55.26
4ck8_(1)	603.43	663.64	-7.5	35.475	34.202
4ck8_(1)	534.09	958.64	-8.9	0.0	0.0
4ck8_(1)	534.09	958.64	-8.7	2.792	2.475
4ck8_(1)	534.09	958.64	-8.7	8.883	2.527



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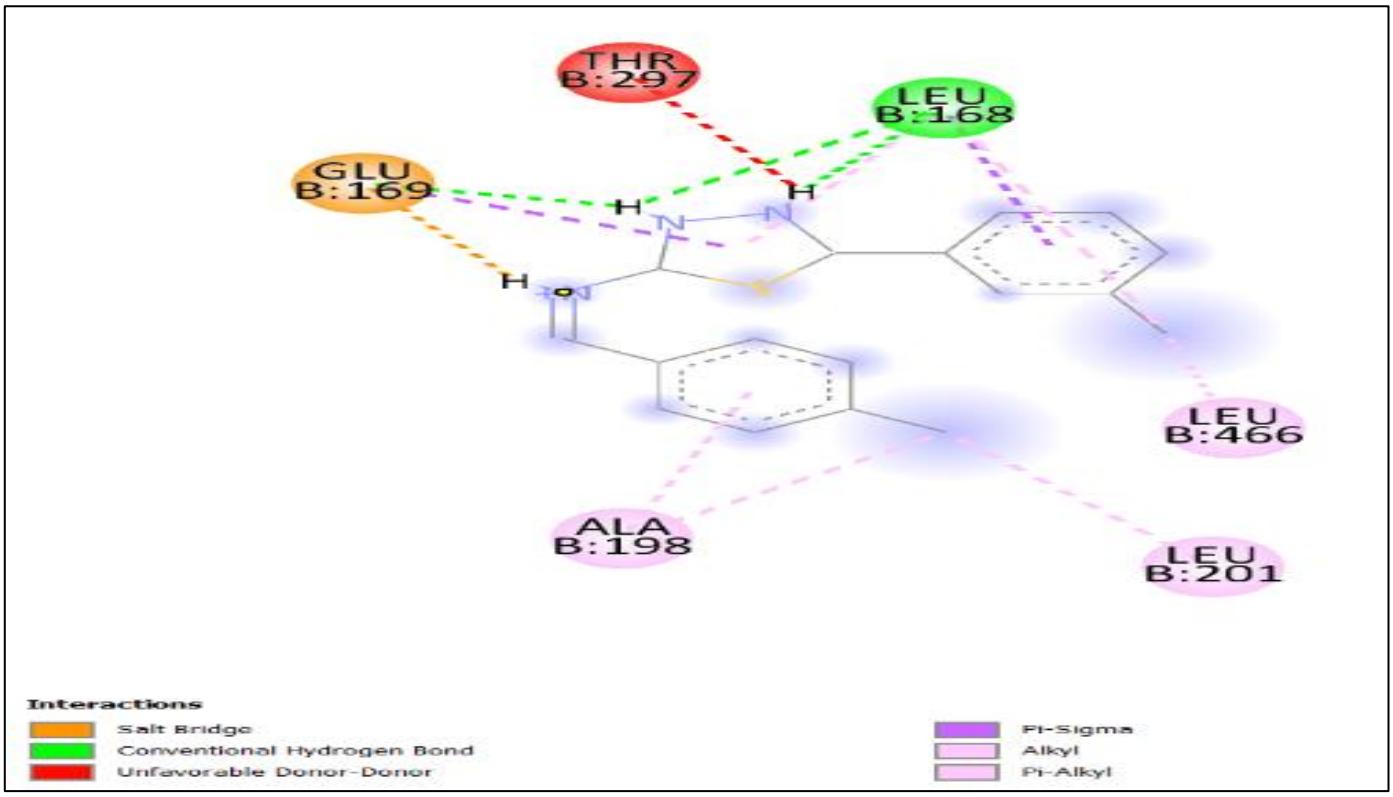
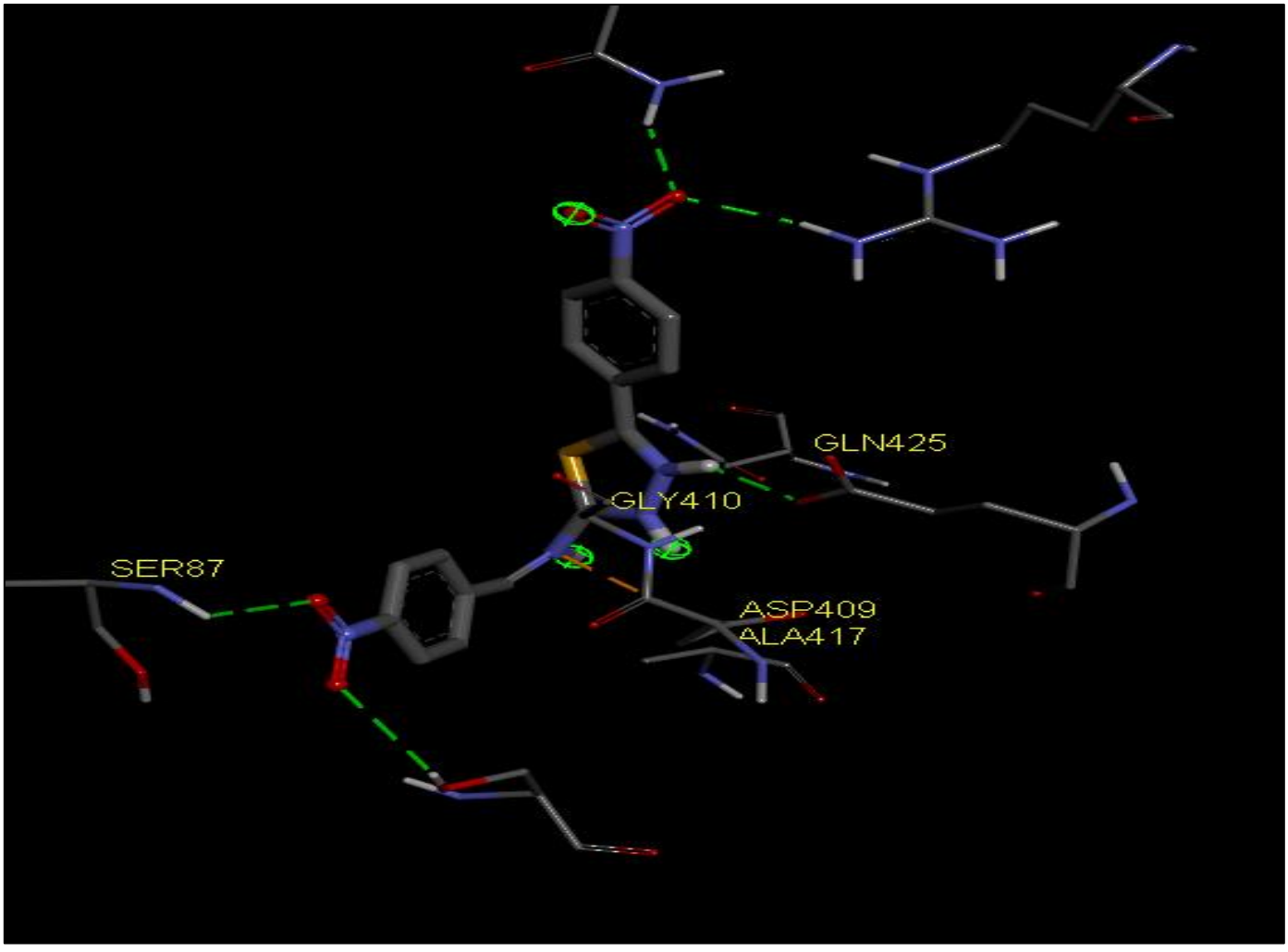


Fig 4 14 α-Demethylase Molecular Docking and Binding Mode of Compound 1A



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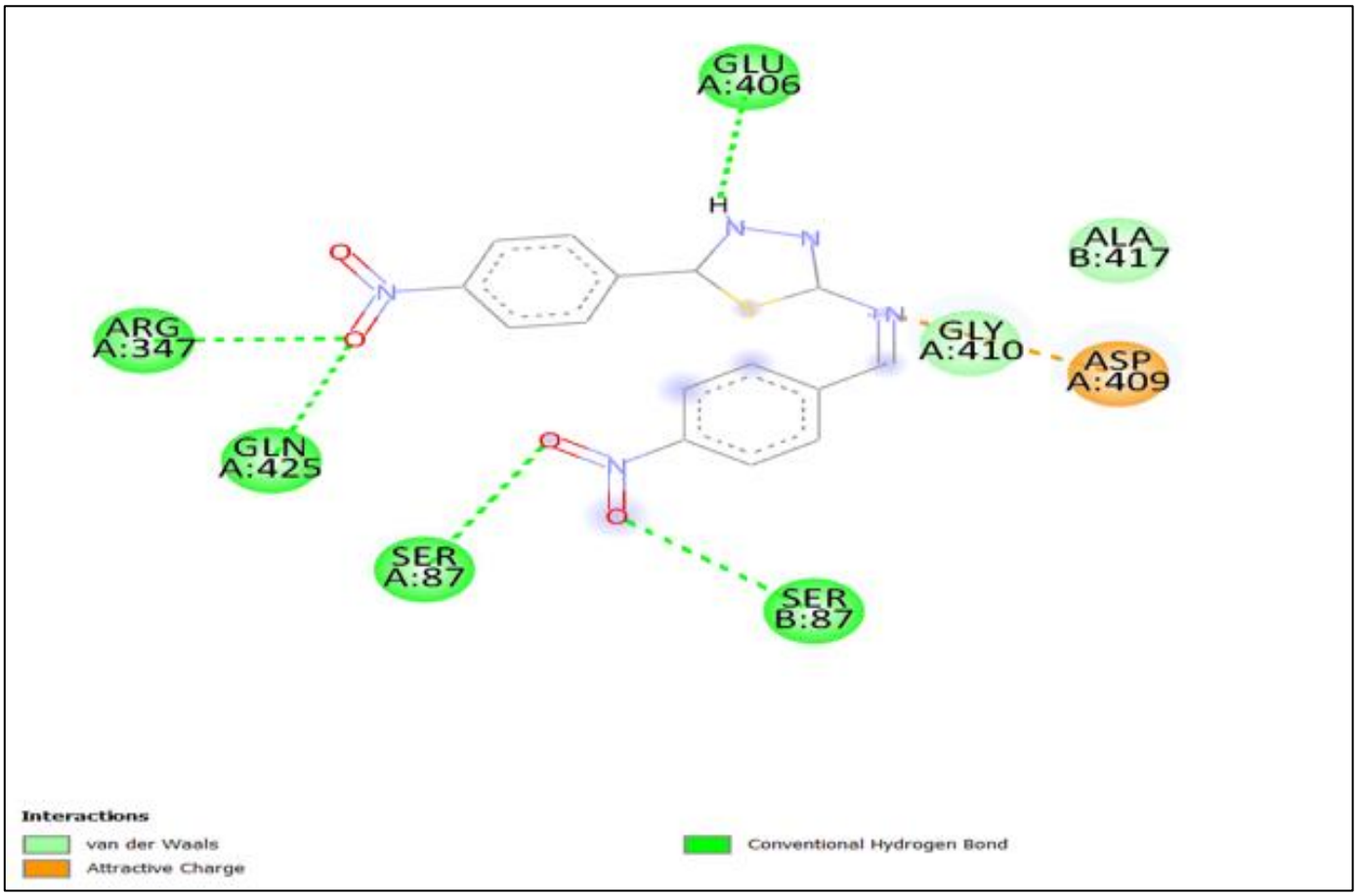
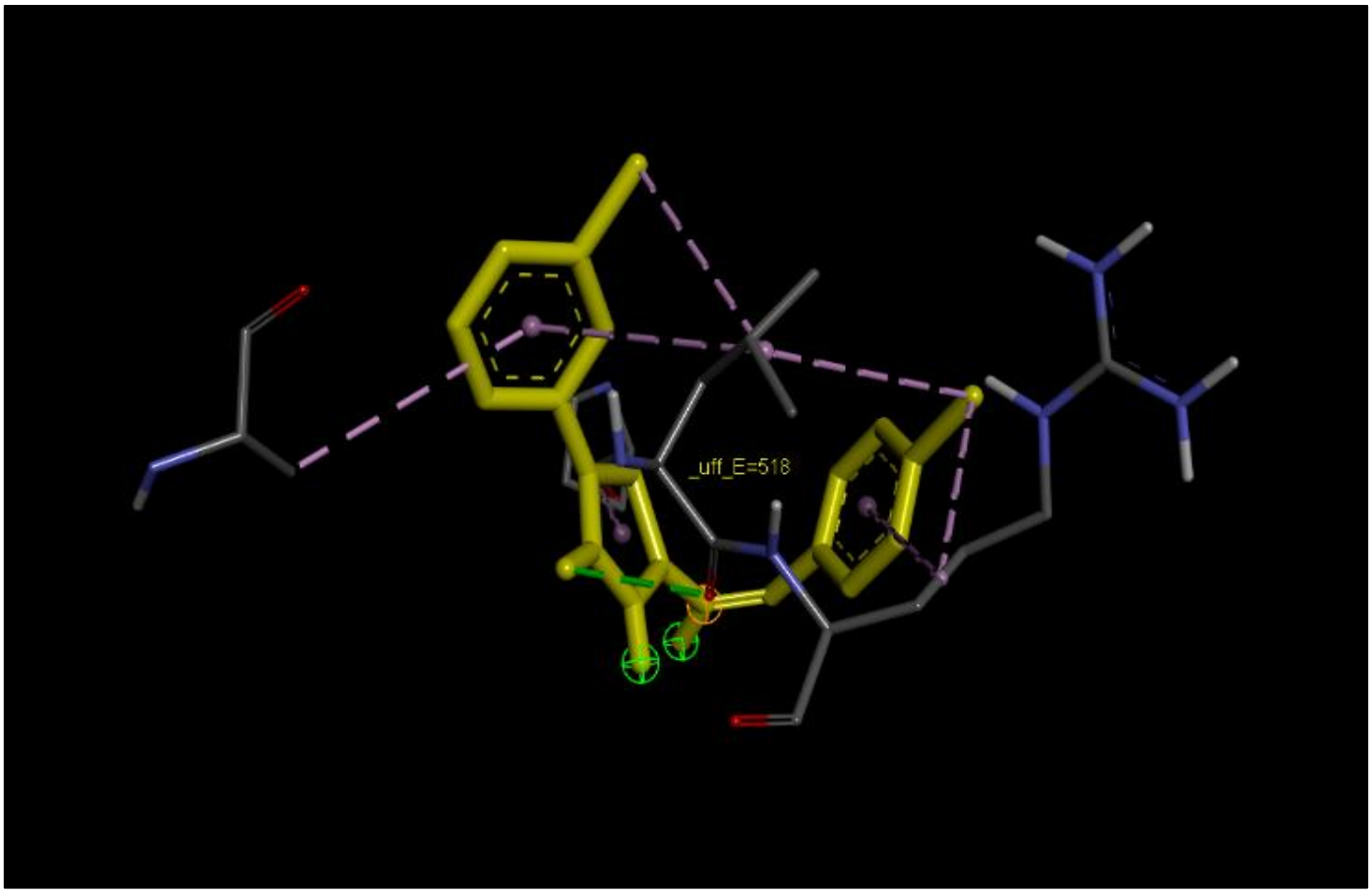


Fig 5 14 α -Demethylase Molecular Docking and Binding Mode of Compound 2B in 2D form



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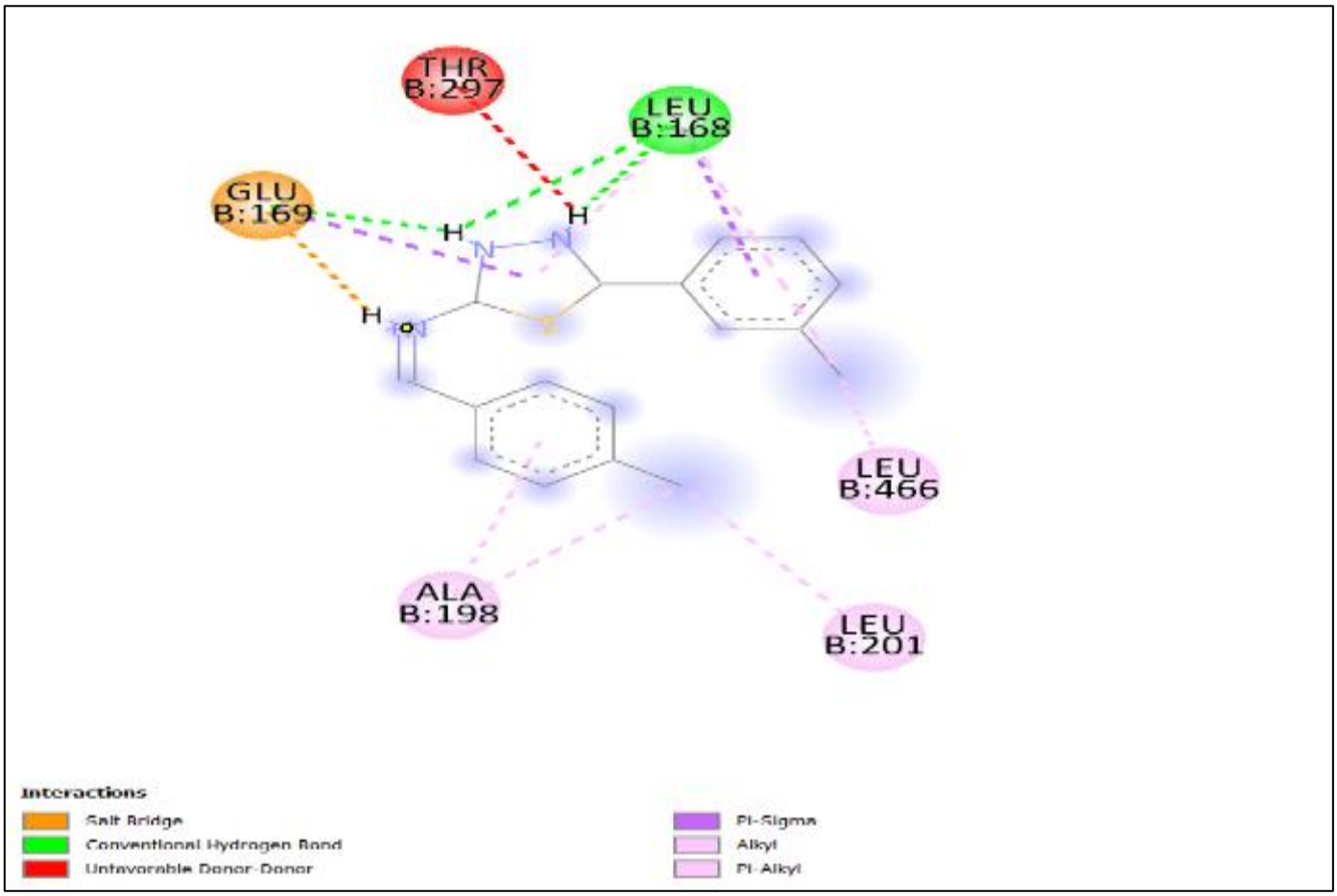
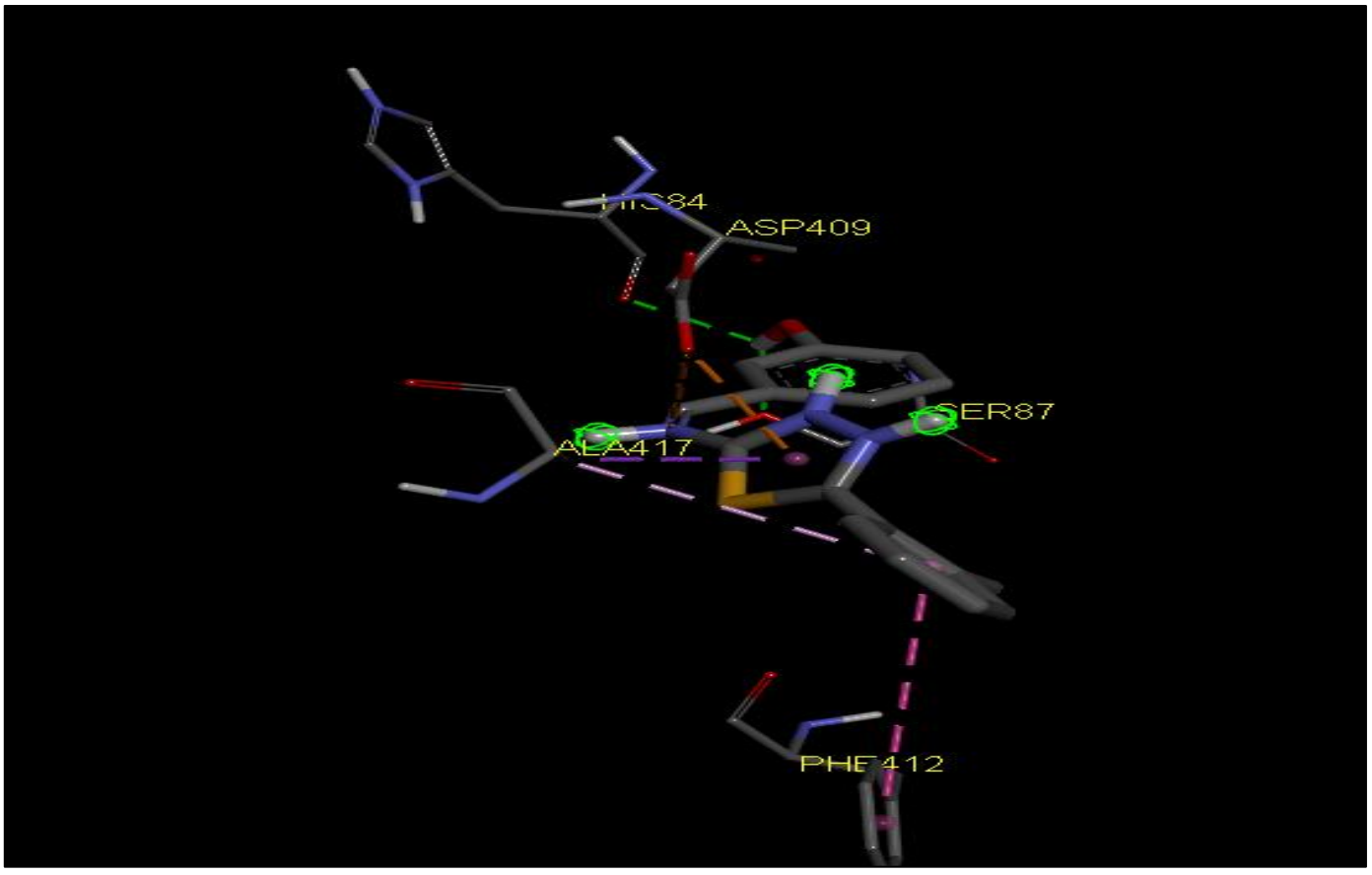


Fig 6 14 α -Demethylase Molecular Docking and Binding Mode of Compound 3C in 2D form



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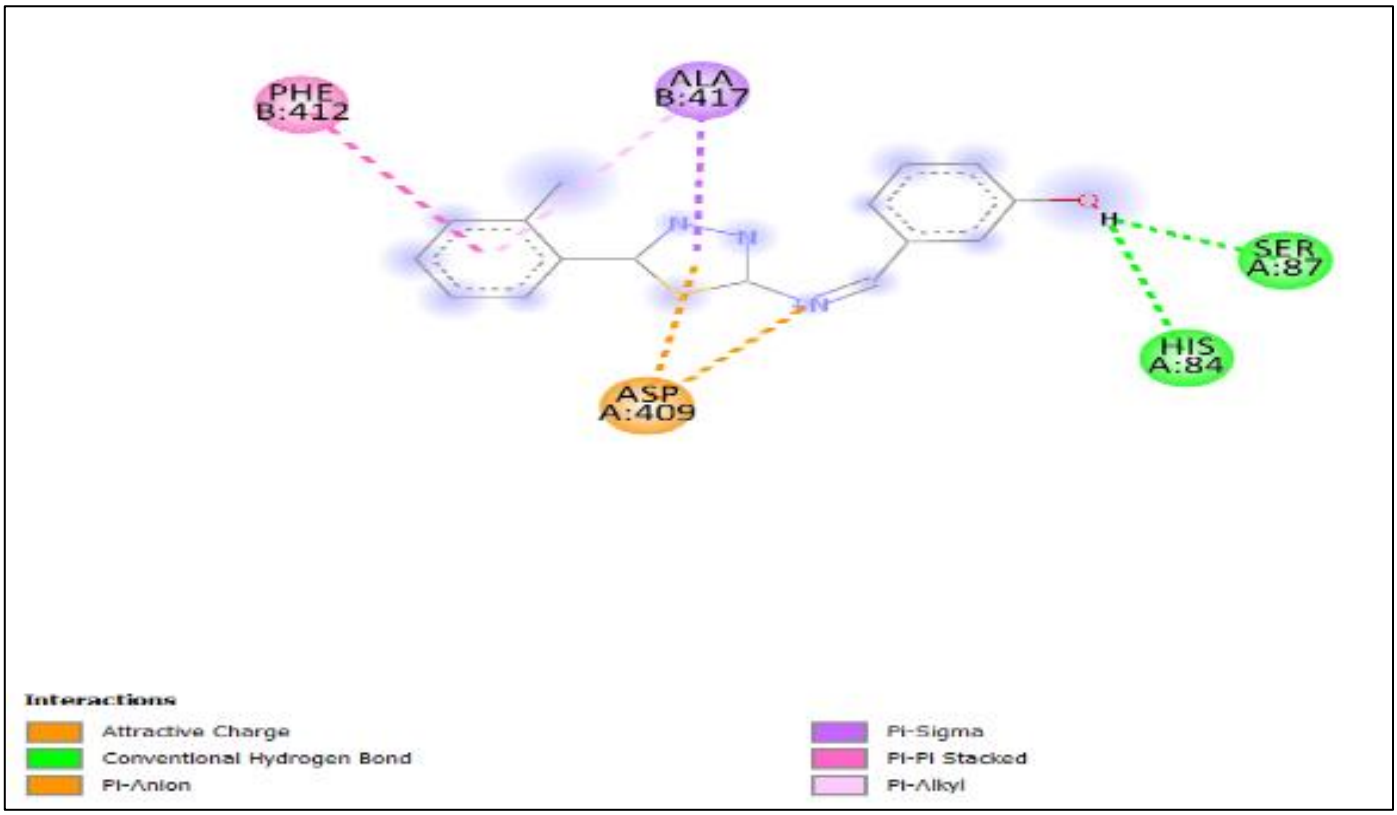
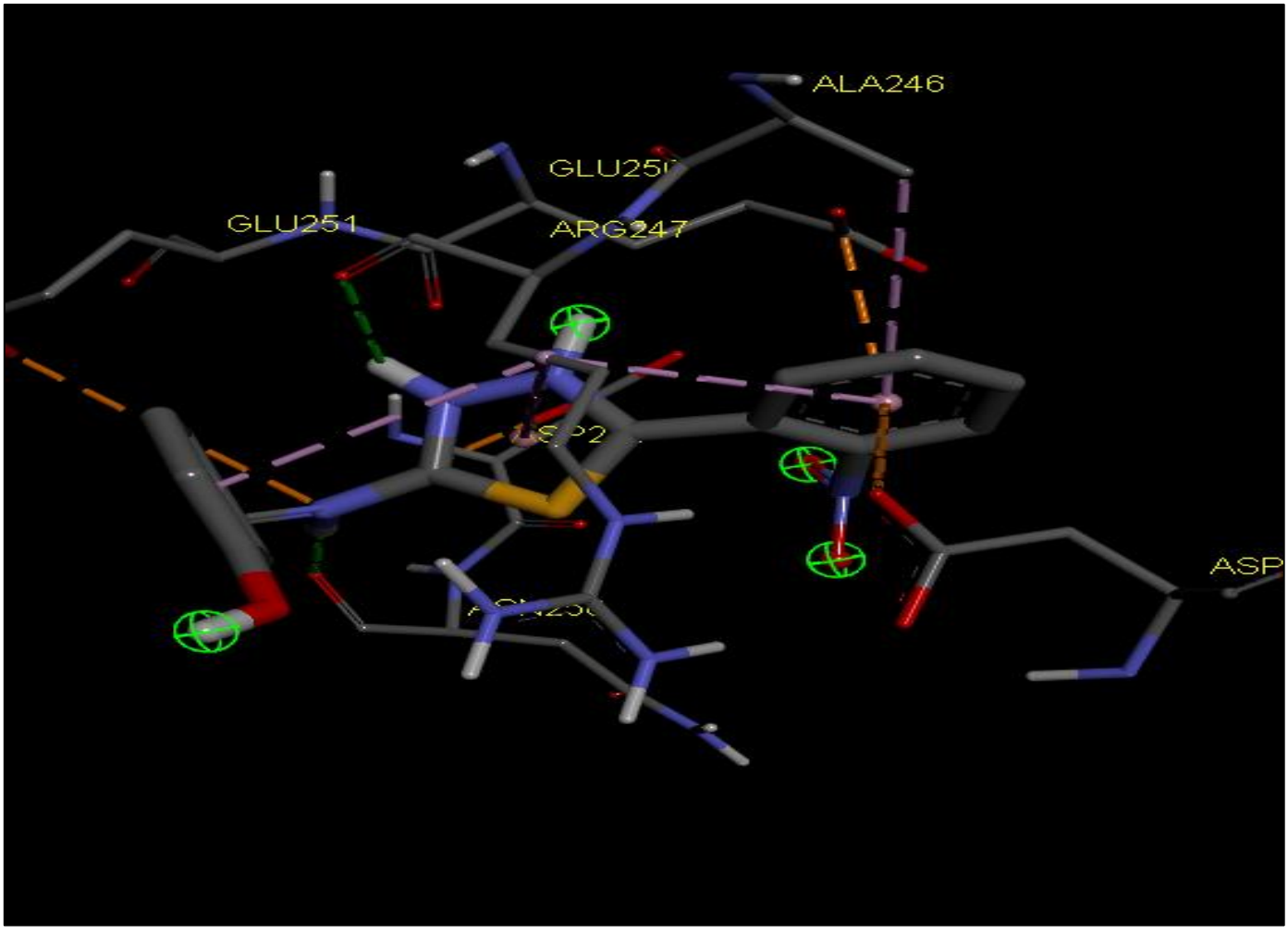


Fig 7 14 α -Demethylase Molecular Docking and Binding Mode of Compound D1 in 2D form



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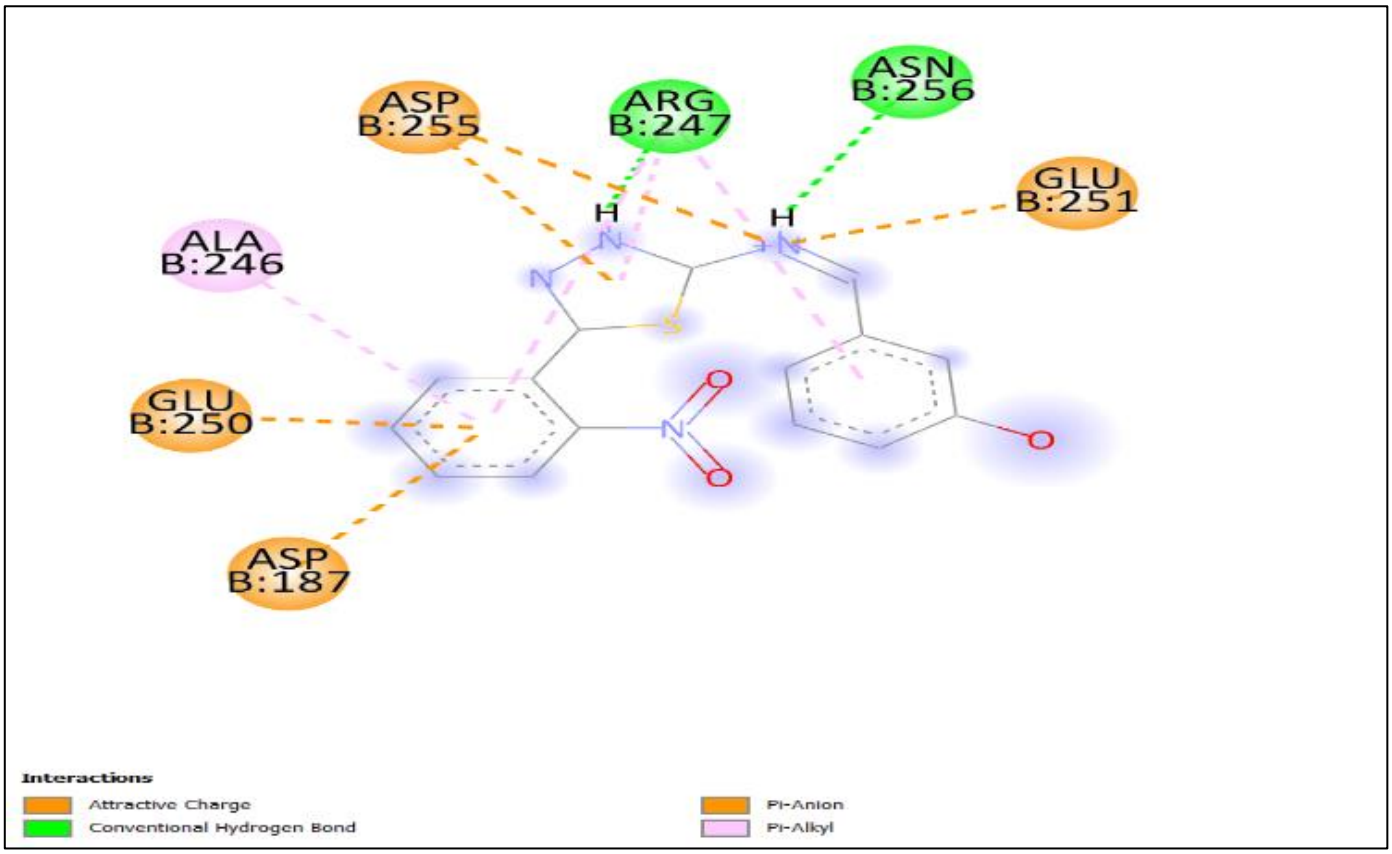
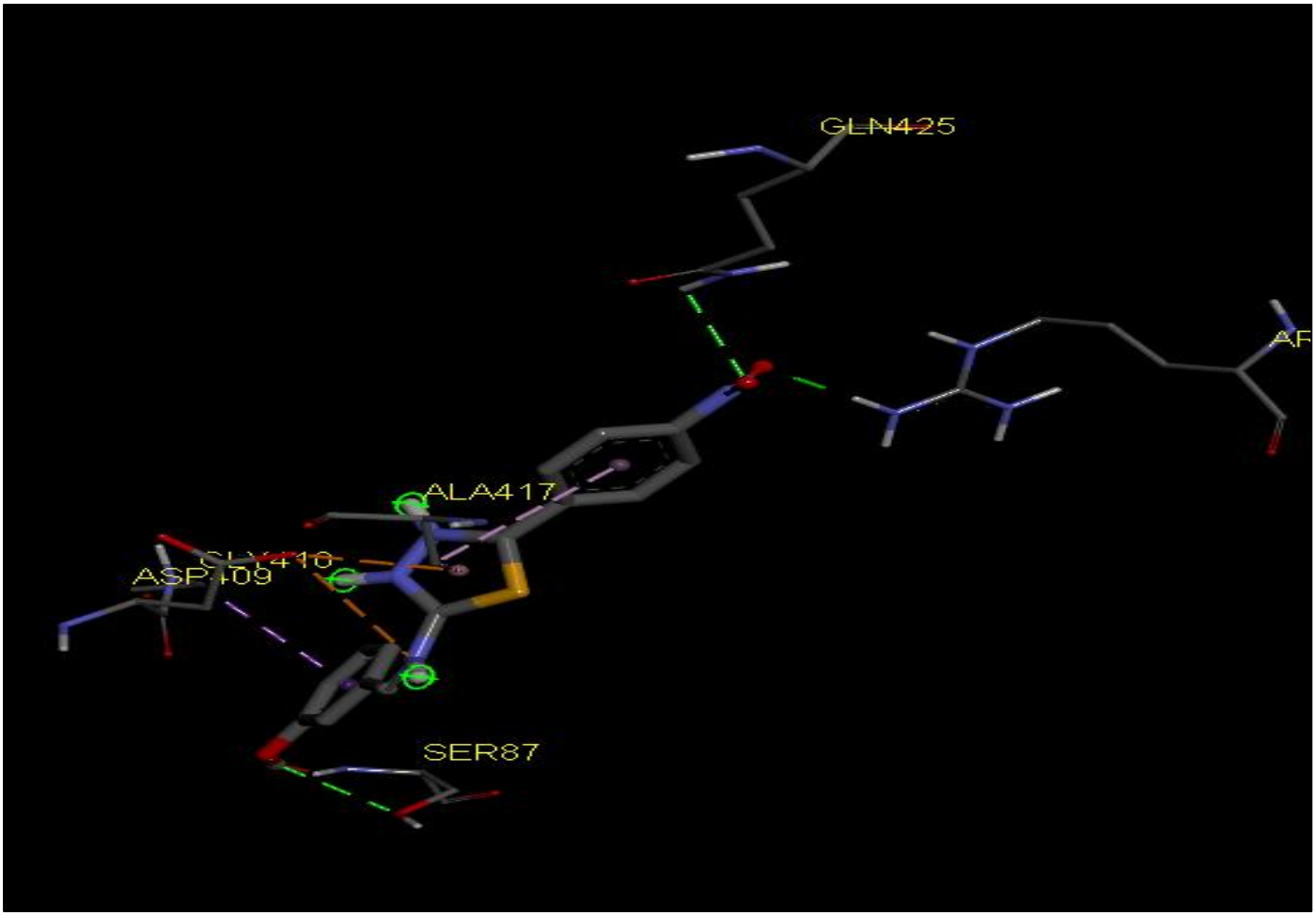


Fig 8 14 α -Demethylase Molecular Docking and Binding Mode of Compound D2 in 2D form



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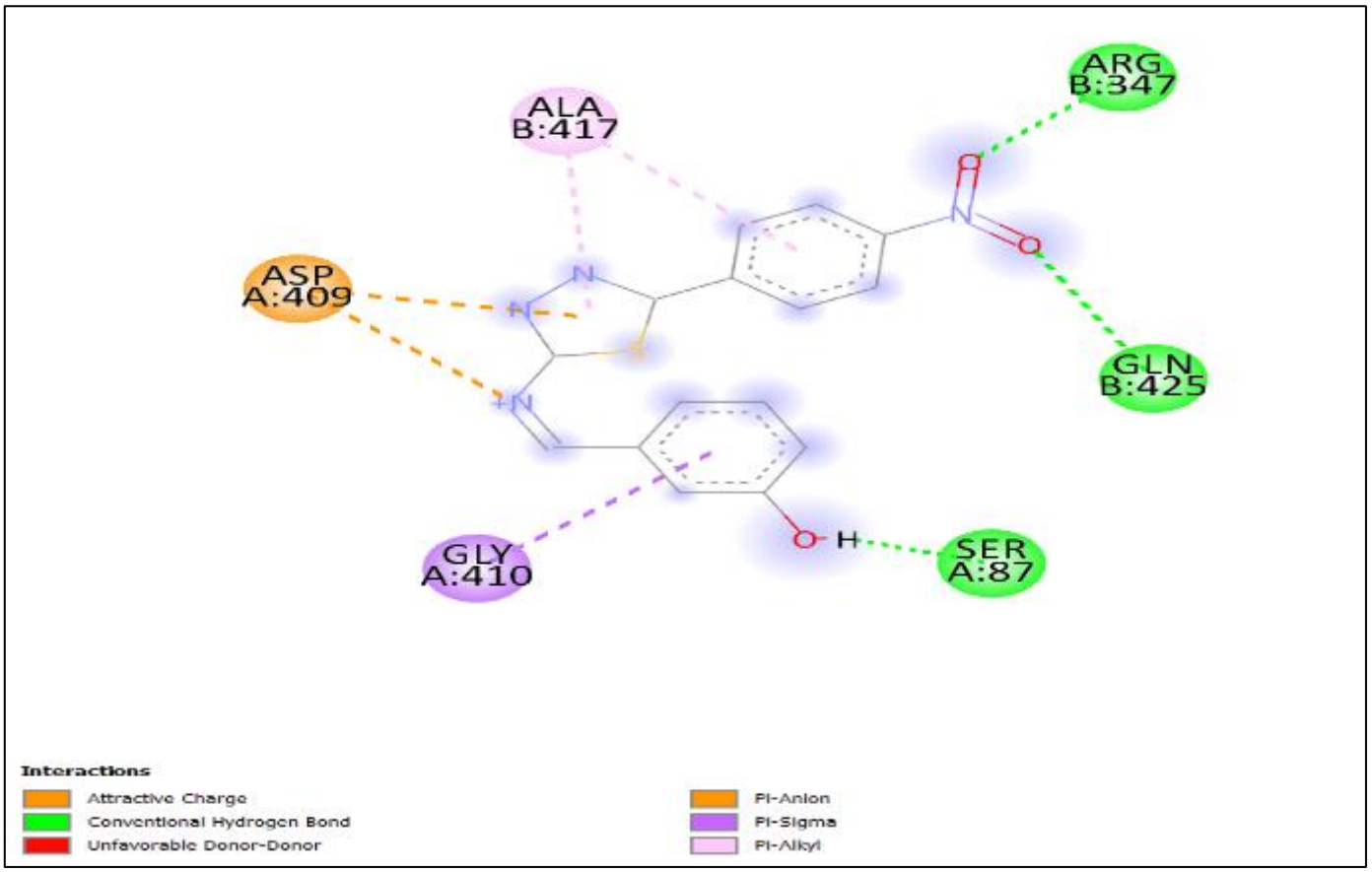
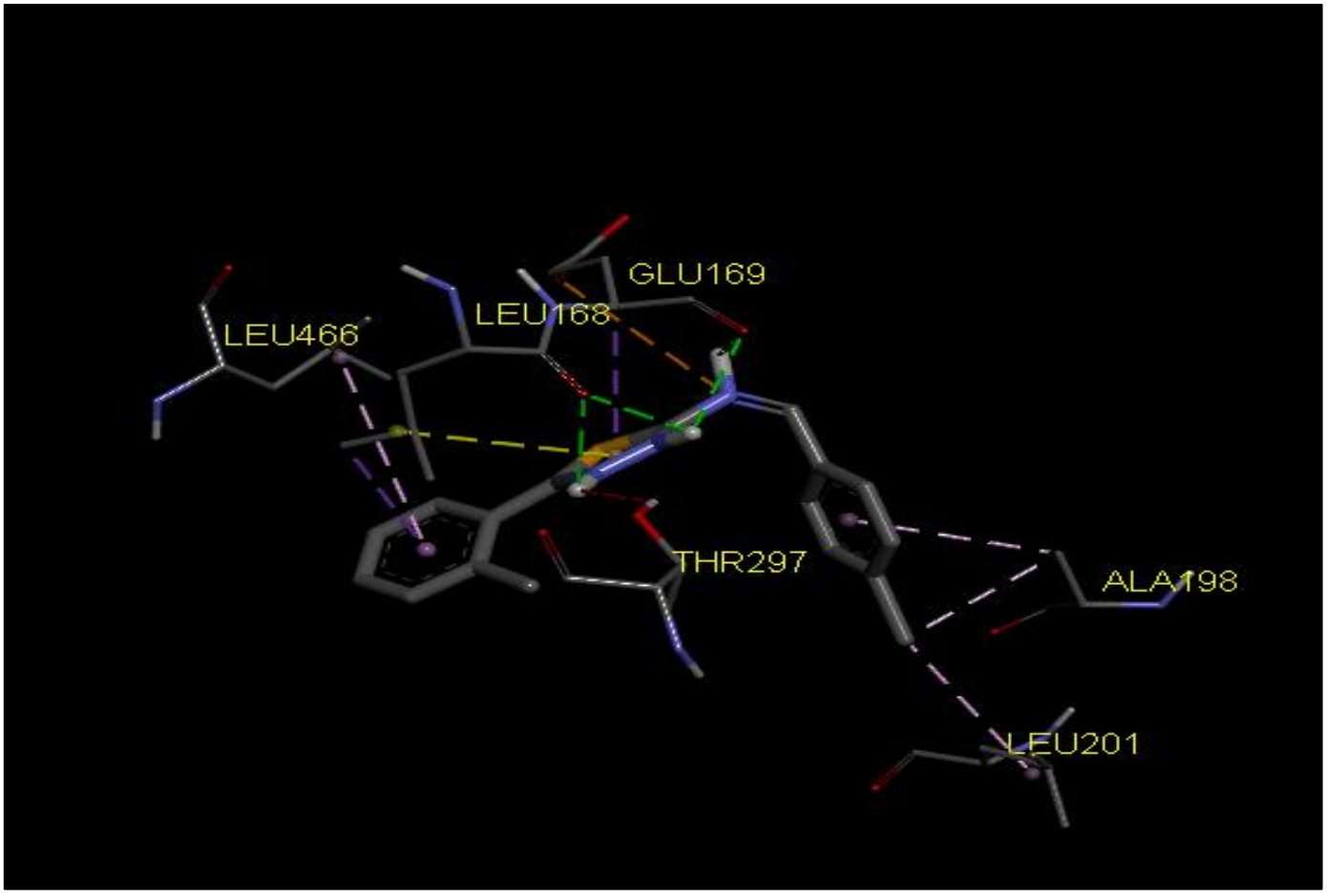


Fig 9 14 α -Demethylase Molecular Docking and Binding Mode of Compound D3 in 2D form



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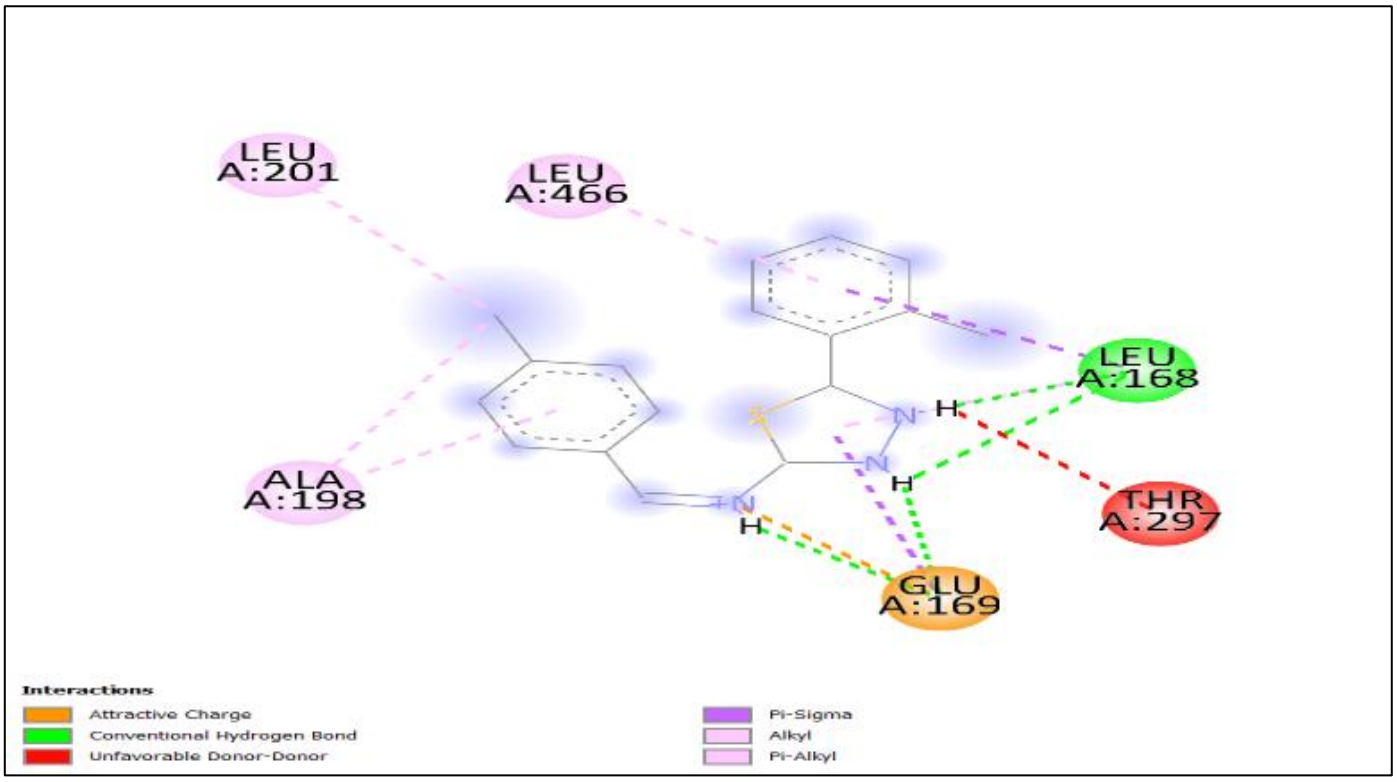

Fig 10 14 α -Demethylase Molecular Docking and Binding Mode of Compound 4E in 2D for

IV. SUMMARY AND CONCLUSION

This work has seen the molecular design and simulation studies of 14-alpha demethylase inhibitors as a fast, inexpensive tool for the identification of numerous new classes of molecules. This, again, may provide new insights for the creation of antimycotic agents distinctly different from those presently available, possibly leading to a newer generation of antifungal drugs that are better targeted against fungal infection.

In this study, 1,3,4-thiadiazole derivatives were designed through the simple reaction and then subjected to an evaluation of their predictive antifungal activity using computational tools. In those docking studies, we found that all the derivatives interacted with 14α-demethylase coordination, in the target enzyme. Various π−π and π-cation interactions are involved in drug–target interfacial relationships. 'Molecular modeling studies and experimental results well explain powerful and selective inhibitory actions of these compounds.' Computational studies may provide some significative insights needed to understand the mode of action and assist in designing or modifications of a series of compounds derived from fungal 14α-demethylase inhibitors.

Derivatives of 1,3,4-thiadiazole, in the study, were docked to evaluate possible antifungal activities against various fungal strains. shared described synthesis of the molecules.

FUTURE OUTCOME AND STUDIES

Molecules selected will be synthesized following the approved synthetic pathway in the laboratory. Synthesized molecules will be further purified and characterized using appropriate techniques, IR and/or NMR, or LC-MS or HR-MS. These synthesized molecules will be subjected to in-vitro-antifungal evaluations.

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