INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES
[ISSN: 0975-4725; CODEN(USA): IJPS00]
Journal Homepage: https://www.ijpsjournal.com

Research Article

1,2,4-Triazole Derivatives Targeting Fungal 14-Alpha Demethylase Enzyme: An Insilico Approach

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ARTICLE INFO

Published: 13 Aug 2025
Keywords:
1,2,4-triazole derivatives, antifungal agents, molecular docking, ADMET, toxicity prediction, drug-likeness
DOI:
10.5281/zenodo.16856764

ABSTRACT

Fungal infections remain a major health concern due to increasing resistance against existing antifungal agents. In this review, novel 1,2,4-triazole derivatives were synthesized and evaluated for their antifungal potential using in silico molecular docking and ADMET predictions. Docking studies revealed strong binding affinities of several compounds toward fungal target proteins, comparable or superior to standard azole drugs. Pharmacokinetic profiling showed good oral bioavailability, compliance with Lipinski's rule, acceptable solubility, and high gastrointestinal absorption. Toxicity predictions indicated low risks of mutagenicity, carcinogenicity and hepatotoxicity with minimal inhibition of major CYP450 enzymes, suggesting a low potential for drug-drug interactions. Overall, the findings highlight the therapeutic promise of these synthesized triazole derivatives and warrant further invitro and in vivo evaluation of antifungal drug development.

INTRODUCTION

Fungal infection is growing health concern, with an estimated 1.5million deaths annually caused by invasive fungal infection. These infections are caused by a variety of fungal species, including Candida, Aspergillus, and Cryptococcus. Antifungal therapies are used to treat these infections, but rise of antifungal resistance has become a major challenge in the field. Fungal infections are caused by fungi that invade the tissues of humans and other animals. There are many different types of fungi that can cause infections, including yeasts and Molds. Some common fungal infections including athlete's foot, jock itch, ringworm, and thrush. Fungal infections can affect different parts of the body, including the skin, nails and lungs. Other types of fungal infections can affect the lungs, like aspergillosis and histoplasmosis. Some types of fungal infections can be serious and even life-threatening, especially in people with weakened immune

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Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

systems, such as those with HIV/AIDS or cancer or those taking immunosuppressive medications. Some of the common fungal infections: **Athlete's foot:** It is also known as tinea pedis, is a common fungal infection that affects the skin on the feet. Athlete's foot can cause symptoms such as itching, burning and cracking of the skin between the toes and the soles of the feet. **Ringworm:** Ringworm is a common fungal infection that affects the skin, hair and nails. Ringworm is highly contagious and can spread through direct contact with an infected person, animal or object. The azole antifungal includes two broad classes, imidazole and triazoles. The systemic triazoles are more slowly metabolized and have less effect on human sterol synthesis than do the imidazole's. Because of these advantages, new congeners under the development are mostly triazoles, not imidazole's(1).

MECHANSIM OF ACTION

The major effects of triazoles on fungi is inhibition of 14-alpha-demethylase, a microsomal cytochrome 450-dependent enzyme system. Triazoles thus impair the biosynthesis of ergosterol for the cytoplasmic membrane and lead to the accumulation of 14-alpha-methylsterols.These methyl sterols may disrupt the close packing acyl chains of phospholipids, impairing the functions of certain membrane bound enzyme systems such as ATPase and enzymes of the electron transport system and thus inhibiting growth of the fungi(2,3,4).

INTRODUCTION ABOUT TRIAZOLE

In the last few decades, the chemistry of 1,2,4 triazoles and their fused heterocyclic derivatives. Have received considerable attention owing to their synthetic and effective biological importance.1,2,4 triazole moiety has been incorporated into a wide variety of therapeutically interesting drug candidates including antifungal, antibacterial, analgesics and anti-inflammatory, Antineoplastic, anticonvulsant, antiviral etc. The triazole is the five-membered three nitrogen containing heterocyclic aromatic ring. Triazole play a key role in various biological mechanism related to infections, cancer, Convulsions, inflammation and neurodegeneration. The 1,2,4-triazole are five membered and sp^3 hybridization molecule. The synthesis and development of new 1,2,4-triazoles with low toxicity and inhibit the fungal Growth.

CHEMISTRY AND STRUCTURE ACTIVITY RELATIONSHIP

- 1,2,4 triazole is one of a pair of isomeric chemical compounds.
- Molecular formula: $\mathbf{C_2H_3N_3}$
- It has five-membered ring of two carbon atoms and three nitrogen atoms.
- 1,2,4 triazole is a basic aromatic heterocycle(5).

DRUG DISCOVERY- Drug discovery is a multidisciplinary scientific process aimed at identifying new therapeutic compounds that can prevent, cure or manage diseases. The modern drug discovery process integrates principles from chemistry, biology, pharmacology, and computational sciences to design and develop novel molecules with optimal efficacy and safety profiles.(6)

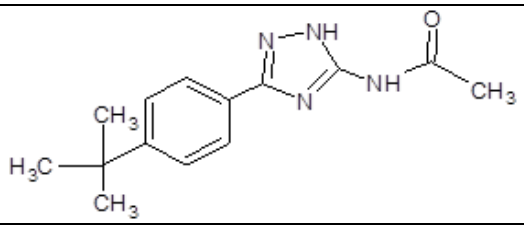
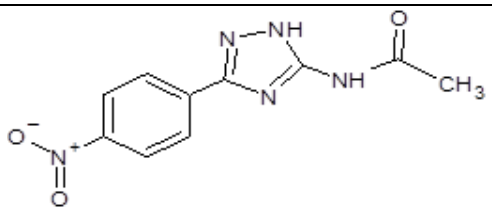
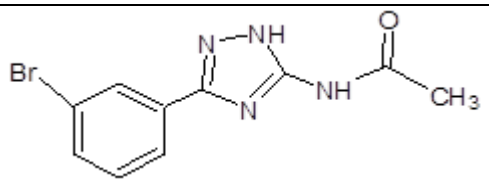
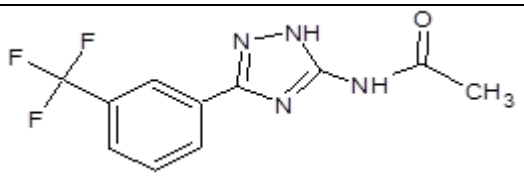
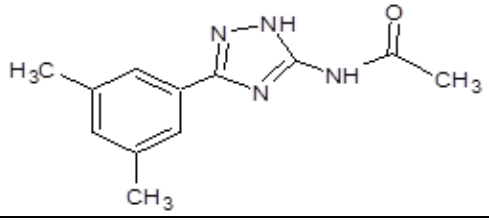
MOLECULAR DOCKING -Molecular docking is a powerful computational technique used to predict the interaction between a ligand and a target molecule, typically a protein or nucleic acid. The fundamental principle of molecular docking is to stimulate the binding of a ligand to the active site of a target molecules to evaluate the strength of this interaction using scoring functions(7).

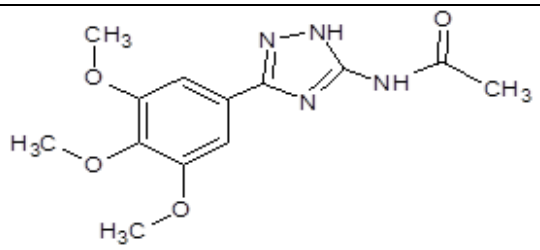
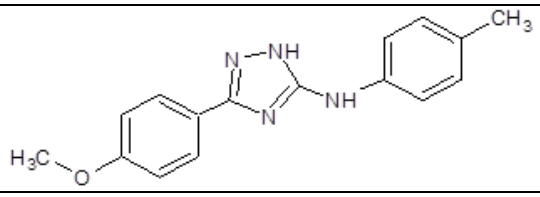
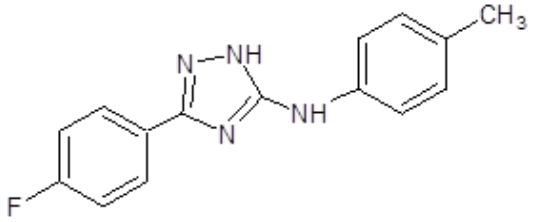
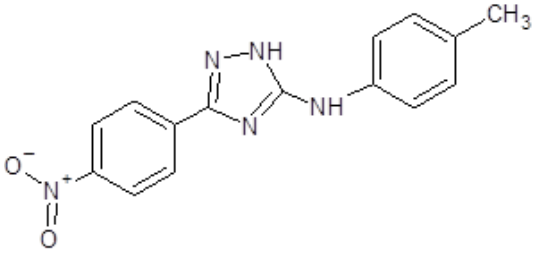
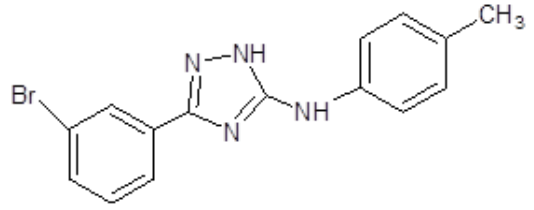
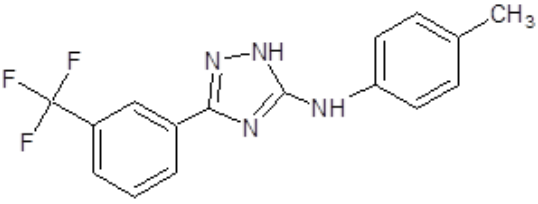
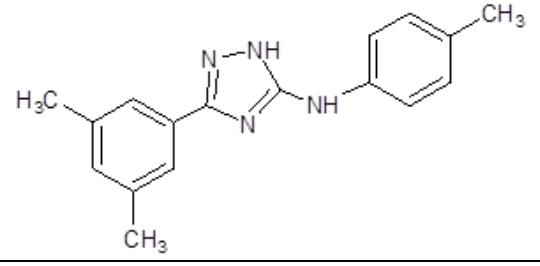
SWISS ADME- Swiss ADME is a free, web-based computational tool, for predicting the physicochemical properties, pharmacokinetics properties. It is widely used in drug discovery and development to assess the **Absorption, Distribution, ,Metabolism, and Excretion.** One of its standout features is the **BOILED -EGG model**, which provides a visual prediction of gastrointestinal absorption and blood brain permeability.

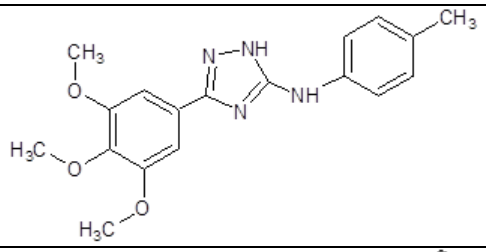
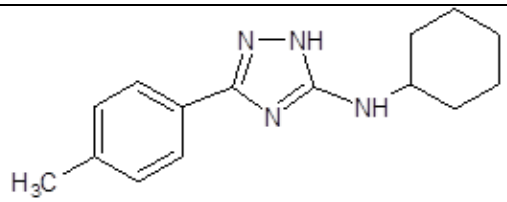
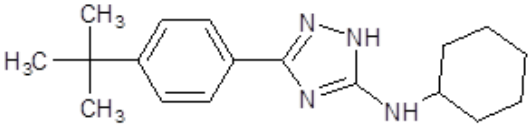
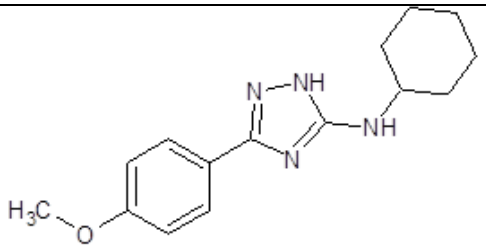
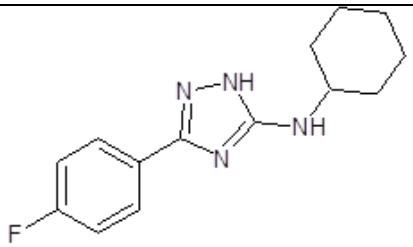
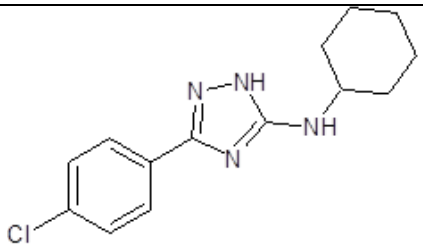
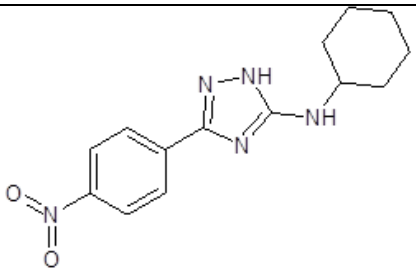
PROTOX III-Protox is online tool used for toxicity prediction in drug discovery and chemical research. It helps researcher predict the potential toxicity of small molecules based on their chemical structure. It is designed to predict LD_{50} values (lethal dose for 50% of population),Toxicity classes(I to VI),Possible toxicological pathways, Organ toxicity. The objective of this study was to compare the docking efficiency of PyRx , a free molecular docking software with that of an Auto dock 4.2.6, which is used and to find a potent 14-alpha demethylase using the best docking software found(8).

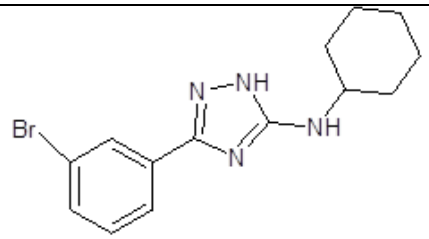
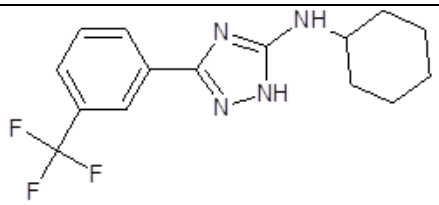
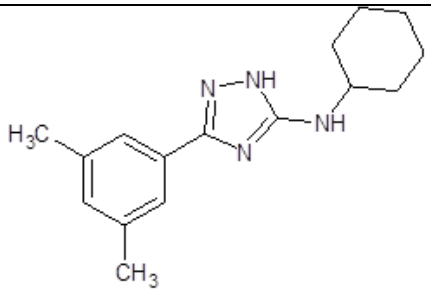
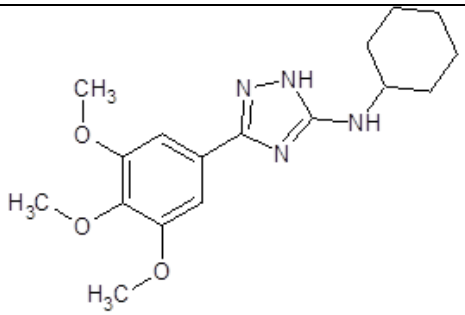
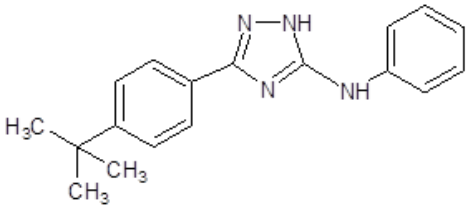
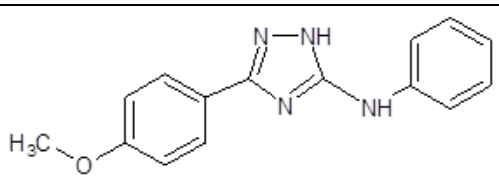
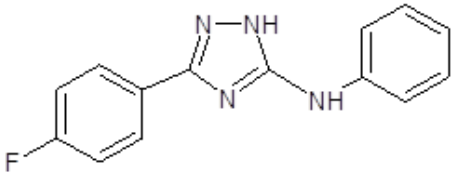
MATERIALS AND METHODS

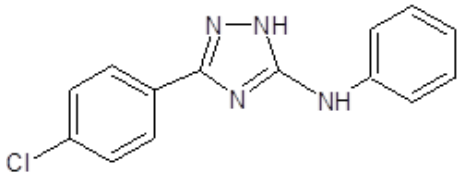
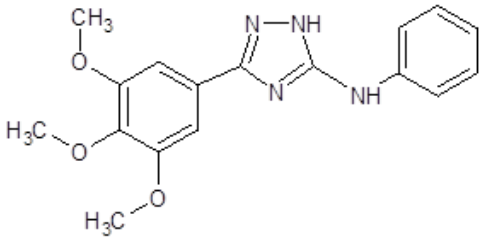
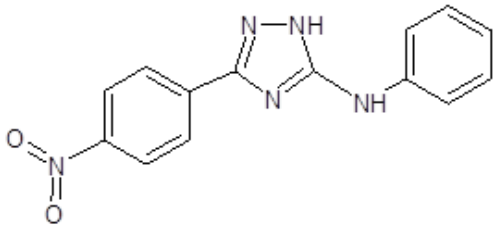
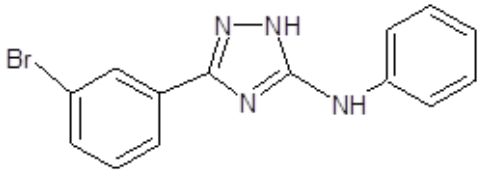
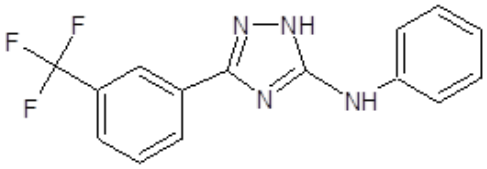
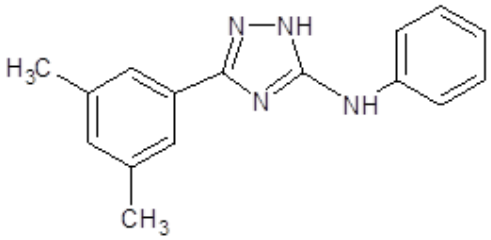
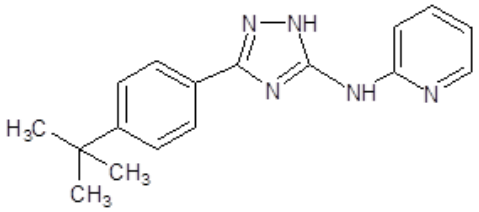
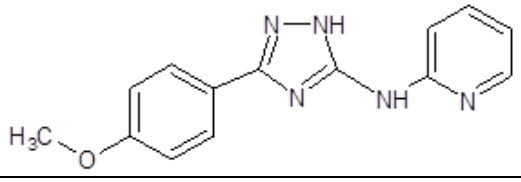
Table 1: Derivative structure and its IUPAC name

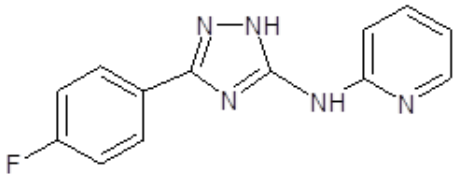
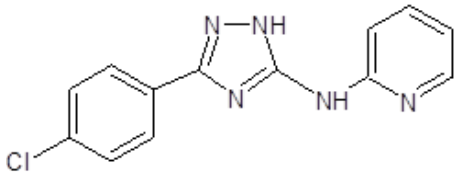
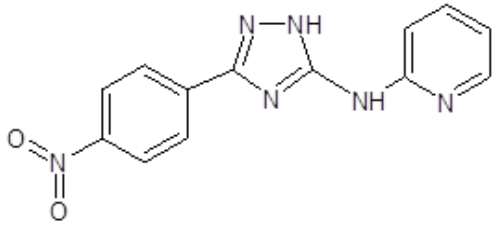
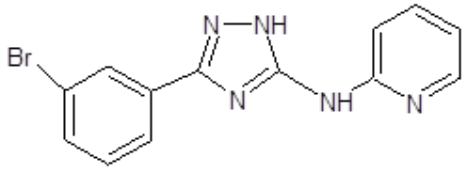
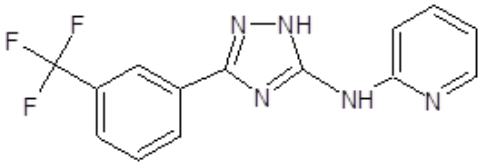
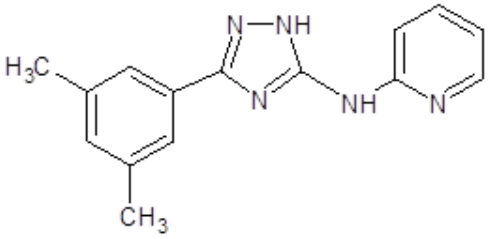
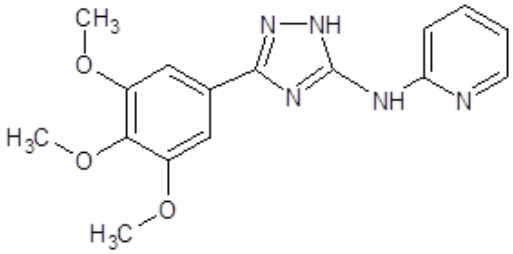
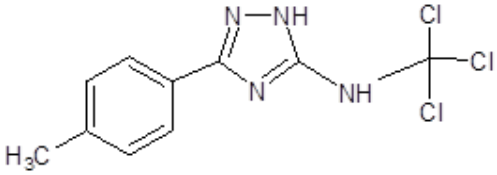
SR.NO	STRUCTURE	IUPAC NAME
1.		*N*-[3-(4-*tert*-butylphenyl)-1*H*-1,2,4-triazol-5-yl]acetamide
2.		*N*-[3-(4-nitrophenyl)-1*H*-1,2,4-triazol-5-yl]acetamide
3.		*N*-[3-(3-bromophenyl)-1*H*-1,2,4-triazol-5-yl]acetamide
4.		*N*-{3-[3-(trifluoromethyl)phenyl]-1*H*-1,2,4-triazol-5-yl}acetamide
5.		*N*-[3-(3,5-dimethylphenyl)-1*H*-1,2,4-triazol-5-yl]acetamide

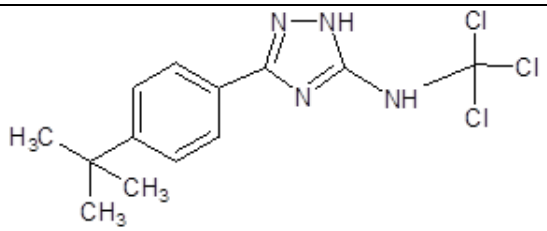
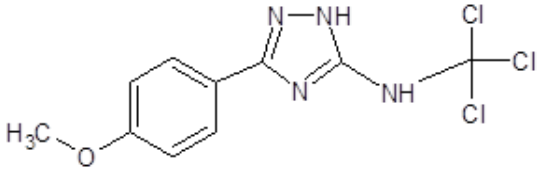
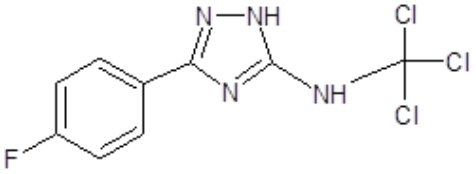
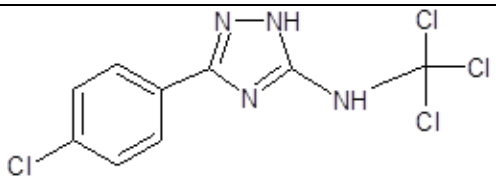
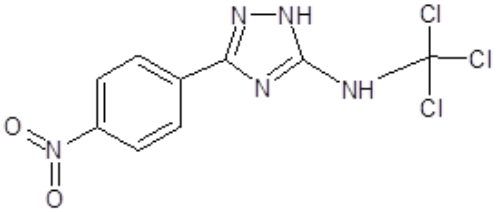
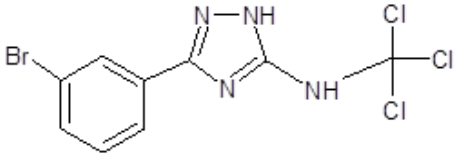
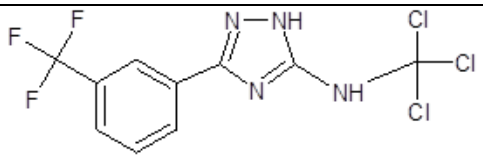
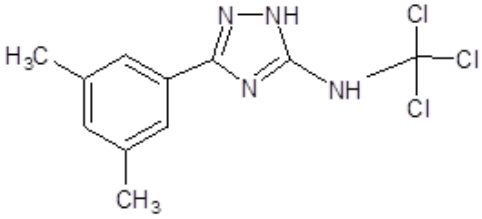
6.		*N*-[3-(3,4,5-trimethoxyphenyl)-1*H*-1,2,4-triazol-5-yl]acetamide
7.		3-(4-methoxyphenyl)-*N*-(4-methylphenyl)-1*H*-1,2,4-triazol-5-amine
8.		3-(4-fluorophenyl)-*N*-(4-methylphenyl)-1*H*-1,2,4-triazol-5-amine
9.		*N*-(4-methylphenyl)-3-(4-nitrophenyl)-1*H*-1,2,4-triazol-5-amine
10.		3-(3-bromophenyl)-*N*-(4-methylphenyl)-1*H*-1,2,4-triazol-5-amine
11.		*N*-(4-methylphenyl)-3-[3-(trifluoromethyl)phenyl]-1*H*-1,2,4-triazol-5-amine
12.		3-(3,5-dimethylphenyl)-*N*-(4-methylphenyl)-1*H*-1,2,4-triazol-5-amine

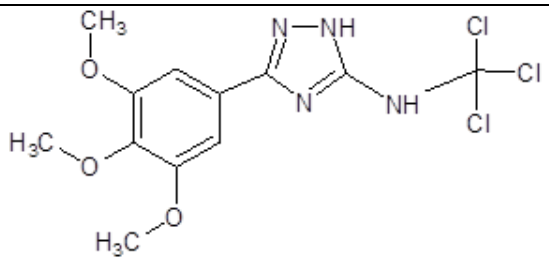
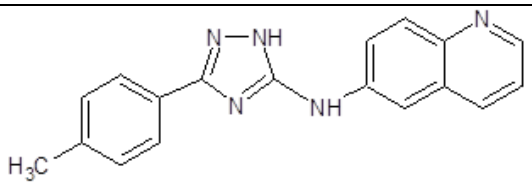
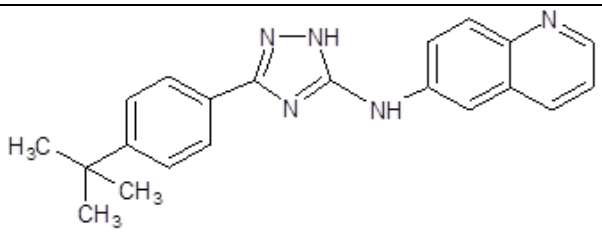
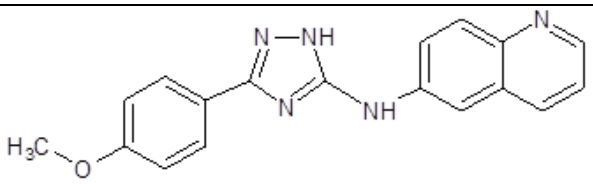
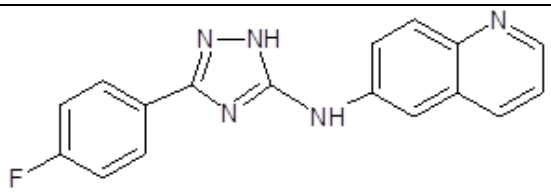
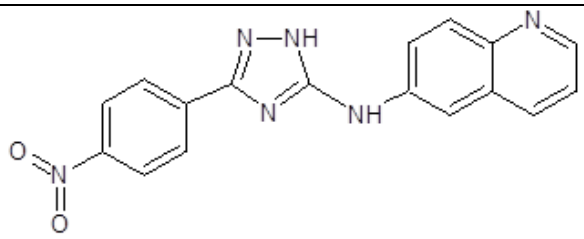
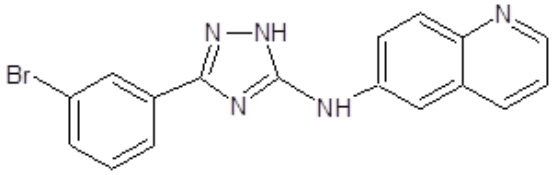
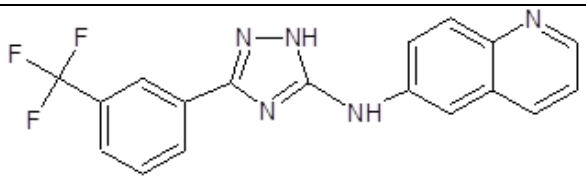
13.		*N*-(4-methylphenyl)-3-(3,4,5-trimethoxyphenyl)-1*H*-1,2,4-triazol-5-amine
14.		*N*-cyclohexyl-3-(4-methylphenyl)-1*H*-1,2,4-triazol-5-amine
15.		3-(4-*tert*-butylphenyl)-*N*-cyclohexyl-1*H*-1,2,4-triazol-5-amine
16.		*N*-cyclohexyl-3-(4-methoxyphenyl)-1*H*-1,2,4-triazol-5-amine
17.		*N*-cyclohexyl-3-(4-fluorophenyl)-1*H*-1,2,4-triazol-5-amine
18.		3-(4-chlorophenyl)-*N*-cyclohexyl-1*H*-1,2,4-triazol-5-amine
19.		*N*-cyclohexyl-3-(4-nitrophenyl)-1*H*-1,2,4-triazol-5-amine

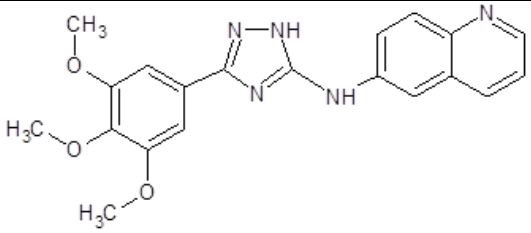
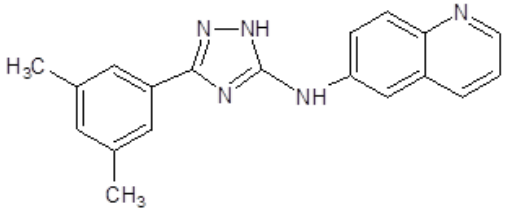
20.		3-(3-bromophenyl)-*N*-cyclohexyl-1*H*-1,2,4-triazol-5-amine
21.		*N*-cyclohexyl-3-[3-(trifluoromethyl)phenyl]-1*H*-1,2,4-triazol-5-amine
22.		*N*-cyclohexyl-3-(3,5-dimethylphenyl)-1*H*-1,2,4-triazol-5-amine
23.		*N*-cyclohexyl-3-(3,4,5-trimethoxyphenyl)-1*H*-1,2,4-triazol-5-amine
24.		3-(4-*tert*-butylphenyl)-*N*-phenyl-1*H*-1,2,4-triazol-5-amine
25.		3-(4-methoxyphenyl)-*N*-phenyl-1*H*-1,2,4-triazol-5-amine
26.		3-(4-fluorophenyl)-*N*-phenyl-1*H*-1,2,4-triazol-5-amine

27.		3-(4-chlorophenyl)-*N*-phenyl-1*H*-1,2,4-triazol-5-amine
28.		*N*-phenyl-3-(3,4,5-trimethoxyphenyl)-1*H*-1,2,4-triazol-5-amine
29.		3-(4-nitrophenyl)-*N*-phenyl-1*H*-1,2,4-triazol-5-amine
30.		3-(3-bromophenyl)-*N*-phenyl-1*H*-1,2,4-triazol-5-amine
31.		*N*-phenyl-3-[3-(trifluoromethyl)phenyl]-1*H*-1,2,4-triazol-5-amine
32.		3-(3,5-dimethylphenyl)-*N*-phenyl-1*H*-1,2,4-triazol-5-amine
33.		*N*-[3-(4-*tert*-butylphenyl)-1*H*-1,2,4-triazol-5-yl]pyridin-2-amine
34.		*N*-[3-(4-methoxyphenyl)-1*H*-1,2,4-triazol-5-yl]pyridin-2-amine

35.		*N*-[3-(4-fluorophenyl)-1*H*-1,2,4-triazol-5-yl]pyridin-2-amine
36.		*N*-[3-(4-chlorophenyl)-1*H*-1,2,4-triazol-5-yl]pyridin-2-amine
37.		*N*-[3-(4-nitrophenyl)-1*H*-1,2,4-triazol-5-yl]pyridin-2-amine
38.		*N*-[3-(3-bromophenyl)-1*H*-1,2,4-triazol-5-yl]pyridin-2-amine
39.		*N*-{3-[3-(trifluoromethyl)phenyl]-1*H*-1,2,4-triazol-5-yl}pyridin-2-amine
40.		*N*-[3-(3,5-dimethylphenyl)-1*H*-1,2,4-triazol-5-yl]pyridin-2-amine
41.		*N*-[3-(3,4,5-trimethoxyphenyl)-1*H*-1,2,4-triazol-5-yl]pyridin-2-amine
42.		3-(4-methylphenyl)-*N*-(trichloromethyl)-1*H*-1,2,4-triazol-5-amine

43.		3-(4-*tert*-butylphenyl)-*N*-(trichloromethyl)-1*H*-1,2,4-triazol-5-amine
44.		3-(4-methoxyphenyl)-*N*-(trichloromethyl)-1*H*-1,2,4-triazol-5-amine
45.		3-(4-fluorophenyl)-*N*-(trichloromethyl)-1*H*-1,2,4-triazol-5-amine
46.		3-(4-chlorophenyl)-*N*-(trichloromethyl)-1*H*-1,2,4-triazol-5-amine
47.		3-(4-nitrophenyl)-*N*-(trichloromethyl)-1*H*-1,2,4-triazol-5-amine
48.		3-(3-bromophenyl)-*N*-(trichloromethyl)-1*H*-1,2,4-triazol-5-amine
49.		*N*-(trichloromethyl)-3-[3-(trifluoromethyl)phenyl]-1*H*-1,2,4-triazol-5-amine
50.		3-(3,5-dimethylphenyl)-*N*-(trichloromethyl)-1*H*-1,2,4-triazol-5-amine

51.		*N*-(trichloromethyl)-3-(3,4,5-trimethoxyphenyl)-1*H*-1,2,4-triazol-5-amine
52.		*N*-[3-(4-methylphenyl)-1*H*-1,2,4-triazol-5-yl]quinolin-6-amine
53.		*N*-[3-(4-*tert*-butylphenyl)-1*H*-1,2,4-triazol-5-yl]quinolin-6-amine
54.		*N*-[3-(4-methoxyphenyl)-1*H*-1,2,4-triazol-5-yl]quinolin-6-amine
55.		*N*-[3-(4-fluorophenyl)-1*H*-1,2,4-triazol-5-yl]quinolin-6-amine
56.		*N*-[3-(4-nitrophenyl)-1*H*-1,2,4-triazol-5-yl]quinolin-6-amine
57.		*N*-[3-(3-bromophenyl)-1*H*-1,2,4-triazol-5-yl]quinolin-6-amine
58.		*N*-{3-[3-(trifluoromethyl)phenyl]-1*H*-1,2,4-triazol-5-yl}quinolin-6-amine

59.		*N*-[3-(3,4,5-trimethoxyphenyl)-1*H*-1,2,4-triazol-5-yl]quinolin-6-amine
60.		*N*-[3-(3,5-dimethylphenyl)-1*H*-1,2,4-triazol-5-yl]quinolin-6-amine /0

Software Used

- Chemsketch Ultra
- Discovery Studio
- PyRx
- Autodock 1.3.7
- SWISS ADME
- PROTOX III

Preparation Of Ligand

Synthetic 1,2,4 triazole derivatives are drawed using chemsketch against 14 alpha demethylase enzymes. Total 60 derivative were selected all of these derivative analogues were added with hydrogens, energy minimization is done.

Preparation Of Protein Structure

The crystal structure of 3JUV and 5FRB protein fragment retrieved from Protein Data Bank(PDB) have the pharmacological targets for development of new drugs to treat fungal disease. We removed all of the heteroatoms of both receptors such as water molecules, bound ligands and any other co crystallized solvent from the PDB file.

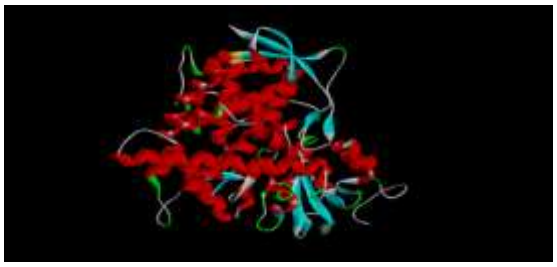


Figure 1: 5FRB protein structure

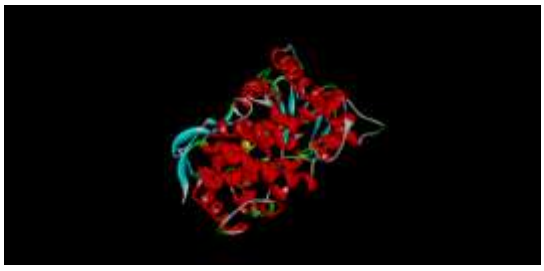


Figure 2: 3JUV protein structure

PyRx

PyRx is a user-friendly open-source virtual screening software that integrates several computational tools for drug discovery. It is widely used in academic and research settings for molecular docking and virtual screening studies. PyRx utilizes Autodock and Autodock Vina as its docking engines. Ligand structures can be prepared by minimizing their energy using open babel, which is integrated into PyRx. The software allows flexible ligand docking by treating the ligand as a rotatable torsion tree, while the protein is usually kept rigid. The binding site of the protein can be defined by setting up a grid box, which

focuses the docking simulation in a specific region of interest. PyRx supports batch docking of multiple ligands, which is particularly useful for screening phytochemicals. Each ligand is docked into the proteins active site, and binding affinities(binding energy scores) are calculated using the Autodock vina scoring function. The conformations with the lowest binding energies are considered the most favourable and further analysed to assess their interactions with the active site residue of the target protein.

Autodock 4.2.6

Autodock 4.2.6 is a widely used molecular docking tool designed for predicting the binding of small molecules (ligands) to a receptor(usually a protein). It utilises a Lamarckian Genetic Algorithm, which is a combination of a genetic algorithm and local search method, to explore the conformational space of the ligand. In this study, flexible ligand docking was performed using Autodock. The ligand molecules were drawn and energy minimized and converted to PDBQT format using Autodock Tools. The protein structure of the 3JUV and 5FRB was retrieved from the RCSB Protein Data Bank and the receptor was prepared by removing water molecules and adding polar hydrogens. Kollman charges were added to the protein. The grid box was set around the active site of the receptor to define the docking region. Autodock uses an energy-based scoring function to evaluate binding poses, accounting for electrostatic interactions, hydrogen binding, desolvation effects, and van der Waals forces(9,10).

RESULTS AND DISCUSSION

Table 2 :Comparison of docking score using PyRx and Autodock 4.2.6 with standard antifungal drugs

SR.NO	PYRX		AUTODOCK	
	3JUV	5FRB	3JUV	5FRB
Fluconazole	-8.6	-6.2	-8.224	-7.658
Isavuconazole	-8.1	-7.5	-9.231	-9.231
Itraconazole	-7.6	-8.1	-7.652	-8.474
Posaconazole	-8.5	-8.8	-8.211	-8.333
Voriconazole	-5.3	-6.9	-6.111	-7.984
Deri 1	-7.2	-8.8	-6.500	-8.631
Deri 2	-8.0	-8.3	-8.022	-9.778
Deri 3	-7.2	-8.4	-8.828	-8.532
Deri 4	-8.2	-9.0	-7.859	-8.844
Deri 5	-8.6	-8.9	-8.512	-8.922
Deri 6	-7.2	-7.8	-8.202	-9.043
Deri 7	-8.9	-8.8	-8.411	-9.722
Deri 8	-8.8	-8.8	-6.589	-8.247
Deri 9	-9.2	-9.1	-7.883	-7.878
Deri 10	-7.6	-9.0	-7.667	-8.557
Deri 11	-9.1	-10.1	-7.923	-7.550
Deri 12	-9.3	-9.8	-7.228	-9.203
Deri 13	-7.6	-8.4	-6.500	-8.631
Deri 14	-9.0	-8.6	-7.982	-8.202
Deri 15	-7.9	-9.5	-10.249	-8.411
Deri 16	-6.9	-8.3	-9.142	-6.589
Deri 17	-7.5	-8.3	-8.631	-7.883
Deri 18	-7.5	-8.6	-9.778	-7.667
Deri 19	-9.4	-8.3	-8.532	-7.923
Deri 20	-6.8	-8.4	-8.844	-7.228
Deri 21	-7.9	-9.8	-8.922	-8.560
Deri 22	-7.1	-9.1	-9.043	-9.001
Deri 23	-7.0	-8.1	-9.722	-6.880
Deri 24	-7.8	-9.4	-8.247	-7.122
Deri 25	-6.3	-8.3	-7.878	-9.445
Deri 26	-8.0	-8.9	-8.557	-9.288
Deri 27	-7.2	-8.8	-7.550	-6.552
Deri 28	-6.5	-8.2	-9.203	-9.445
Deri 29	-7.4	-8.6	-7.694	-8.635
Deri 30	-7.6	-8.6	-8.336	-9.801
Deri 31	-8.0	-9.6	-8.306	-8.430
Deri 32	-7.5	-9.4	-8.011	-8.871
Deri 33	-7.6	-9.1	-10.590	-8.956
Deri 34	-7.2	-8.2	-7.846	-8.107
Deri 35	-7.3	-8.8	-6.500	-7.982
Deri 36	-7.3	-8.7	-8.022	-10.249
Deri 37	-6.5	-8.5	-8.828	-9.142
Deri 38	-7.1	-8.5	-7.859	-8.631
Deri 39	-8.2	-9.6	-8.512	-9.778
Deri 40	-7.5	-9.3	-8.202	-8.532
Deri 41	-6.7	-7.3	-8.411	-8.844
Deri 42	-6.7	-7.2	-6.589	-8.922
Deri 43	-6.7	-7.2	-7.883	-9.043
Deri 44	-6.1	-7.4	-7.667	-9.722
Deri 45	-7.3	-7.6	-7.923	-8.247
Deri 46	-6.7	-7.2	-7.228	-7.878
Deri 47	-7.0	--7.4	-8.560	-8.557

Deri 48	-6.5	-7.3	-9.001	-7.550
Deri 49	-8.2	-8.5	-6.880	-9.203
Deri 50	-7.2	-7.8	-7.122	-7.694
Deri 51	-6.1	-6.9	-9.445	-8.336
Deri 52	-8.4	-8.7	-9.288	-6.500
Deri 53	-8.6	-9.2	-6.552	-8.022
Deri 54	-7.1	-8.2	-9.445	-8.828
Deri 55	-8.0	-8.7	-8.635	-7.859
Deri 56	-8.9	-8.5	-9.801	-8.512
Deri 57	-8.4	-8.3	-8.430	-8.202
Deri 58	-8.5	-9.5	-8.871	-8.411
Deri 59	-7.8	-7.9	-8.956	-6.589
Deri 60	-7.8	-9.1	-8.107	-7.883

Molecular docking was performed to evaluate the binding affinities of synthesized 1,2,4-triazole derivatives (Deri1-Deri60) compared to standard antifungal drug(fluconazole, Isavuconazole, Itraconazole, Posaconazole and Voriconazole). Docking studies were carried out using two different software platforms, PyRx and 4.2.6 against two fungal target proteins 3JUV and 5FRB. The standard drugs exhibited docking score ranging from PyRx:-5.3 to -8.8kcal/mol. Autodock:-6.211 to -9.231kcal/mol. Among them, isavuconazole and posaconazole showed the most favourable binding energies both targets.

The synthesised derivatives displayed a wide range of binding affinities. Notably, many derivatives exhibited better docking scores than standard drugs. Derivative 28 showed a docking score of -9.203(3JUV) and -9.445(5FRB) using auto dock, surpassing even the reference drugs. Derivative 34, derivative 35 and derivative 38 also demonstrated strong binding affinities, with values around -10.590 and-10.249(3JUV), suggesting excellent interaction with the protein binding sites. The data confirms that several synthesized triazole derivatives particularly deri28,deri34 and deri38,may possess promising antifungal agents(11,12).

Table 3: Comparing the pharmacokinetic properties with standard antifungal drug and 1,2,4 triazole derivatives

Compound	M.W (g/mol)	Number of heavy Atoms	Num aromatic heavy atoms	Fraction Csp3	No. rotatable bonds	No. H bond Acceptors	No.H bond donors	Molar refractivity	TPSA	LOG $P_{O/W}$	Log S
S1	306.27	22	16	0.23	1	7	1	70.71	81.65	-0.41	-2.17
S2	437.47	31	22	0.18	6	1	7	111.46	115.86	-2.93	-4.91
S3	705.63	49	28	0.37	7	11	0	194.53	104.70	-5.26	-7.48
S4	700	51	28	0.41	12	1	9	194.12	115.70	5.22	-6.69
S5	306.27	22	16	0.23	5	1	7	70.71	81.65	0.41	-2.17
1.	260.33	19	6	0.43	4	3	3	86.43	65.52	-2.32	-3.75
2.	247.21	18	11	0.10	4	5	2	64.95	111.49	0.17	-2.18
3.	283.12	16	6	0.20	3	2	3	74.86	65.52	-2.82	-3.10
4.	272.23	19	6	0.27	4	5	3	72.16	65.52	-2.93	-3.29
5.	232.28	17	6	0.33	3	2	3	77.09	65.52	-2.96	-3.13
6.	294.31	21	6	0.38	6	6	3	86.64	93.21	-2.22	-2.50
7.	282.34	21	12	0.19	4	3	3	94.83	57.68	-2.14	-4.64
8.	270.30	20	12	0.13	3	3	3	88.30	48.45	-1.65	-4.58
9.	297.31	22	12	0.13	4	4	3	97.16	94.27	-0.98	-4.00
10.	331.21	20	12	0.13	3	2	3	96.04	48.45	-1.52	-4.95
11.	320.31	23	12	0.19	4	5	3	93.34	48.45	-1.28	-4.88
12.	280.37	21	12	0.24	3	2	3	98.27	48.45	-2.75	-4.64
13.	342.39	25	6	0.28	6	5	3	107.81	76.14	-1.16	-4.25
14.	258.36	19	6	0.53	3	2	3	89.04	48.45	-2.53	-3.66
15.	300.44	12	6	0.61	4	2	3	103.35	48.45	-.34	-4.65
16.	274.36	20	6	0.53	4	3	3	90.57	57.68	-1.82	-3.44
17.	262.33	19	6	0.50	3	3	3	84.03	48.45	-2.45	-3.52
18.	278.78	19	6	0.50	3	2	3	89.09	48.45	-1.50	-3.96
19.	289.33	21	6	0.50	4	4	3	92.90	94.27	-1.86	-3.43

20.	323.23	19	6	0.50	3	2	3	89.08	48.45	-1.87	-4.27
21.	312.33	22	6	0.53	4	5	3	94.01	48.45	-2.48	-4.23
22.	272.39	20	6	0.56	3	2	3	103.55	48.45	-3.97	-4.22
23.	334.41	24	6	0.59	6	5	3	102.64	76.14	-0.92	-3.60
24.	294.39	22	12	0.28	4	2	3	89.86	48.45	-2.30	-5.01
25.	268.31	20	12	0.13	4	3	3	83.33	57.68	-2.58	-3.81
26.	256.28	19	12	0.07	3	3	3	88.38	48.45	-2.76	-4.35
27.	272.73	19	12	0.07	3	2	3	102.85	48.45	-1.97	-3.94
28.	328.37	24	12	0.24	6	5	3	92.19	76.14	-2.44	-3.80
29.	283.29	21	12	0.07	4	4	3	95.2	94.27	-3.34	-4.66
30.	317.18	19	12	0.07	3	2	3	91.07	48.45	-2.07	-3.91
31.	306.29	22	12	0.13	4	5	3	88.37	48.45	-2.32	-4.58
32.	266.34	20	12	0.19	3	2	3	93.30	48.45	-2.43	-4.35
33.	295.38	22	12	0.29	4	3	3	100.44	61.34	-3.79	-4.55
34.	269.30	20	12	0.14	4	4	3	87.66	70.57	-2.43	-3.35
35.	257.27	19	12	0.08	3	4	3	81.13	61.34	-3.23	-3.45
36.	273.72	19	12	0.08	3	3	3	86.18	61.34	2.07	3.89
37.	284.27	21	12	0.08	4	5	3	89.99	107.16	-2.44	-3.34
38.	318.17	19	12	0.08	3	3	3	88.87	61.34	-2.44	-4.20
39.	307.27	22	12	0.08	4	6	3	86.17	61.34	-3.31	-4.13
40.	267.33	20	12	0.14	3	3	3	91.10	61.34	-2.81	-3.89
41.	329.35	24	12	0.20	6	6	3	100.64	89.03	-2.06	-3.48
42.	293.58	17	12	0.30	3	2	3	81.55	48.45	-2.14	-4.21
43.	335.66	20	12	0.46	4	2	3	95.85	48.45	-1.72	-4.98
44.	309.58	18	12	0.30	4	3	3	83.07	57.68	-2.49	-3.99
45.	297.54	17	12	0.22	4	3		76.54	48.45	-1.91	-3.86
46.	314.00	17	12	0.22	3	2	3	81.59	48.45	-1.94	-4.51
47.	324.55	19	12	0.22	3	4	3	85.40	94.27	-2.46	-3.76
48.	358.45	17	12	0.22	4	2	3	84.28	48.45	-1.84	-4.83
49.	347.55	20	12	0.30	3	5	3	81.58	48.45	-2.26	-4.55
50.	307.31	18	12	0.36	4	2	3	86.51	48.45	-1.85	-4.30
51.	369.63	22	12	0.42	3	5	3	96.06	76.14	-1.09	-3.93
52.	303.36	23	12	0.11	6	3	3	103.64	61.34	-2.74	-4.58
53.	345.44	26	12	0.24	3	3	3	117.94	61.34	-1.81	-5.54
54.	319.36	24	12	0.11	4	4	3	105.17	70.57	-2.29	-4.35
55.	307.32	23	12	0.06	3	4	3	98.63	61.34	-1.70	-4.44
56.	334.33	25	12	0.06	4	5	3	107.50	107.66	-1.93	-4.33
57.	368.23	23	12	0.06	3	3	3	106.37	61.34	-1.68	-5.19
58.	357.33	26	12	0.11	4	6	3	103.68	61.34	-2.02	-5.12
59.	379.41	28	12	0.20	6	6	3	118.15	89.03	-1.78	-4.48
60.	317.39	24	12	0.16	3	3	3	108.61	61.34	-1.55	-4.88

The pharmacokinetic properties and drug likeness of the synthesized 1,2,4-triazole derivatives were evaluated using Swiss ADME and compared with standard antifungal drugs. Most of the derivatives followed Lipinski's rule of Five, confirming their potential as orally active drug candidates. The molecular weight of the majority of synthesized compounds was below the threshold of 500 Da, aligning with favourable drug-likeness criteria. The topological polar surface area(TPSA) values for most derivatives were within the recommended range(<140A^2),suggesting good membrane permeability. The logP values, indicative of lipophilicity, were mostly within the optimal range of -0.4 to +5.0. in terms of water solubility(LogS), the derivative demonstrated moderate to good solubility, which is advantageous for formulation and systemic bioavailability.(13)

Table 4: Predicted pharmacokinetic properties and enzyme interaction with standard antifungal drug and 1,2,4 triazole derivatives

Sr. No	Compounds	GI absorption	BBB Permeant	PgP substrate	CYP1A2	CYP2C19	CYP2C9	CYP2D6	CYP3A4
1.	Fluconazole	High	No	Yes	No	No	No	No	No
2.	Isavuconazole	High	Yes	Yes	No	No	No	No	No
3.	Itraconazole	High	No	Yes	No	No	No	No	No
4.	Posaconazole	High	Yes	Yes	No	No	No	No	No
5.	Voriconazole	High	Yes	Yes	No	No	No	No	No
6.	Derivative 1	High	No	Yes	No	No	No	No	No
7.	Derivative 2	High	No	Yes	No	No	No	No	No
8.	Derivative 3	High	No	Yes	No	No	No	No	No
9.	Derivative 4	High	Yes	Yes	No	No	No	No	No
10.	Derivative 5	High	Yes	Yes	No	No	No	No	No
11.	Derivative 6	High	No	Yes	No	No	No	No	No
12.	Derivative 7	High	Yes	Yes	No	No	No	No	No
13.	Derivative 8	High	Yes	Yes	No	No	No	No	No
14.	Derivative 9	High	No	Yes	Yes	No	No	No	No
15.	Derivative 10	High	Yes	Yes	No	No	No	No	No
16.	Derivative 11	High	Yes	Yes	No	No	No	No	No
17.	Derivative 12	High	Yes	Yes	No	No	No	No	No
18.	Derivative 13	High	No	Yes	No	No	No	No	No
19.	Derivative 14	High	Yes	Yes	No	No	No	No	No
20.	Derivative 15	High	Yes	Yes	No	No	No	No	No
21.	Derivative 16	High	No	Yes	No	No	No	No	No
22.	Derivative 17	High	Yes	Yes	No	No	No	No	No
23.	Derivative 18	High	Yes	Yes	No	No	No	No	No
24.	Derivative 19	High	No	Yes	No	No	No	No	No
25.	Derivative 20	High	Yes	Yes	No	No	No	No	No
26.	Derivative 21	High	Yes	Yes	No	No	No	No	No
27.	Derivative 22	High	Yes	Yes	No	No	No	No	No
28.	Derivative 23	High	No	Yes	No	No	No	No	No
29.	Derivative 24	High	Yes	Yes	No	No	No	No	No
30.	Derivative 25	High	No	Yes	No	No	No	No	No
31.	Derivative 26	High	Yes	Yes	No	No	No	No	No
32.	Derivative 27	High	Yes	Yes	No	No	No	No	No
33.	Derivative 28	High	No	Yes	No	No	No	No	No
34.	Derivative 29	High	No	Yes	No	No	No	No	No
35.	Derivative 30	High	Yes	Yes	No	No	No	No	No
36.	Derivative 31	High	Yes	Yes	No	No	No	No	No
37.	Derivative 32	High	Yes	Yes	No	No	No	No	No
38.	Derivative 33	High	Yes	Yes	No	No	No	No	No
39.	Derivative 34	High	No	Yes	No	No	No	No	No
40.	Derivative 35	High	No	Yes	No	No	No	No	No
41.	Derivative 36	High	No	Yes	No	No	No	No	No
42.	Derivative 37	High	No	Yes	No	No	No	No	No
43.	Derivative 38	High	No	Yes	No	No	No	No	No
44.	Derivative 39	High	Yes	Yes	No	No	No	No	No
45.	Derivative 40	High	No	Yes	No	No	No	No	No
46.	Derivative 41	High	No	Yes	No	No	No	No	No
47.	Derivative 42	High	Yes	Yes	No	No	No	No	No

48.	Derivative 43	High	Yes	Yes	No	No	No	No	No
49.	Derivative 44	High	No	Yes	No	No	No	No	No
50.	Derivative 45	High	Yes	Yes	No	No	No	No	No
51.	Derivative 46	High	Yes	Yes	No	No	No	No	No
52.	Derivative 47	High	No	No	Yes	yes	Yes	No	No
53.	Derivative 48	High	Yes	Yes	Yes	No	No	No	No
54.	Derivative 49	High	Yes	Yes	No	No	No	No	No
55.	Derivative 50	High	Yes	Yes	No	No	No	No	No
56.	Derivative 51	High	No	Yes	No	No	No	No	No
57.	Derivative 52	High	Yes	Yes	No	No	No	No	No
58.	Derivative 53	High	Yes	Yes	No	No	No	No	No
59.	Derivative 54	High	No	Yes	No	No	No	No	No
60.	Derivative 55	High	Yes	Yes	No	No	No	No	No
61.	Derivative 56	High	No	Yes	No	No	No	No	No
62.	Derivative 57	High	Yes	Yes	No	No	No	No	No
63.	Derivative 58	High	Yes	Yes	No	No	No	No	No
64.	Derivative 59	High	No	Yes	No	No	No	No	No
65.	Derivative 60	High	Yes	Yes	No	No	No	No	No

Table 5: Predicted toxicity and pharmacokinetic parameters of standard and synthesized 1,2,4-triazole derivative

Sr. No	Compounds	Predicted LD_{50} mg/kg	Predicted toxicity class	Hepato toxicity	Carcino genicity	Immuno Toxicity	Mutagenicity	Cytotoxicity
5.	Fluconazole	1271	4	Active	Inactive	Inactive	Inactive	Inactive
6.	Isavuconazole	1000	4	Active	Inactive	Inactive	Inactive	Inactive
7.	Itraconazole	320	4	Active	Inactive	Active	Inactive	Inactive
8.	Posaconazole	320	4	Active	Inactive	Active	Inactive	Inactive
9.	voriconazole	352	4	Active	Inactive	Active	Inactive	Inactive
10.	Derivative 1	1000	4	Active	Active	Inactive	Inactive	Inactive
11.	Derivative 2	600	4	Active	Active	Inactive	Active	Inactive
12.	Derivative 3	1000	4	Active	Active	Inactive	Inactive	Inactive
13.	Derivative 4	1000	4	Active	Active	Inactive	Inactive	Inactive
14.	Derivative 5	1000	4	Active	Active	Inactive	Inactive	Inactive
15.	Derivative 6	750	4	Active	Active	Inactive	Inactive	Inactive
16.	Derivative 7	440	4	Active	Active	Inactive	Active	Inactive
17.	Derivative 8	500	4	Active	Active	Inactive	Inactive	Inactive
18.	Derivative 9	1190	4	Active	Inactive	Active	Inactive	Inactive
19.	Derivative 10	500	4	Active	Inactive	Inactive	Inactive	Inactive
20.	Derivative 11	500	4	Active	Active	Inactive	Inactive	Inactive
21.	Derivative 12	500	4	Active	Active	Inactive	Inactive	Inactive
22.	Derivative 13	440	4	Active	Active	Active	Active	Active
23.	Derivative 14	680	4	Inactive	Active	Inactive	Inactive	Inactive
24.	Derivative 15	2000	4	Inactive	Active	Inactive	Inactive	Inactive
25.	Derivative 16	1000	4	Inactive	Active	Inactive	Inactive	Inactive
26.	Derivative 17	1760	4	Active	Inactive	Inactive	Inactive	Inactive
27.	Derivative 18	1000	4	Inactive	Inactive	Inactive	Inactive	Inactive
28.	Derivative 19	1760	4	Inactive	Active	Inactive	Active	Inactive
29.	Derivative 20	1760	4	Inactive	Inactive	Inactive	Inactive	Inactive
30.	Derivative 21	1760	4	Active	Active	Inactive	Inactive	Inactive
31.	Derivative 22	680	4	Inactive	Active	Inactive	Inactive	Inactive

32.	Derivative 23	750	4	Inactive	Active	Active	Inactive	Inactive
33.	Derivative 24	440	4	Inactive	Active	Inactive	Inactive	Inactive
34.	Derivative 25	440	4	Inactive	Active	Inactive	Inactive	Inactive
35.	Derivative 26	500	4	Active	Inactive	Inactive	Inactive	Inactive
36.	Derivative 27	500	4	Inactive	Inactive	Inactive	Inactive	Inactive
37.	Derivative 28	440	4	Inactive	Active	Active	Inactive	Active
38.	Derivative 29	680	4	Inactive	Inactive	Inactive	Active	Inactive
39.	Derivative 30	500	4	Active	Active	Inactive	Inactive	Inactive
40.	Derivative 31	500	4	Active	Active	Inactive	Inactive	Inactive
41.	Derivative 32	500	4	Inactive	Active	Inactive	Inactive	Inactive
42.	Derivative 33	680	4	Active	Active	Inactive	Inactive	Inactive
43.	Derivative 34	650	4	Active	Active	Inactive	Active	Inactive
44.	Derivative 35	680	4	Active	Inactive	Inactive	Inactive	Inactive
45.	Derivative 36	500	4	Active	Inactive	Inactive	Inactive	Inactive
46.	Derivative 37	680	4	Active	Active	Inactive	Active	Inactive
47.	Derivative 38	680	4	Active	Inactive	Inactive	Inactive	Inactive
48.	Derivative 39	680	4	Active	Active	Inactive	Inactive	Inactive
49.	Derivative 40	680	4	Active	Active	Inactive	Inactive	Inactive
50.	Derivative 41	680	4	Active	Active	Active	Inactive	Active
51.	Derivative 42	500	4	Active	Active	Inactive	Inactive	Inactive
52.	Derivative 43	500	4	Active	Active	Inactive	Inactive	Inactive
53.	Derivative 44	500	4	Active	Inactive	Inactive	Inactive	Inactive
54.	Derivative 45	680	4	Active	Inactive	Inactive	Inactive	Inactive
55.	Derivative 46	1000	4	Active	Inactive	Inactive	Inactive	Inactive
56.	Derivative 47	680	4	Active	Active	Inactive	Active	Inactive
57.	Derivative 48	680	4	Active	Inactive	Inactive	Inactive	Inactive
58.	Derivative 49	500	4	Active	Active	Inactive	Inactive	Inactive
59.	Derivative 50	500	4	Active	Active	Inactive	Inactive	Inactive
60.	Derivative 51	750	4	Active	Active	Active	Inactive	Inactive
61.	Derivative 52	680	4	Active	Active	Active	Active	Inactive
62	Derivative 53	680	4	Active	Active	Active	Inactive	Inactive
63.	Derivative 54	680	4	Active	Inactive	Active	Inactive	Inactive
64.	Derivative 55	680	4	Active	Active	Active	Active	Inactive
65.	Derivative 56	680	4	Active	Active	Active	Inactive	Inactive
66.	Derivative 57	680	4	Active	Active	Active	Inactive	Inactive
67.	Derivative 58	650	4	Active	Active	Inactive	Inactive	Active
68.	Derivative 59	500	4	Active	Inactive	Inactive	Inactive	Inactive
69.	Derivative 60	680	4	Inactive	Active	Inactive	Inactive	Inactive

The toxicity and enzyme interaction profiles of the synthesized 1,2,4-triazole derivatives were evaluated using Protox III software. Most compounds exhibited low predicted toxicity, with no signs of mutagenicity, carcinogenicity, cytotoxicity or immunotoxicity. Hepatotoxicity was predicted for a few compounds, but the majority were found to be safe. Additionally, most derivative did not inhibit major cytochrome P450 enzymes (CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4) indicating low risk for drug-drug interaction. These finding support the favourable safety and metabolic stability of the synthesized derivatives for further drug development.

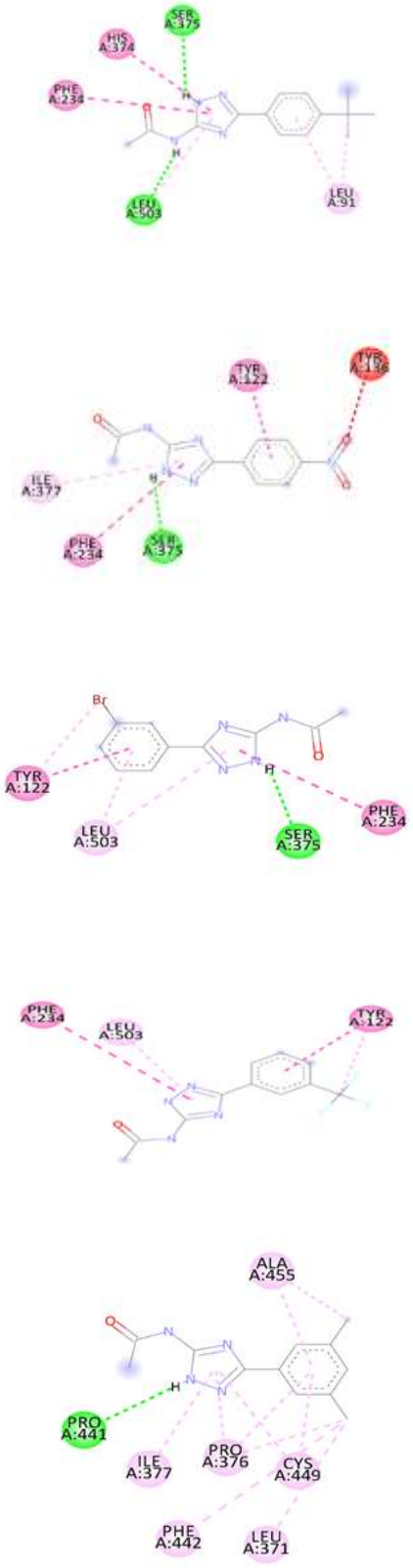


Figure 3: image of ligand interaction with 3JUV and 5FRB protein

CONCLUSION

The present review highlights the synthesis and evaluation of novel 1,2,4-triazole derivatives as potential antifungal agents. Insilico analyses, including molecular docking and ADMET predictions, revealed that several synthesized compounds exhibited strong binding affinities toward fungal target proteins, along with favourable pharmacokinetic and drug-likeness profiles. Most derivatives complied with Lipinski' rule and showed good oral bioavailability, moderate solubility, and minimal toxicity risks. Predicted toxicity studies further confirmed that the compounds are largely non-carcinogenic, non-mutagenic and safe in terms of hepatotoxicity and cytotoxicity. Enzymes interaction data showed minimal inhibition cytochrome P450 enzymes, reducing the potential for drug-drug interactions. Overall, the synthesized 1,2,4-triazoles derivatives show significant potential for further development as effective and safe antifungal agents.

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HOW TO CITE: Sowmiya L, Dr. D. Nagavalli, 1,2,4-Triazole Derivatives Targeting Fungal 14-Alpha Demethylase Enzyme: An Insilico Approach, Int. J. of Pharm. Sci., 2025, Vol 3, Issue 8, 1471-1489. https://doi.org/10.5281/zenodo.16856764