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IN-SILICO ADME PREDICTION AND MOLECULAR DOCKING STUDY OF NOVEL BENZIMIDAZOLE-1,3,4-OXADIAZOLE DERIVATIVES AS CYP51 INHIBITORS FOR ANTIMICROBIAL ACTIVITY

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ABSTRACT
A class of innovative benzimidazole-1,3,4-Oxadiazole derivatives is a significant heterocyclic molecule for therapeutic development. In heterocyclic chemistry, the novel 1,3,4-Oxadiazole nucleus has a wide range of uses, including antibacterial, treatment. Molecular docking is frequently employed in contemporary drug design to comprehend drug-receptor interaction. Swiss dock, PyRx, and discovery studio visualizer (DSV) tools were used to predict *in-silico* ADME properties. In the current investigation, substituted benzimidazole-1,3,4-Oxadiazole derivatives were taken for docking studies against 6AYB an *Naegleria fowleri* CYP51-ketoconazole complex. The main objective of the study is to perform docking of the selected benzimidazole-1,3,4-oxadiazole derivatives on the protein and compare the docking score with standard ketoconazole. The molecular docking study was conducted using PyRx and the discovery studio visualizer (DSV) program, *Naegleria fowleri* CYP51-ketoconazole complex (6AYB) was obtained from the protein data bank (PDB) site. It was found that the docking score of all sixteen 1,3,4-Oxadiazole compounds ranged from -8.1 to -8.9 Kcal/mol. The novel benzimidazole with 1,3,4-Oxadiazole derivatives has been found to possess antibacterial properties, many substituted 1,3,4-Oxadiazole derivatives have been reported for the activity.

INTRODUCTION

Various targets in important sections of the bacterial cell cycle have been investigated in recent years as a potential new approach to the problem of antibiotic resistance. Fatty acid biosynthesis (FAB) is one of the most appealing metabolic processes to use as a target for novel antibacterial medicines. The potential of bacteria to acquire resistance to antimicrobial drugs is making treatment for bacteria more difficult by the day [1]. Antibiotics have developed resistance to microorganisms as a result of over-prescription and incorrect use by patients. Even when previously used antibiotics or antimicrobial medications are no longer effective, this complicates treatment, and infections become increasingly difficult to treat [2].

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As a result, it is critical to develop and find new antimicrobial medications that are both safer and more effective [3]. According to a review of the literature, 1,3,4-oxadiazole has antifungal [4,5], antimicrobial [6-8], antihypertensive [9], anticonvulsant [10], antiviral [11], anti-inflammatory [12], and anticancer activity [13]. The strongest antibacterial activity has been discovered in new 2,5-disubstituted 1,3,4-oxadiazole-based entities [14]. CYP51 is a crucial enzyme in the manufacture of ergosterol found in eukaryotes and other biological kingdoms (including humans). Because the novel structures fit so well in the active site of the lasterol 14-demethylase enzyme, they inhibit sterol formation. It plays a role in the formation of ergosterol, the primary sterol component of the fungal cell membrane, as well as metabolic activities such as membrane permeability, membrane fluidity, enzyme activity, cell shape, and cell cycle progression. Inhibition of this enzyme results in cell death and malfunction. 1, 3, 4-Oxadiazole inhibits lanosterol 14-demethylation into sterol, which is a significant component of fungal cytoplasmic membranes and a bioregulator of membrane asymmetry, fluidity, and integrity [15-19]. Figure-1 shows examples of biologically active compounds including oxadiazole, coumarin, as well as the benzimidazole entity. We designed ADME prediction, and molecular docking study of 1,3,4-oxadiazole nucleus containing benzimidazole derivatives and investigated the influence of various substituents at the phenyl-oxadiazole moiety on biological activity. The goal was to find a more effective antibacterial agent.

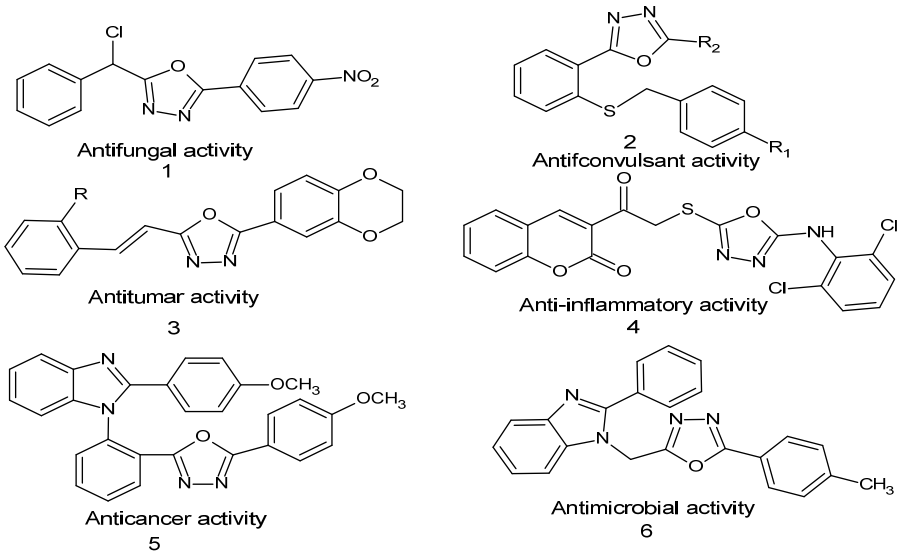


Fig.1: Biologically active compounds are phenyl oxadiazole, coumarin, 1,3,4-thiadiazole, and benzimidazole entity linked with 1,3,4-oxadiazole moiety

MATERIALS AND METHODS

Software required

The study of molecular docking was carried out on a system with computational specifications (HP Pavilion AMD Ryzen™ 5 Hexa Core 5500 APU @ 2.1GHz with turbo boost up to 4GHz Processor version 5500U and 16.00 GB RAM with 64-bit Windows-11 operating system), swiss dock, PyRx, and Biovia discovery studio visualizer tools.

Preparation of target protein

The three-dimensional structure of protein CYP51, sterol 14alpha-demethylase (PDB ID: 6AYB), was downloaded from RCSB protein data bank (https://www.rcsb.org/) [20]. Naegleria fowleri CYP51-ketoconazole complex (figure 2) is loaded into the discovery studio client the crystal structure of the protein-receptors binding domain with bound ligand and crystallographic water is shown in a 3D window. The hierarchy view has been cleared of water molecules. Hydrogen atoms are now added to the protein structure after it has been cleaned. The associated ligand has been removed and the binding site of the ligand can be predicted from the present pose, saving the file in the PDB format.

Ligand and macromolecule preparation:

The chemical structures of ligands used in this study were designed and optimized using Chemsketch freeware 2021 and saved in. mol format, later converted into PDB format by Open Bable-2.3.2 software, required for execution in PyRx software. Macromolecule (target enzyme) was prepared before starting the molecular docking process, which involved the removal of the

water molecules and native ligand attached to the target enzyme. After that, hydrogen atoms were added to target the investigation ligand was loaded, their torsions and rotatable bonds were assigned, and the files were saved as ligand pdbqt.

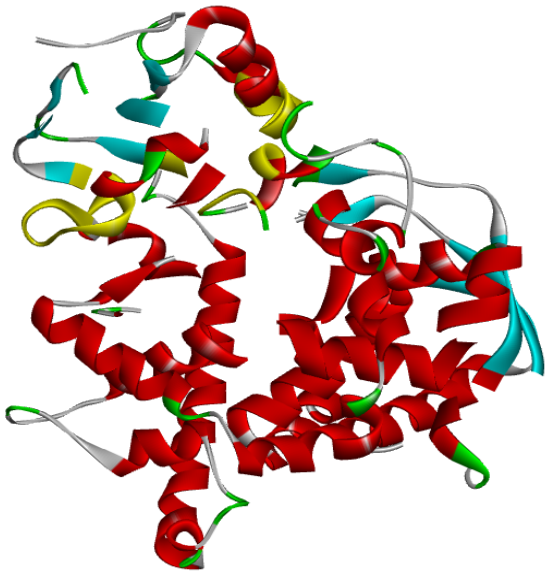


Fig.2: Naegleria fowleri CYP51-ketoconazole complex (PDB ID: 6AYB)

Docking of Naegleria fowleri CYP51-ketoconazole complex with benzimidazole-1,3,4-oxadiazole derivatives using PyRx and discovery studio visualizer

Molecular docking studies were carried out to calculate the binding efficacy of the compound with proteins. Target proteins in *Naegleria fowleri* CYP51-ketoconazole complex were downloaded from the RCSB PDB (protein data bank) in PDB format in 3D orientation and protein preparation, removal of water molecules, and the addition of hydrogen was carried out by using BIOVIA Discovery Studio 2021[21], it was saved in PDB format. Docking calculations were carried out by using PyRx software, energy minimization and conversion to PDBQT format were also done in the same software prior to the docking procedure [22] and 2D structure was generated by using BIOVIA Discovery studio visualizer 2021.

Ligand Identification

The ligands were derivatives of benzimidazole-1,3,4-oxadiazole (Table 2). The current antibacterial drugs include amoxicillin, ciprofloxacin, and azithromycin, etc. They were acquired from the drug bank database and included in docking and comparative studies (Table-1). The known structures were downloaded in SDF format and converted to PDB format using the Open Babel programme. PyRx and biovia discovery studio visualizer tools were then used for docking investigations.

In silico ADME (Absorption, Distribution, Metabolism and Excretion Studies):

ADME describes the pharmacokinetics of substances in an organism's body. It assesses the danger associated with administering a pharmaceutical substance to an individual or another creature. Pre ADMET (https://preadmet.bmdrc.kr/), Swiss ADME (http://www.swissadme.ch/), and other online tools are used to identify these pharmacokinetic features in silico. The molecules become inactive when there are two or more violations of Lipinski's rule of five. To assess whether a molecule is similar to existing drugs on the market, a complex balancing act involving several chemical properties and structural traits must be performed. A molecule's behaviour in a living organism is influenced by a variety of factors, such as its transport properties, bioavailability, reactivity, affinity to proteins, toxicity, metabolic stability, and many more. These properties include a molecule's hydrophobicity, hydrogen bonding characteristics, electronic distribution, flexibility, and size [24].

In this way, the 16 different conformers were generated (Figure-3) and blind docking was performed to know whether these molecules bind in the active site or anywhere in the target was demonstrated by the biovia discovery studio program.

RESULTS AND DISCUSSION

Benzimidazole-1,3,4-oxadiazole derivative analogues were subjected to in silico ADME experiments utilising a variety of software programmes, including ChemSketch, Molinspiration, Swiss Dock, PyRx, and Discovery Studio Visualizer (DSV). Molecular descriptors and smiles notation were computed using Molinspiration software. Molinspiration software was used to analyse the Lipinski Rule of Five, and it was discovered that all of the analogues adhered to it. The methodology created by Molinspiration predicted the drug likeness profile of analogues.

A chemical must possess strong biological activity at low effective doses, low toxicity, and the capacity to continue acting until the desired outcome manifests for it to be a successful medicine. New compounds incorporating benzimidazole-1,3,4-Oxadiazole are designed for its antimicrobial activity, targeting the sterol biosynthesis inhibitor activity, as the 1,3,4-Oxadiazole

nucleus is widely documented to treat microbial infection. Table-2 listed all the designed compounds. The proposed chemical was discovered to exhibit sterol biosynthesis inhibitory activity with a low incidence of adverse drug reactions.

Absorption, distribution, metabolism and excretion (ADME) results

We can say that the molecules are orally active because all the created compounds adhere to the same rule. Tables 3 and 4 present the findings of ADME investigations. The octanol water partition coefficient (mol log P) of the proposed compounds must not be larger than 5. The compounds' good oral bioavailability is indicated (Table 3). The logarithm of molar concentration is used to represent the water solubility. The usual range for the skin permeability of designed compounds is between -5.50 to -6.07 cm/s.

The suggested compounds are only moderately water-soluble because they have lipophilic functionalities intended to increase cell permeability. Using a volume of distribution, blood-brain barrier permeability, and fraction unbound, the drug's distribution in the body was estimated. A higher value for volume of distributions denotes a better drug distribution in tissues compared to plasma, and a log volume of distributions value greater than 0.40 denotes a greater tissue distribution.

Synthesis Scheme 1:

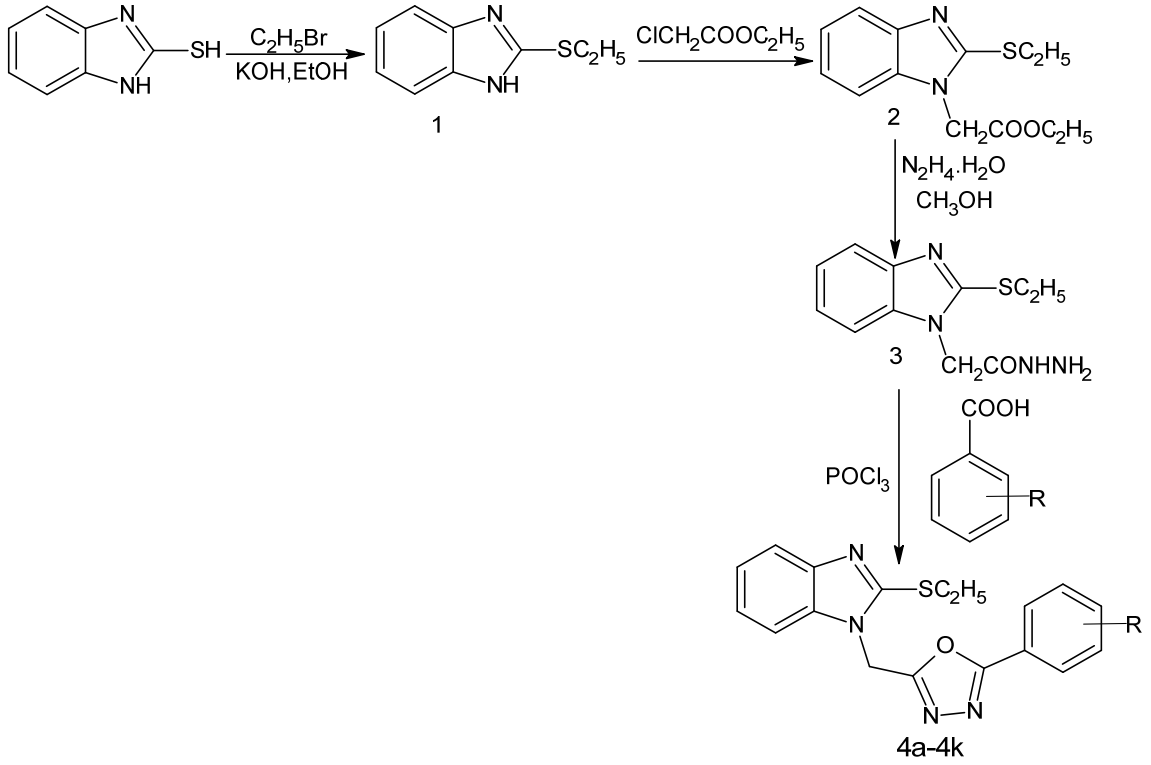


Fig.3: Synthetic Scheme

Table-1 Showing Structure and Standard of known drug.

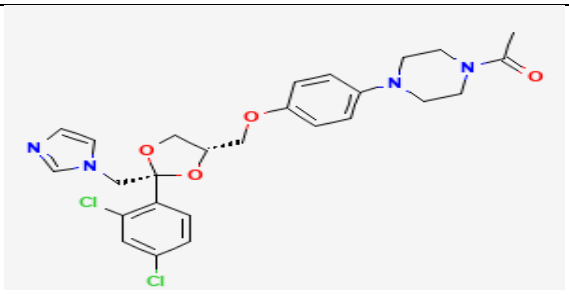
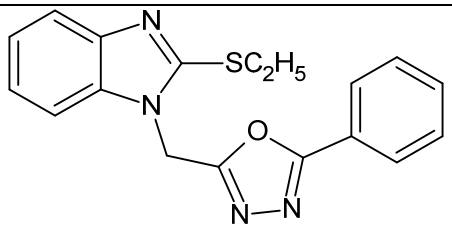
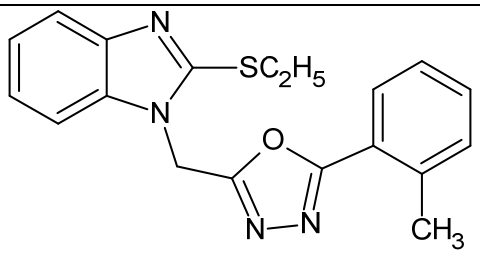
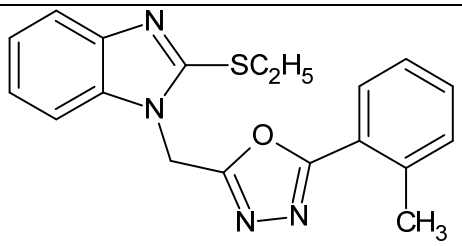
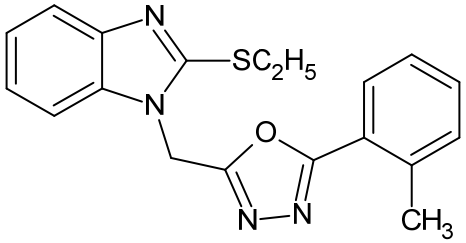
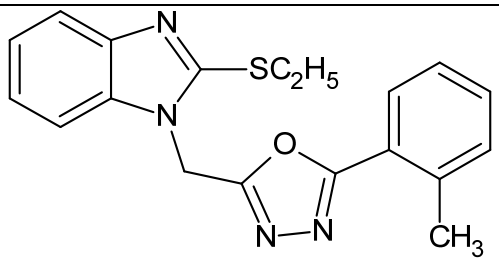
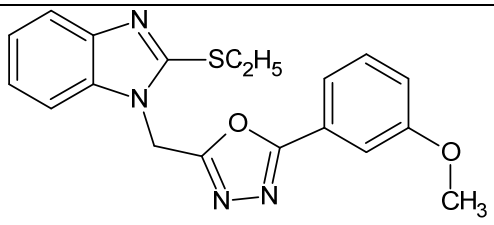
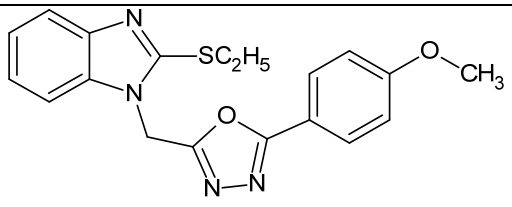
Sl. No.	Ligand	PubChem CID	Structures
1	Ketoconazole	456201	

Table 2: Showing structures of Benzimidazole-1,3,4-oxadiazole derivatives used as ligands. (4a-4p)

Ligand code	IUPAC /Ligand name	Structures
4a	2-(ethylsulfanyl)-1-[(5-phenyl-1,3,4-oxadiazol-2-yl)methyl]-1*H*-benzimidazole	
4b	2-(ethylsulfanyl)-1-{[5-(2-methylphenyl)-1,3,4-oxadiazol-2-yl]methyl}-1*H*-benzimidazole	
4c	2-(ethylsulfanyl)-1-{[5-(3-methylphenyl)-1,3,4-oxadiazol-2-yl]methyl}-1*H*-benzimidazole	
4d	2-(ethylsulfanyl)-1-{[5-(4-methylphenyl)-1,3,4-oxadiazol-2-yl]methyl}-1*H*-benzimidazole	
4e	2-(ethylsulfanyl)-1-{[5-(2-methoxyphenyl)-1,3,4-oxadiazol-2-yl]methyl}-1*H*-benzimidazole	
4f	2-(ethylsulfanyl)-1-{[5-(3-methoxyphenyl)-1,3,4-oxadiazol-2-yl]methyl}-1*H*-benzimidazole	
4g	2-(ethylsulfanyl)-1-{[5-(4-methoxyphenyl)-1,3,4-oxadiazol-2-yl]methyl}-1*H*-benzimidazole	

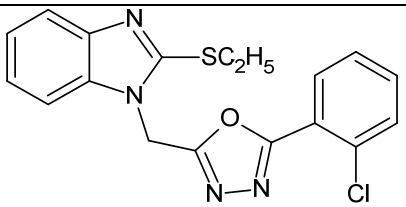
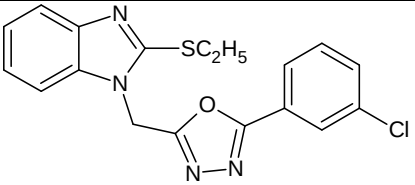
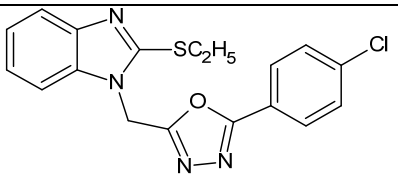
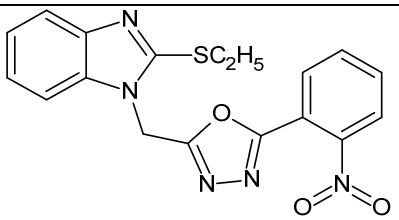
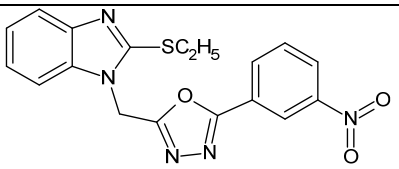
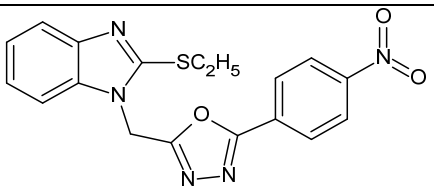
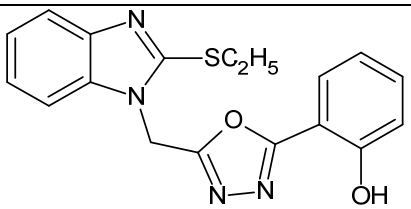
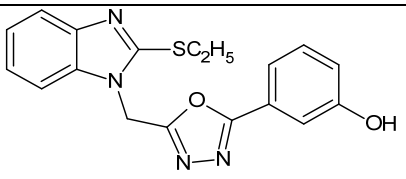
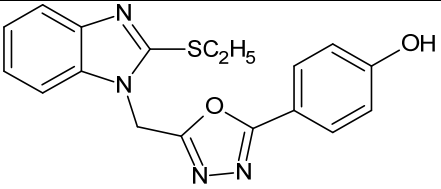
4h	1-{[5-(2-chlorophenyl)-1,3,4-oxadiazol-2-yl]methyl}-2-(ethylsulfanyl)-1*H*-benzimidazole	
4i	1-{[5-(3-chlorophenyl)-1,3,4-oxadiazol-2-yl]methyl}-2-(ethylsulfanyl)-1*H*-benzimidazole	
4j	1-{[5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl]methyl}-2-(ethylsulfanyl)-1*H*-benzimidazole	
4k	2-(ethylsulfanyl)-1-{[5-(2-nitrophenyl)-1,3,4-oxadiazol-2-yl]methyl}-1*H*-benzimidazole	
4l	2-(ethylsulfanyl)-1-{[5-(3-nitrophenyl)-1,3,4-oxadiazol-2-yl]methyl}-1*H*-benzimidazole	
4m	2-(ethylsulfanyl)-1-{[5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl]methyl}-1*H*-benzimidazole	
4n	2-(5-{[2-(ethylsulfanyl)-1*H*-benzimidazol-1-yl]methyl}-1,3,4-oxadiazol-2-yl)phenol	
4o	3-(5-{[2-(ethylsulfanyl)-1*H*-benzimidazol-1-yl]methyl}-1,3,4-oxadiazol-2-yl)phenol	
4p	4-(5-{[2-(ethylsulfanyl)-1*H*-benzimidazol-1-yl]methyl}-1,3,4-oxadiazol-2-yl)phenol	

Table-3: Drug likeness analysis of designed Benzimidazole-1,3,4-Oxadiazole derivatives (4a-4p)

Comp Code	Physicochemical Properties						Lipinski's Rule	%Abs[d]	N viol[e]	N rot[f]
	R	MW[a]	TPSA[b]	milogP[c]	H_A	H_D				
4a	H	336.42	56.75	3.81	5	0	Yes	89.42	0	5
4b	2-CH_3	350.45	56.75	4.21	5	0	Yes	89.42	0	5
4c	3-CH_3	350.45	56.75	4.23	5	0	Yes	89.42	0	5
4d	4-CH_3	350.45	56.75	4.26	5	0	Yes	89.42	0	5
4e	2-OCH_3	366.45	65.98	3.82	6	0	Yes	86.23	0	6
4f	3-OCH_3	366.45	65.98	3.84	6	0	Yes	86.23	0	6
4g	4-OCH_3	366.45	65.98	3.87	6	0	Yes	86.23	0	6
4h	2-Cl	370.87	56.75	4.44	5	0	Yes	89.42	0	5
4i	3-Cl	370.87	56.75	4.46	5	0	Yes	89.42	0	5
4j	4-Cl	370.87	56.75	4.49	5	0	Yes	89.42	0	5
4k	2-NO_2	381.42	102.57	3.72	8	0	Yes	73.61	0	6
4l	3-NO_2	381.42	102.57	3.74	8	0	Yes	73.61	0	6
4m	4-NO_2	381.42	102.57	3.77	8	0	Yes	73.61	0	6
4n	2-OH	352.42	76.98	3.54	6	1	Yes	82.44	0	5
4o	3-OH	352.42	76.98	3.31	6	1	Yes	82.44	0	5
4p	4-OH	352.42	76.98	3.33	6	1	Yes	82.44	0	5

[a]**MW:** molecular weight, [b]**TPSA:** total polar surface area, [c]**miLogP:** molinspiration partition coefficient, [d]**%Abs:** %Abs = 109 − (0.345 × TPSA), [e]**nviol:** number of violations, [f]**nrotb:** number of rotatable bonds, **H_A:** number of hydrogen bond acceptors, **H_D:** number of hydrogen bond donors

Table-4: *In silico* ADME properties of Benzimidazole-1,3,4-Oxadiazole designed derivatives. (4a-4p)

Comp. Code	R	Intestinal absorption (%absorbed)	CYP1A2 inhibitor	CYP2C19 inhibitor	CYP2C9 inhibitor	CYP2D6 inhibitor	CYP3A4 inhibitor	Log K_p (skin permeation) (cm/s)
4a	-H	High	Yes	Yes	Yes	Yes	Yes	-5.68
4b	2-CH_3	High	Yes	Yes	Yes	Yes	Yes	-5.50
4c	3-CH_3	High	Yes	Yes	Yes	Yes	Yes	-5.50
4d	4-CH_3	High	Yes	Yes	Yes	Yes	Yes	-5.50
4e	2-OCH_3	High	Yes	Yes	Yes	Yes	Yes	-5.88
4f	3-OCH_3	High	Yes	Yes	Yes	Yes	Yes	-5.88
4g	4-OCH_3	High	Yes	Yes	Yes	Yes	Yes	-5.88
4h	2-Cl	High	Yes	Yes	Yes	No	Yes	-5.44
4i	3-Cl	High	Yes	Yes	Yes	No	Yes	-5.44
4j	4-Cl	High	Yes	Yes	Yes	No	Yes	-5.44
4k	2-NO_2	Low	Yes	Yes	Yes	No	Yes	-6.07
4l	3-NO_2	Low	Yes	Yes	Yes	No	Yes	-6.07
4m	4-NO_2	Low	Yes	Yes	Yes	No	Yes	-6.07
4n	2-OH	High	Yes	Yes	Yes	Yes	Yes	-6.02
4o	3-OH	High	Yes	Yes	Yes	Yes	Yes	-6.02
4p	4-OH	High	Yes	Yes	Yes	Yes	Yes	-6.02

Table-5: Docking score of the designed benzimidazole-1,3,4-Oxadiazole derivatives.

Comp. Code	R	Rmsd/ub	Rmsd/lb	Docking Score (kcal/mol)	Interacting amino acids
4a	-H	0	0	-8.5	ALA182, HIS296, LEU291, ILE179, SER183, LEU200, ILE288, ARG230, VAL233, HIS205
4b	2-CH_3	0	0	-8.7	SER183, LEU200, VAL233, ALA229, ILE288, ARG230, LEU291, HIS205, ILE179, HIS296, ALA182
4c	3-CH_3	0	0	-8.8	SER183, LEU200, VAL233, ILE288, ARG226, VAL113, ARG230, HIS205, LEU291, HIS296, ILE179, ALA182
4d	4-CH_3	0	0	-8.2	SER183, LEU200, ARG230, VAL113, ARG226, VAL233, HIS205, LEU291, ILE179, HIS296, ALA182
4e	2-OCH_3	0	0	-8.6	SER183, LEU200, ILE288, VAL233, ARG226, ARG230, HIS205, LEU291, HIS296, ILE179, ALA182
4f	3-OCH_3	0	0	-8.4	VAL319, MET341, LEU344, TYR450, ILE446, SER445, MET327, LEU448, GLU322, GLU152, LEU333
4g	4-OCH_3	0	0	-8.1	VAL319, LEU344, MET341, TYR450, MET327, LEU448, GLU152, SER445, LYS331, ILE446, LEU333, GLU322
4h	2-Cl	0	0	-8.8	SER183, LEU200, VAL233, ILE288, ARG230, LEU291, HIS205, ILE179, HIS296, ALA182
4i	3-Cl	0	0	-8.4	SER183, LEU200, ARG226, VAL113, LEU291, HIS205, ILE179, ALA182, HIS296
4j	4-Cl	0	0	-8.6	SER183, LEU200, ARG230, VAL113, ARG226, LEU291, HIS205, VAL233, ILE179, HIS296, ALA182
4k	2-NO_2	0	0	-8.5	LEU200, HIS205, ASP206, ALA229, ARG230, ALA182, HIS296, SER183, LEU291, ILE179
4l	3-NO_2	0	0	-8.9	SER183**, LEU200, VAL233,** ILE288**, VAL113, ARG230, HIS205,** LEU291, **HIS296, ILE179,** ALA182
4m	4-NO_2	0	0	-8.2	VAL319, LEU344, MET341, TYR450, ILE446, SER445, MET327, LEU448
4n	2-OH	0	0	-8.6	VAL319, LEU344, MET341, ILE446, SER445, MET327, LEU448
4o	3-OH	0	0	-8.3	VAL319, LEU344, MET341, TYR450, GLU152, MET327, LEU448
4p	4-OH	0	0	-8.3	ARG391, VAL388, PRO87, VAL383, ILE61, HIS86, ASP70, SER65, ILE62
Ketoconazole (Standard)		**0**	**0**	**-9.1**	**LEU200, LEU195, VAL233, VAL113, ILE179, ARG226, LEU203, ARG230, ALA229, HIS205, HIS296, ALA175**

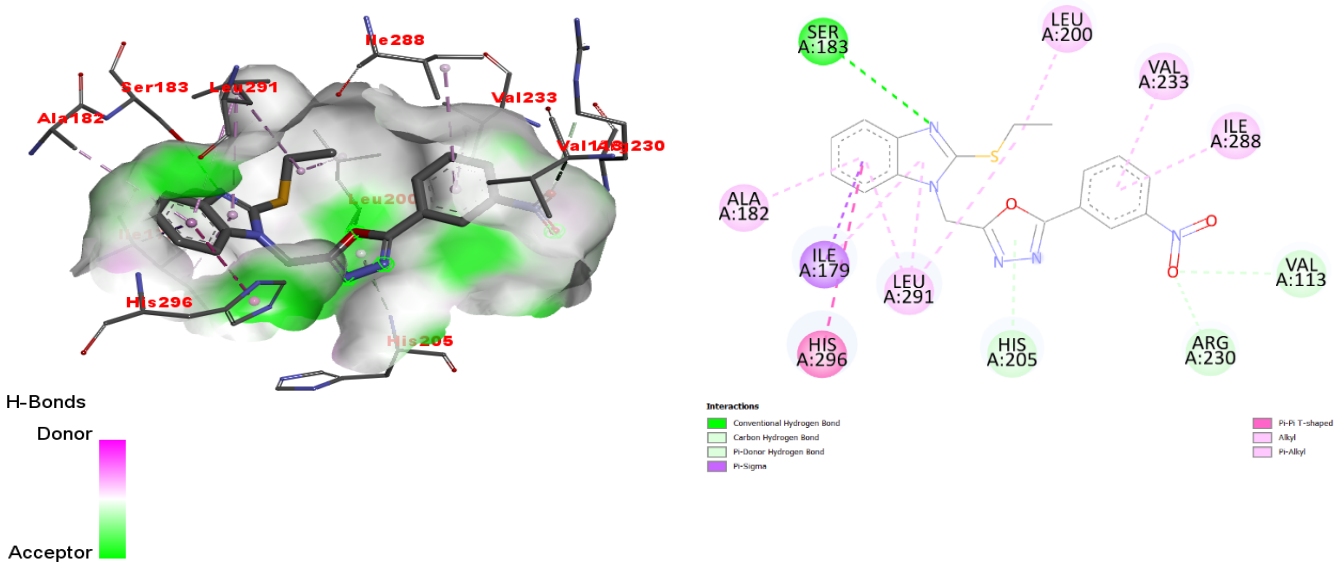


Fig.4: Binding interaction of compound 4l with 6AYB protein.

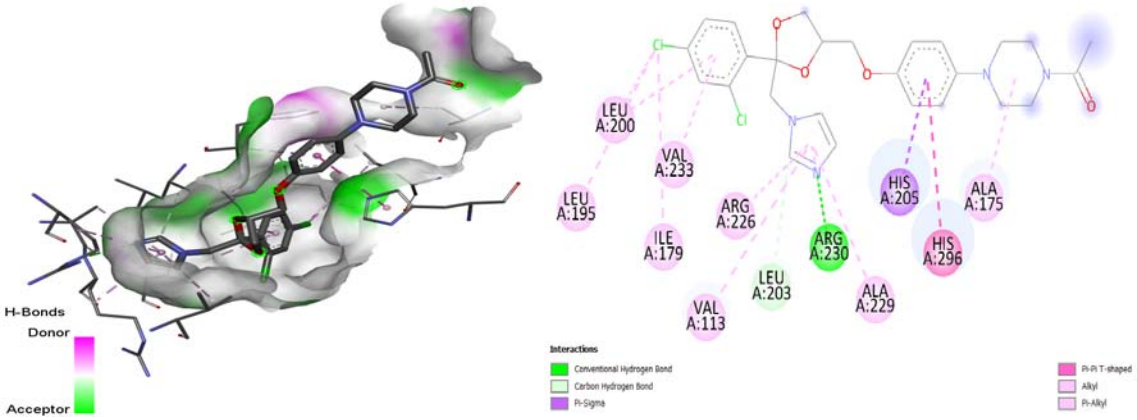


Fig. 5: Binding interaction of Ketoconazole (Standard) with 6AYB protein

There is a good chance that the developed compounds will be able to reach their intended targets. Calculations of the intestinal absorption (percent absorbed) and permeability of the Log Kp were made using Swiss ADME tools (skin permeation). Every designed molecule engages in either a substrate or an inhibitory interaction with cytochromes. It will take more research to discover the hepatotoxic dose level because the chemicals are likely to be liver-toxic. The proposed compounds can all be regarded as likely lead candidates because they all exhibit favourable ADME and toxicity characteristics.

Molecular docking results

A crucial tool in structure-based computer-assisted drug design is molecular docking, which predicts the primary binding mechanism of a ligand with a target protein having a known 3D structure. Using PyRx software, the proposed benzimidazole-1,3,4-Oxadiazole derivatives are docked successfully into the target protein's active site (PDB ID: 6AYB). The intended compounds 4b, 4c, 4d, and 4l exhibit suitable hydrogen bonding with the target protein. The CYP51 protein binding site was within a distance up to 5 radius of the interactions the active drugs established. The majority of the compounds were active, and 4l was chosen as a powerful inhibitor because it has the lowest binding affinity. Additionally, the creation of hydrogen bonds between the molecules SER and HIS is widely acknowledged as seen in Tables 4 and 5. Docking studies showed the most active compounds modes of binding with the designer compound and the target protein.

CONCLUSION

The 1,3,4-benzimidazole compounds were created, and their in-silico parameters were researched. All developed compounds can be considered lead molecules in accordance with ADME

research. According to a molecular docking investigation, of the derivatives, 4l shows the most powerful inhibitor. These compounds ADME analysis demonstrates that they are suited for drug-likeness. These compounds have effective digestive and dermal absorption capabilities. The tests suggest that 4l compounds exhibit strong inhibitory activity against CYP51 as an antibacterial agent.

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CONFLICT OF INTEREST
The authors declare no conflict of interest

AUTHOR CONTRIBUTION
Shivanand Kolageri did a proper literature survey, collected data, design the work, and wrote a portion of the paper. Hemanth S and Mahesh Parit provided maximum effort in the correction, both did a proper literature survey and design the manuscript. Shivanand Kolageri Conceived and design the analysis. The final draft was checked by all the authors.

REFERENCES
[1] Tenover F. Mechanisms of Antimicrobial Resistance in Bacteria. *Am J Med.* **119(6A)**, 3-10 (2006).

[2] Glomb T, Swiatek P. Antimicrobial Activity of 1,3,4-Oxadiazole Derivatives. *Int J Mol Sci*. **22(13)**, 1-23 (2021).

[3] Kavitha S, Nasarullah Z, Kannan K. Synthesis and Biological Evaluation of Sulfonamide-Based 1,3,4-Oxadiazole Derivatives. *Bull Chem Soc Ethiop.* **33(2)**, 307-319 (2019).

[4] Karaburun AÇ, Kaya Çavuşoğlu B, Acar Çevik U, Osmaniye D, Sağlık BN, Levent S, Özkay Y, Atlı Ö, Koparal AS, Kaplancıklı ZA. Synthesis and antifungal potential of some novel benzimidazole-1,3,4-oxadiazole compounds. *Molecules*, **24(1)**, 191 (2019)

[5] Sengupta P, Mal M, Mandal S, Singh J, Maity TK. Evaluation of antibacterial and antifungal activity of some 1,3,4-oxadiazoles. *Iranian Journal of Pharmacology & Therapeutics*, **7(2),** 165-7 (2008).

[6] Ahrabi N, Souldozi A, Sarveahrabi Y. Synthesis of New Three Component Derivatives of 1,3,4-Oxadiazole and Evaluation of Their In Vitro Antibacterial and Antifungal Properties. *Med Lab J.*, **15(5)**, 1-6 (2021).

[7] Ilango K, PV Alentina, Vivek G. Synthesis and antimicrobial activity of 2,5-disubstituted 1,3,4-oxadiazole derivative. *Asian Journal of Chemistry*, **21(9)**, 6915-6919 (2009).

[8] Tresse C, Radigue R, Von Borowski RG, Thepaut M, Le HH, Demay F, Georgeault S, Dhalluin A, Trautwetter A, Ermel G, Blanco C. Synthesis and evaluation of 1,3,4-oxadiazole derivatives for development as broad-spectrum antibiotics. *Bioorganic & medicinal chemistry*. **27(21)**, 115097 (2019).

[9] Vardan S, Harold S, Mookherjee S, Eichr. Effects of tiodazosin, a new antihypertensive, hemodynamics and clinical variables. *Clin Pharmacol Therapeutics*. **34(3),** 290-296 (1983).

[10] Rajak H, Deshmukh R, Veerasamy R, Sharma A, Mishra P, Kharya M. Novel semicarbazones based 2,5-disubstituted-1,3,4-oxadiazoles: One more step towards establishing four binding site pharmacophoric model hypothesis for anticonvulsant activity. *Bioorganic Med Chem Lett*. **20(14)**, 4168-4172 (2010).

[11] Benmansour F, Eydoux C, Querat G, Lamballerie X, Canard B, Alvarez K. Novel 2-phenyl-5-[(E)-2-(thiophen-2-yl)ethenyl]-1,3,4-oxadiazole and 3-phenyl-5-[(E)-2-(thiophen-2-yl)ethenyl]-1,2,4-oxadiazole derivatives as dengue virus inhibitors targeting NS5 polymerase. *Eur J Med Chem.* **109**, 146-156 (2015).

[12] Glomb T, Wiatrak B, Gebczak K, Gebarowski T, Bodetko D, Czyznikowska Z. New 1,3,4-Oxadiazole Derivatives of Pyridothiazine-1,1-Dioxide with Anti-Inflammatory Activity. *Int J Mol Sci.* **21(23)**, 1-22 (2020).

[13] Wang Y, Zhang H, He P, Zhou Z. Effectiveness and tolerability of targeted drugs for the treatment of metastatic castration-resistant prostate cancer: a network meta-analysis of randomized controlled trials. *J Cancer Res Clin Oncol.* **144(1)**, 1751-1768 (2018).

[14] Almalki A, Syed N, Malebari A, Ali N, Elhenawy A, Alghamdia. Synthesis and Biological Evaluation of 1,2,3-Triazole Tethered Thymol-1,3,4-Oxadiazole Derivatives as

Anticancer and Antimicrobial Agents. *Pharmaceuticals*. **14(9)**, 1-18 (2021).

[15] Rabelo V, Santos T, Santana TL, Castro M, Rodrigues H. Clinical and Pharmacological Parameters Determine Relapse during Clopidogrel Treatment of Acute Coronary Syndrome. *Clin Pharmacol.* **62(6)**, 1-38 (2016).

[16] Monk B, Sagatova A, Hosseini P, Ruma Y, Wilson R, Keniya M, et al. Fungal Lanosterol 14α-demethylase: A target for next generation antifungal design. *Biochim Biophys Acta Proteins Proteom.* **1868(3)**, 1-65 (2019).

[17] Daina A, Michielin O, Zoete V. Swiss ADME: a free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. *Sc Rep.* **7(1)**, 1-13 (2017).

[18] Can N, Cevik U, Saglik B, Levent S, Korkut B, Ozkay Y. Molecular Docking Studies, and Antifungal Activity Evaluation of New Benzimidazole-Triazoles as Potential Lanosterol 14αDemethylase Inhibitors. *J Cham*. **(9387102),** 1-15 (2017).

[19] Ertl P, Rohde B, Selzer P. Fast Calculation of Molecular Polar Surface Area as a Sum of Fragment-Based Contributions and Its Application to the Prediction of Drug Transport Properties. *J Med Chem.* **43(20)**, 3714-3717 (2000).

[20] RCSB. Protein data bank; Available from: https://www.rcsb.org/ . [Last accessed on (June 2022)

[21] Albayrak S, Gök Y, Sari Y, Tok TT, Aktaş A. Benzimidazolium Salts Bearing 2-methyl 1,4-benzodioxane Group: Synthesis, Characterization, Computational Studies, In vitro Antioxidant and Antimicrobial Activity. *Biointerface Res. Appl. Chem*. **11(5)**, 13333-13346 (2021).

[22] Dallakyan S, Olson AJ. Small-molecule library screening by docking with PyRx. *Methods Mol Biol*. **1263**, 243-250 (2015).

[23] Daina A, Michielin O, Zoete V. Swiss ADME: a free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. *Sc Rep.* **7(1)**, 1-13 (2017).

[24] Yates C, Shaver S, Schotzinger R, Hoekstra W. Design and Optimization of Highly-Selective, Broad Spectrum Fungal CYP51 Inhibitors. *Bioorg Med Chem Lett.* **27(15)**, 3243-3238 (2017).