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TO DESIGN, MOLECULAR DOCKING AND *IN-SILICO* ADME SCREENING OF HETEROCYCLIC COMPOUNDS FOR ANTI-MICROBIAL ACTIVITY

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ABSTRACT

A key element of the molecular modeling system which demonstrates the ligand-protein interaction is molecular docking. Molecular docking is based on a process related to silico structure-based drug discovery that is frequently used. Which is Detecting a ligand's low-energy binding modes within a referred-structural receptor's active site is known as docking. A number of new substituted benzimidazole compounds were created with antibacterial properties in mind. docking studies and oral bioavailability scores obtained through the investigation of Lipinski's rule. The Pyrx program is used for molecular docking. The Pyrx program showed the score for the new compounds that indicated good activity in comparison to the standard drug (Thiabendazole). And used also Drug Discovery studio for Visualization of 2D and 3D structure of substituted Benzimidazole derivatives with enzyme (PDB ID: 6CR2). Therefore, compounds that were designed were examined for their ability to be absorbed, distributed, metabolized, and excreted. They showed promising qualities that could make them suitable candidates for oral drugs.

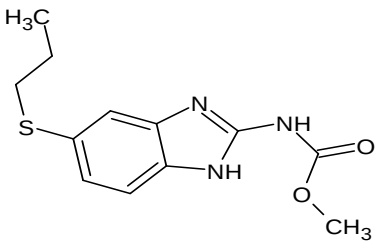
KEYWORDS: Substituted Benzimidazole, Molecular docking, protein (PDB ID: 6CR2). ADME study. Antibacterial properties.

1.0 INTRODUCTION

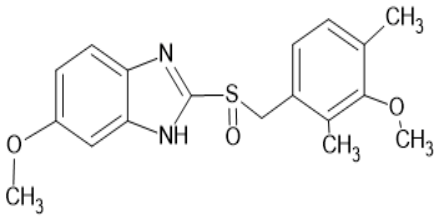
One important heterocyclic ring that is widely utilized in medicinal chemistry is the benzimidazole. The heterobicyclic aromatic chemicals known as benzimidazole derivatives are produced when imidazole and benzene cling to one another.

Numerous possible pharmacological actions are shown by substituted benzimidazole. It can be found in several pharmacologically useful compounds, An exciting area of science is the investigation of novel heterocycles exhibiting noteworthy biological activity. Benzofused heterocycles with nitrogen/sulfur methyl and heteroatoms like benzothiazole, isatin, and benzimidazole have gained a positive reputation in recent decades because of their diverse pharmacological activities. including omeprazole, Telmisartan, albendazole, mebendazole, rabeprazole, oxaprozin, pantoprazole, lansoprazole, thiabendazole (fig.1) Many biological activities, such as anticancer, antiviral, antibacterial, antifungal, antihelmentic, anti-inflammatory, antihistaminic, proton pump inhibitor, antioxidant, antihypertensive, and anticoagulant properties, were linked to the substituted benzimidazole structure. and it is also discovered exhibited cytotoxic activity. It was believed that it would be beneficial to create compounds with a number of novel substituted benzimidazole derivatives and test them for antibacterial properties given the significance of benzimidazole in biological systems.

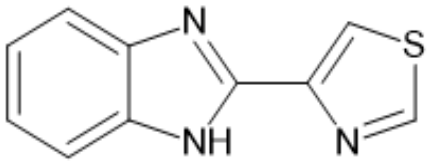
Typically, in the pharmaceutical industry, lead compounds with proven activity undergo chemical alteration to produce new medications. It's possible that molecular change will increase the activity. According to the literature review, drug design through molecular modification is a successful way to create novel medications; as a result, new molecules must be created as possible therapeutic agents. The creation of more potent antioxidant and antibacterial compounds is becoming more and more popular among pharmaceuticals. Additionally, the potential of the benzimidazole center as a healing agent is increased by its capacity to engage with natural targets through hydrogen bonding, π-π interactions, and coordination with steel ions.



Albendazole



Omeprazole



Thiabendazole

Figure 1: shows the molecular structures of biologically active Active Pharmaceutical Ingredients (APIs).

Therefore, the current study set out to find out how well the substituted benzoimidazole derivatives bound to (PDB ID :6CR2) enzyme using molecular docking studies, and compounds with strong binding affinities were screened in vitro for the same molecules and assessed further for ADME/T (drug likeness) characteristics using preADME and SWISSADME.

2.0 MATERIAL AND METHOD

2.1 Retrieval of the 3-D Structure of Target Protein

The process of getting a particular protein's three-dimensional structure, which is crucial for comprehending its interactions, function, and possible significance in biological processes, is known as "retrieval of the 3-D structure of a target protein." can be utilised to find structural folds and families that are comparable and specific to pathogenic organisms in order to choose appropriate medication targets. We downloaded the target protein complexes with monocyclic structure (PDB ID: 6CR2) from the protein data bank.

2.2 Protein Preparation

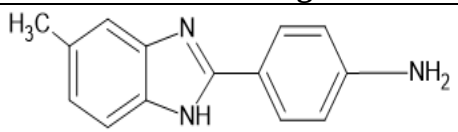
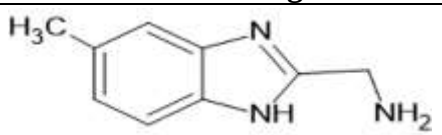
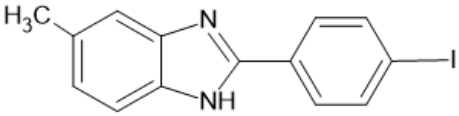
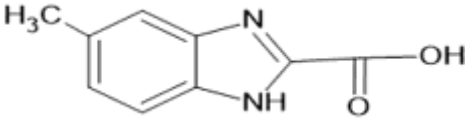
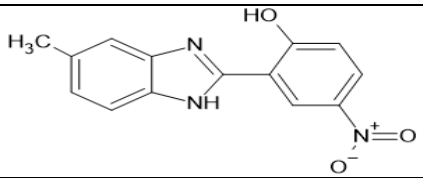
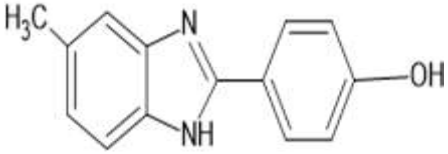
The process of separating and purifying proteins from biological materials for additional examination or experimental usage is known as protein preparation. In molecular biology, biochemistry, and biotechnology, this procedure is essential. Target protein complexes having a monocyclic structure (PDB ID: 6CR2) were used to create their crystal structures using ChimeraX software. Initially, the protein molecule was imported into the ChimeraX program. The protein's optimal and minimised energy structure was specifically achieved by its utilisation. Hydrogen bonds are added to the targeted protein and water molecules are eliminated. They extract the co-crystallized ligand molecules from the protein molecule. Using PyRx software, the protein macromolecule is created.

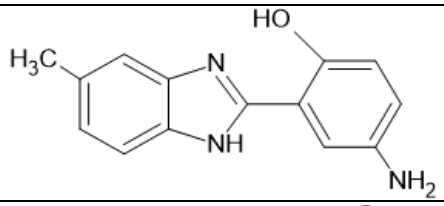
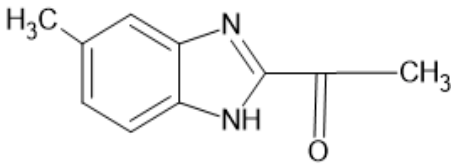
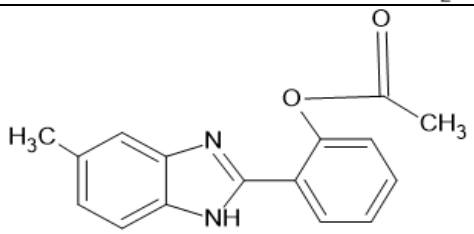
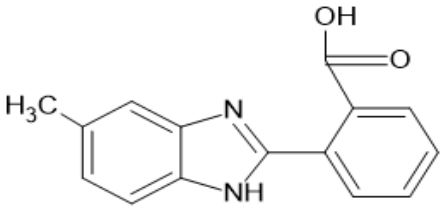
(PDB ID: 6CR2)

2.3 Ligand Preparation

A number of steps are involved in ligand preparation, including ligand characterisation, synthesis, purification, testing, and selection. For use in experiments, the finished ligand needs to be in a stable form, at the right concentration, and in the right buffer. Achieving dependable and repeatable results requires proper preparation, regardless of the ligand's application in structural biology, drug discovery, or protein-ligand interaction research. ChemSketch software was used to create the chemical structures of the designed molecules. All structures of heterocyclic substituted benzimidazoles are depicted using the chemsketch program. PyRx is the program used to prepare the ligand. The ligand's energy minimisation procedure is carried out by these programs. Docking is carried out on all chosen heterocyclic substituted benzimidazole derivatives.

Table No 1: Structure of Ligands used for Molecular docking.

Comp.	Structure of Ligand	Comp.	Structure of Ligand
A_1		A_6	
A_2		A_7	
A_3		A_8	

A_4		A_9	
A_5		A_{10}	

2.4 Molecular Docking

In molecular docking, the three-dimensional structure of macromolecular complexes in biological cells is estimated. Using this computational method, the quaternary structure of complexes made up of two or more biological molecules interacting is modelled. Protein-protein complexes and protein-nucleic acid complexes are the most frequently targeted targets for this type of modelling. A minimised 3D conformation of the ligand and the 3D structure of the biological target are required as inputs for docking programs. Discovery Visual Studio is used to prepare the protein before docking. The protein is downloaded from the Protein Data Bank (PDB) and undesirable elements like cofactors, water molecules, heteroatoms, and unnecessary chains are eliminated to make the protein interaction-ready.

The binding interactions between the target protein and proposed substituted benzimidazole derivatives are predicted using molecular docking. PyRx software is used to perform the docking procedure. ChimeraX software is used to prepare the protein before docking, and the Protein Data Bank (PDB ID:6CR2) is used to obtain the protein structure. The protein is made ready for interaction by eliminating unwanted atoms, such as cofactors, water molecules, heteroatoms, and unnecessary chains. Using Drug Discovery Studio, the protein and ligand are visualised.

2.5 Drug-likeness

Online resources like SwissADME (http://www.swissadme.ch/) are used to determine the drug-likeness characteristics of the synthesised compounds, such as the octanol–water partition coefficient (logP), number of rotatable bonds (NROTB), molecular weight, number of hydrogen donors (HBD), number of hydrogen acceptors (HBA), molecular polar surface area (TPSA), and violations of Lipinski's and CMC rules.

2.6 In silico ADME (Absorption, Distribution, Metabolism and Excretion)

In the body of an organism, the pharmacokinetics of molecules are described by ADME (Absorption, Distribution, Metabolism, and Elimination). The drug-likeness and pharmacokinetic characteristics, such as absorption, distribution, metabolism, and elimination, are estimated through an in silico investigation. The evaluation of a compound's potential as a medicine depends on these factors. Blood-brain barrier (BBB) penetration, Caco-2 permeability, bioavailability, and absorption (including intestinal absorption) are important considerations. A pharmaceutical compound's risk of being administered to humans or other species is evaluated. PreADME (https://preadmet.bmdrc.kr/) is one of the internet tools used to identify these pharmacokinetic features in silico. The intricate balance between structural and chemical traits that determines whether a molecule is similar to an existing medication is known as drug-likeness. A molecule must have minimal toxicity, high biological activity at low effective concentrations, and the capacity to continue to work until the intended therapeutic effect is obtained in order to be considered a successful drug.

3.0 RESULTS AND DISCUSSION

Table 2: Drug-likeness analysis of designed Substituted Benzimidazole derivatives.

Comp.	Molecular Weight	CMC rule Violation	Lipinski's rule violation	Mol Log P	H-bond donor	H-bond acceptor	No. of Rotatable bonds	TPSA (Å2)
A_1	223.27	0	0	2.46	2	1	1	54.70
A_2	334.16	0	0	3.85	1	1	2	28.68
A_3	269.26	0	0	1.37	2	4	3	94.73
A_4	239.27	0	0	1.88	3	2	3	74.93
A_5	266.27	0	0	2.85	1	3	4	54.98
A_6	161.29	0	0	0.75	2	2	4	54.7
A_7	176.17	0	0	0.9	2	3	3	65.98
A_8	224.26	0	0	2.46	2	2	3	48.91
A_9	174.2	0	0	0.97	1	2	4	45.75
A_{10}	252.27	0	0	2.6	2	3	4	65.98

The developed compounds comply to the rule of five and are assessed for druglikeness qualities listed in **Table 2** With an octanol-water partition coefficient (mol log P) of less than 5, the substances are expected to have acceptable oral bioavailability. As a result, we examined the synthetic compounds (A1–A10) to evaluate their drug-likeness characteristics and contrast them with the reference medication, Thaibenazole. According to the results, the compounds had good druglike qualities and broke either Veber's or Lipiniski's rules. An oral active drug candidate must meet four key developmental requirements: logP must not exceed

5, MW must be less than 500 daltons, HBA must not exceed 10, and HBD must not exceed 5. and the created compounds follow all guidelines.

Table 3: *In silico* ADME properties of designed Substituted Benzimidazole derivatives.

Comp.	Absorption	Distribution			Metabolism				
	Caco2 Permeability	Intestinal Absorption	BBB Permeabilty (log BB)	BBB Permeablity	PPB (%)	CYP1A2 Inhibitor	CYP2C19 inhibitor	CYP2C9 inhibitor	CYP2D6 Inhibitor
A_1	2.59549	High	2.05087	Yes	82.87	Yes	No	No	Yes
A_2	48.881	High	11.2929	Yes	97.20	Yes	Yes	No	No
A_3	3.10964	High	0.524234	No	92.32	Yes	No	Yes	Yes
A_4	1.48675	High	1.97476	Yes	79.61	Yes	No	No	Yes
A_5	25.9619	High	2.92494	Yes	90.40	Yes	Yes	No	No
A_6	2.1541	High	1.0412	Yes	25.36	Yes	No	No	No
A_7	19.9363	High	0.865523	Yes	62.57	No	No	No	No
A_8	3.27127	High	4.44013	Yes	86.76	Yes	No	No	Yes
A_9	13.8799	High	2.40125	Yes	70.64	Yes	No	No	No
A_{10}	13.7392	High	1.99735	Yes	84.03	Yes	No	No	No

According to In silico ADME **Table 3**, the developed compounds were assessed. The percentage absorption of the chemicals is predicted by the in silico ADME study because the small intestine is where most oral medications are absorbed. The permeability of Caco2 cells from human colon cancer can be used to predict medication intake because these cells resemble intestinal epithelial cells. A high permeability compound should have a Papp greater than 8 x10-6 246 cm/s. It's interesting to note that every chemical that was created exhibits high Caco-2 permeability. High intestinal absorption was demonstrated by all the substances. In tissues, all of the chemicals exhibit a moderate distribution. With the exception of M3, every chemical complies with BBB permeability. The intended compound's PPB percentage falls between 92 and 100%. There is a good chance that these compounds will be able to reach the intended targets because of the chosen compound.

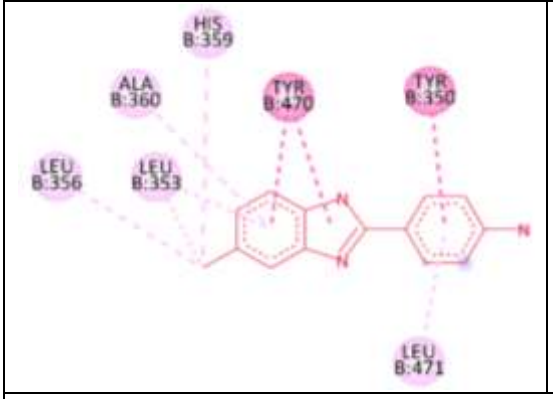
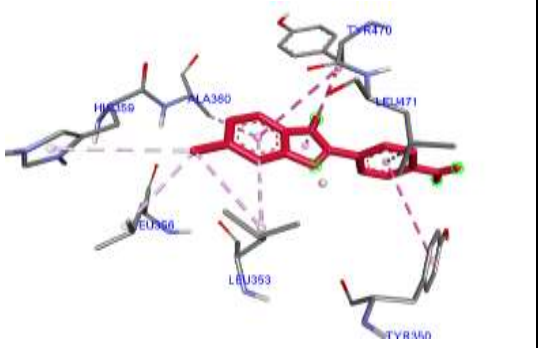
Table 4: Ligand energy and Binding Affinity of designed benzimidazole derivative with Protein (PDB ID: 6CR2).

Compound	Ligand Energy (kcal/mol)	Binding Affinity (kcal/mol)
A_1	334.6	-8.5
A_2	333.81	-8.5
A_3	355.81	-8.8
A_4	344.51	-8.5
A_5	389.35	-8.5
A_6	288.94	-6.7
A_7	286.76	-7.3

A_8	335.49	-8.5
A_9	287.88	-7.1
A_{10}	414.24	-8.6
Native Ligand Thiabendazole	335.62	-7.0
Native Ligand Albendazole	404.79	-6.9

According **to Table 4**, all of the proposed compounds had good binding affinities between -6.7 and -8.8 kcal/mol. Thiabendazole and Albendazole the native ligand, has a binding affinity of Thiabendazole is -7.0, and Albendazole is -6.9 which is lower than the -8.8 of the proposed A3 molecule. The degree of the connection between the target protein and the ligand is known as binding affinity. Usually measured in kcal/mol, it is quantified by a binding energy score. Stronger interactions are indicated by greater negative binding energies, whereas weaker interactions are indicated by less negative or positive values.

Table 5 The 2D and 3D-docking poses of the docked ligands with Protein (PBD ID:6CR2).

Compound A_1	
	
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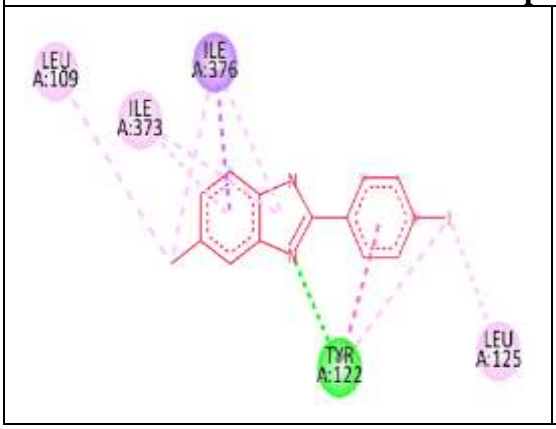	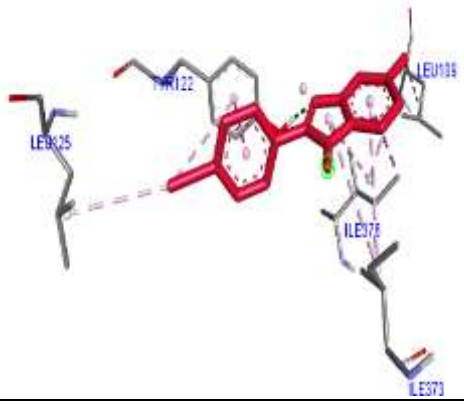

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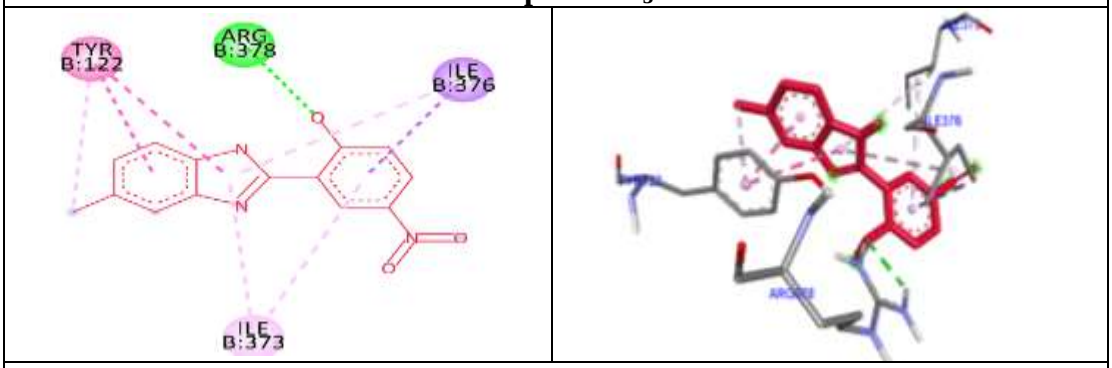
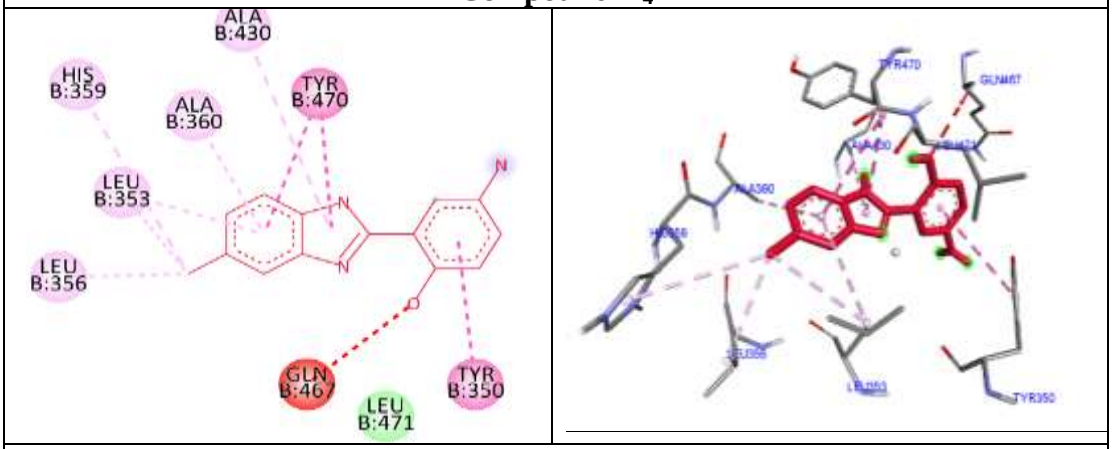
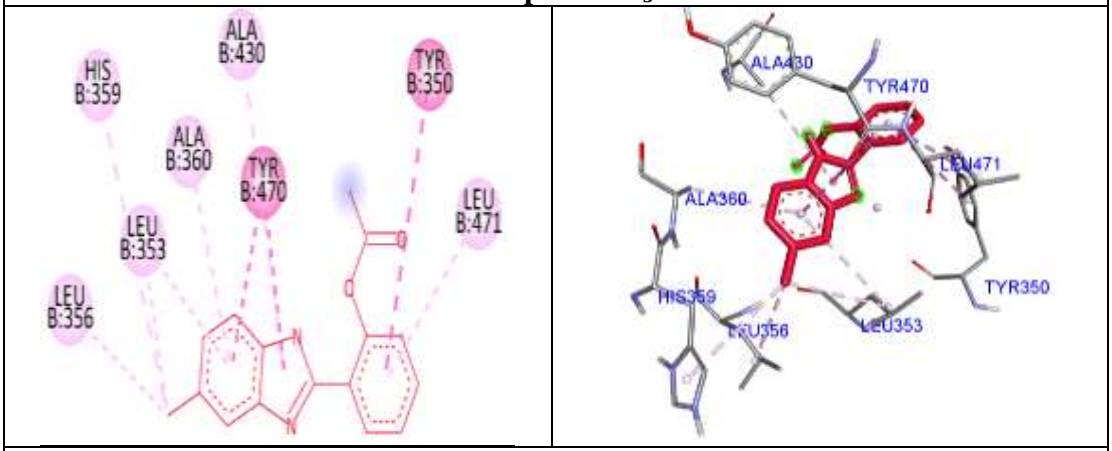


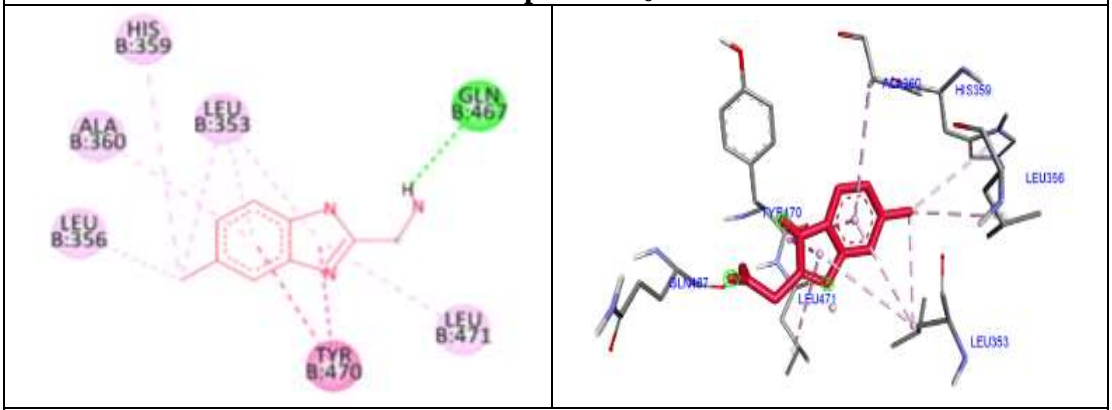
Compound A_4



Compound A_5



Compound A_6



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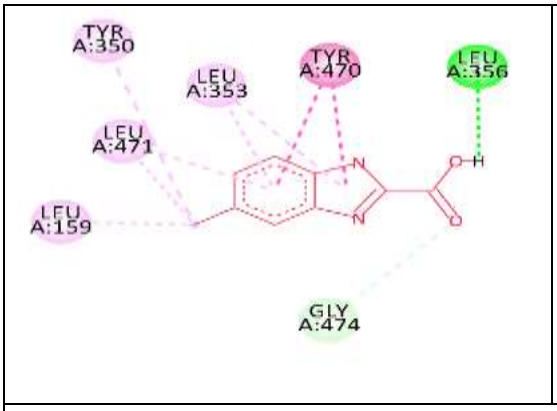
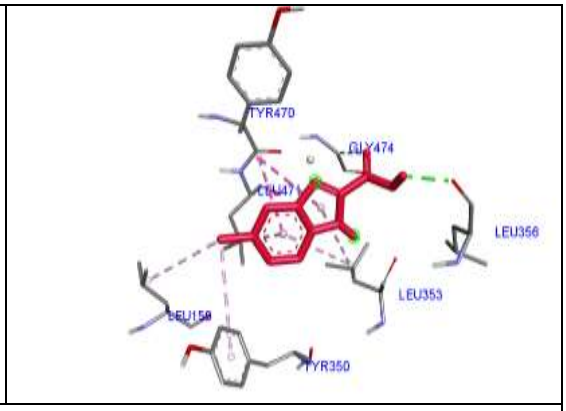
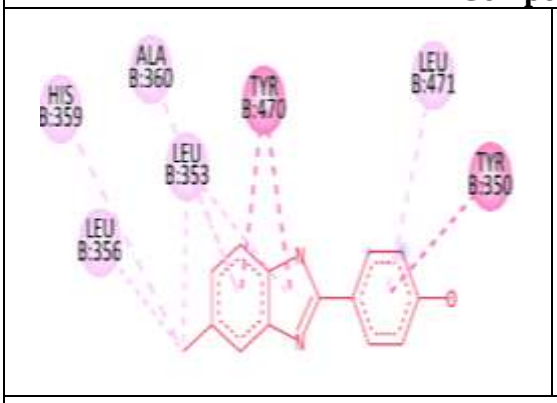
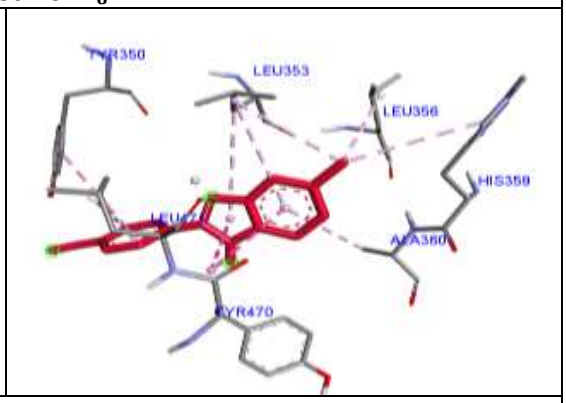




Compound A_8





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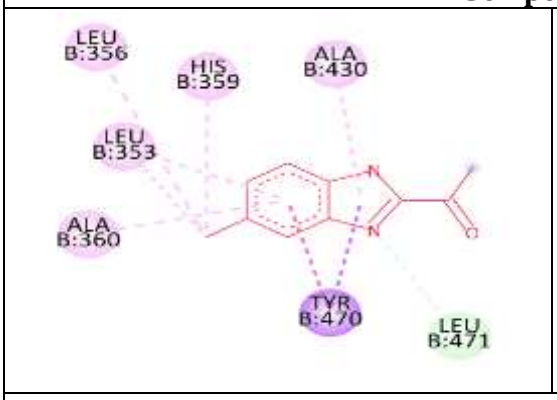
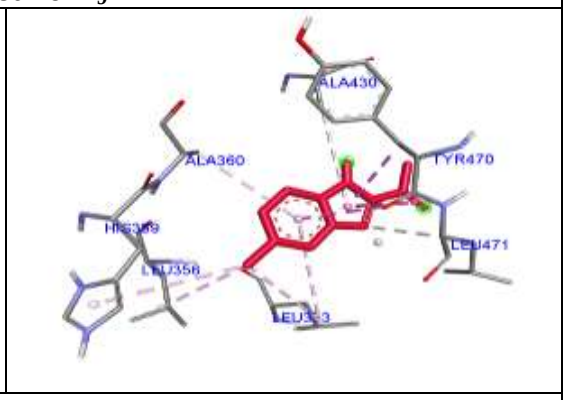
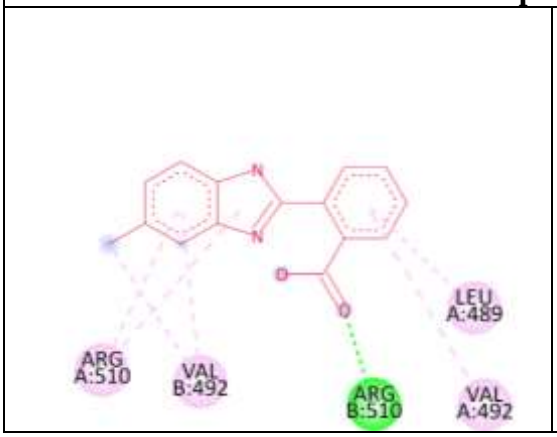
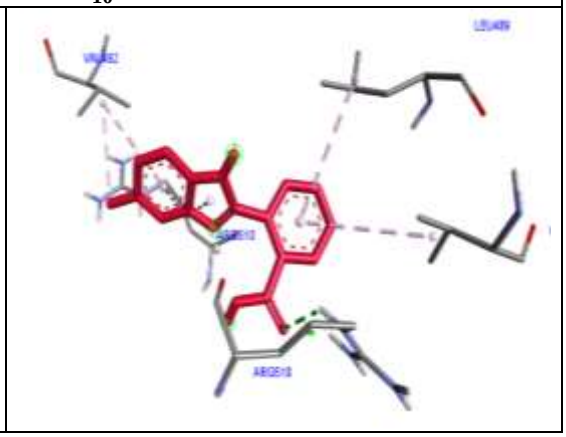




Compound A_{10}





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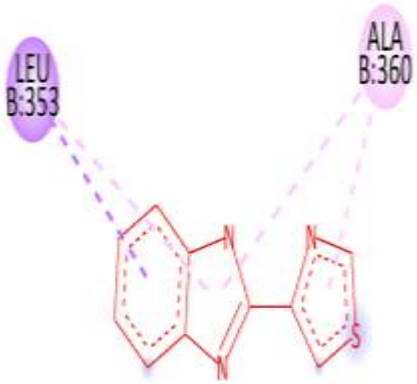	
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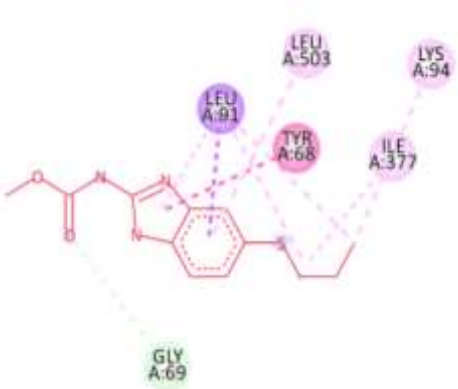	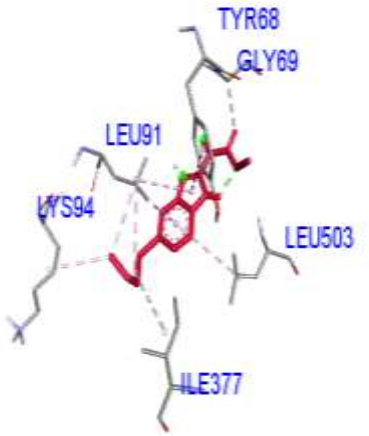

The docked ligands' 2D and 3D docking positions with the protein (PDB ID:6CR2) are shown in **Table** 5**.** The names of the amino acids involved in the docking are included in the 2D and 3D postures.

Table 6: Active amino acid, bond length, bond type and bond category involved in the interaction of the designed Substituted Benzimidazole derivatives interaction with Protein.

Active Amino Acid	Bond Length	Bond Type	Bond category
Compound A_1			
TYR350	5.31526	Hydrophobic	Pi-Pi T-shaped
TYR470	4.18579	Hydrophobic	Amide-Pi Stacked
LEU353	4.47997	Hydrophobic	Pi-Alkyl
LEU356	4.18567	Hydrophobic	Pi-Alkyl
HIS359	5.00286	Hydrophobic	Pi-Alkyl
LEU353	5.13022	Hydrophobic	Pi-Alkyl

ALA360	4.78066	Hydrophobic	Pi-Alkyl
LEU471	5.42166	Hydrophobic	Pi-Alkyl
Compound A_2			
TYR122	2.74443	Hydrogen Bond	Conventional Hydrogen Bond
ILE376	3.79152	Hydrophobic	Pi-Sigma
TYR122	3.65818	Hydrophobic	Pi-Pi Stacked
LEU109	5.27951	Hydrophobic	Alkyl
ILE376	4.53598	Hydrophobic	Alkyl
LEU125	4.25245	Hydrophobic	Alkyl
TYR122	4.91576	Hydrophobic	Pi-Alkyl
ILE73	5.05234	Hydrophobic	Pi-Alkyl
ILE76	4.64634	Hydrophobic	Pi-Alkyl
Compound A_3			
ARG378	1.89566	Hydrogen Bond	Conventional Hydrogen Bond
ARG378	2.58433	Hydrogen Bond	Conventional Hydrogen Bond
ILE376	3.51938	Hydrophobic	Pi-Sigma
TYR122	4.50974	Hydrophobic	Pi-Pi Stacked
ILE73	5.05796	Hydrophobic	Pi-Alkyl
ILE376	5.34035	Hydrophobic	Pi-Alkyl
Compound A_4			
TYR350	4.39911	Hydrophobic	Pi-Pi T-shaped
TYR470	4.11645	Hydrophobic	Amide-Pi Stacked
TYR470	5.17544	Hydrophobic	Amide-Pi Stacked
LEU352	3.81899	Hydrophobic	Alkyl
LEU356	4.73688	Hydrophobic	Alkyl
HIS359	2.02679	Hydrophobic	Pi-Alkyl
LEU353	3.86791	Hydrophobic	Pi-Alkyl
ALA360	5.06509	Hydrophobic	Pi-Alkyl
Compound A_5			
TYR350	4.07705	Hydrophobic	Amide-Pi Stacked
TYR470	4.19222	Hydrophobic	Alkyl
LEU353	4.46781	Hydrophobic	Alkyl
LEU359	4.66785	Hydrophobic	Amide-Pi Stacked
LEU353	4.7446	Hydrophobic	Pi-Alkyl
ALA360	4.99835	Hydrophobic	Pi-Alkyl
ALA430	5.16938	Hydrophobic	Pi-Alkyl
LEU471	5.4111	Hydrophobic	Pi-Pi T-shaped
Compound A_6			
GLN467	2.12525	Hydrogen Bond	Conventional Hydrogen Bond
TYR470	3.70991	Hydrophobic	Amide-Pi Stacked
LEU353	4.44401	Hydrophobic	Amide-Pi Stacked
LEU356	4.25681	Hydrophobic	Alkyl
HIS359	5.17514	Hydrophobic	Pi-Alkyl
LEU353	5.48734	Hydrophobic	Pi-Alkyl

ALA360	4.96293	Hydrophobic	Pi-Alkyl
LEU471	5.30563	Hydrophobic	Pi-Alkyl
Compound A_7			
LEU356	2.21655	Hydrogen Bond	Conventional Hydrogen Bond
GLY474	3.61854	Hydrogen Bond	Carbon Hydrogen Bond
TYR470	4.42808	Hydrophobic	Amide-Pi Stacked
LEU159	5.16803	Hydrophobic	Alkyl
LEU471	4.42786	Hydrophobic	Alkyl
TYR350	5.33768	Hydrophobic	Pi-Alkyl
LEU353	4.79978	Hydrophobic	Pi-Alkyl
LEU471	4.90088	Hydrophobic	Pi-Alkyl
Compound A_8			
TYR350	5.23538	Hydrogen Bond	Pi-Pi T- shaped
TYR470	4.68619	Other	Amide-Pi Stacked
TYR470	4.18459	Hydrophobic	Amide-Pi Stacked
LEU353	4.51572	Hydrophobic	Alkyl
LEU356	4.17529	Hydrophobic	Alkyl
HIS359	4.96072	Hydrophobic	Pi-Alkyl
LEU353	5.12617	Hydrophobic	Pi-Alkyl
ALA360	5.47172	Hydrophobic	Pi-Alkyl
LEU471	5.34264	Hydrophobic	Pi-Alkyl
Compound A_9			
LEU471	3.57734	Hydrogen Bond	Carbon Hydrogen Bond
TYR470	3.71483	Hydrophobic	Amide-Pi Stacked
LEU353	4.29874	Hydrophobic	Alkyl
LEU356	4.53274	Hydrophobic	Amide-Pi Stacked
HIS359	4.84378	Hydrophobic	Pi-Alkyl
LEU353	5.18579	Hydrophobic	Pi-Alkyl
ALA360	5.25459	Hydrophobic	Pi-Alkyl
ALA430	5.48527	Hydrophobic	Pi-Alkyl
Compound A_{10}			
ARG510	2.4436	Hydrogen Bond	Conventional Hydrogen Bond
VAL492	3.77815	Hydrophobic	Alkyl
ARG510	5.20427	Hydrophobic	Pi-Alkyl
VAL492	4.74807	Hydrophobic	Pi-Alkyl
LEU489	5.03335	Hydrophobic	Pi-Alkyl
Native Ligand Thiabendazole			
LEU353	3.72454	Hydrophobic	Pi-Sigma
LEU353	5.3969	Hydrophobic	Pi-Alkyl
ALA360	4.70117	Hydrophobic	Pi-Alkyl
ALA360	3.76855	Hydrophobic	Pi-Alkyl
Native Ligand Albendazole			
GLY69	3.54475	Hydrogen Bond	Carbon Hydrogen Bond
LEU91	3.99216	Hydrophobic	Pi-Sigma
TYR68	5.64881	Hydrophobic	Pi-Pi T- shaped

ILE377	4.84791	Hydrophobic	Alkyl
LYS94	4.14863	Hydrophobic	Alkyl
LEU91	5.02637	Hydrophobic	Pi-Alkyl
LEU503	5.40036	Hydrophobic	Pi-Alkyl

Among these, **Table 6**. The amino acid interactions that occur during molecular docking. how long the bond is between the amino acids. The type and category of bonds that interact with proteins have been designed.

6.0 CONCLUSION

Using molecular docking, druglikeness, and in silico ADME, we have created substituted benzimidazole compounds with antibacterial activity.

The antibacterial activity of substituted benzimidazole derivatives was thoroughly reviewed in the literature. They designed the derivatives of substituted benzimidazoles. Molecular docking was performed on each of the designed molecules. Ten different substituted benzimidazole derivatives were created, and it was found through druglikeness and in silico ADME that none of them broke Lipinski's rule of five. All of the derivatives have characteristics of drugs.

All of the created compounds are compared to the typical medication's binding affinity, Thiabendazole. For every created chemical, molecular docking is done, and the protein is obtained from the protein database. For their antibacterial properties, all of the proposed compounds interacted with proteins. Each of the compounds has strong antibacterial action and a high affinity for binding proteins.

A LIST OF ABBREVIATIONS

ADME = Absorption, Distribution, Metabolism, Excretion

PDB = Protein Data Bank

AMR= Antimicrobial resistance

NROTB= Number of rotatable bonds

HBD= Hydrogen Bond Donors

HBA= Hydrogen Bond Acceptor

TPSA= Topological polar surface area

3D= Three Dimensional

BBB= Blood–brain barrier

2D= Two Dimensional

Da= Dalton

MW= Molecular weight

PPB= Plasma Protein Binding

kcal/mol= Kilocalorie per mole

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