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Research Article

In Silico Design And ADME Study Of Novel Benzimidazole Containing Derivatives As Anthelmintic Agents

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ABSTRACT

Benzimidazole derivative are very useful intermediates or subunits of the development of pharmaceutical or biological interest. Benzimidazole derivative are an important class of bioactive molecules in the field of drugs and pharmaceuticals. It is worth noting that most of the different chemical derivatives of benzimidazole play an effective and critical role in the medical field as a distinct treatment for many different diseases, for example anti-all types of infections. Albendazole is an anthelmintic that was recommended by the WHO to treat soil transmitted helminth infections. ABZ shows a broad spectrum of activity in domestic animals and was subsequently licensed for human use in 1982.Because of its effectiveness, safety and low price, ABZ is one of the main drugs used in PC programs. The excellent safety record of ABZ is related to its mechanism of action, which involves selective binding to □tubulin and disruption of microtubule polymerization. Computer models are suitable substitutes for experimentation in such cases. The ten compounds were virtually screened with the protein target (PDB Code: 7ERI) to find potential lead candidates based on docking scores and residual interactions using molecular docking experiments. Lastly, the compounds' physicochemical characteristics were created in order to investigate their drug-likeness and pharmacokinetic profiles.

INTRODUCTION

Benzimidazole derivative are very useful intermediates or subunits of the development of pharmaceutical or biological interest [1,2]. Benzimidazole derivative are an important class of bioactive molecules in the field of drugs and pharmaceuticals [1,3].. It is worth noting that most of the different chemical derivatives of benzimidazole play an effective and critical role in the medical field as a distinct treatment for many

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different diseases, for example anti-all types of infections[4,5].Albendazole is an anthelmintic that was recommended by the WHO to treat soil transmitted helminth infections[6,7].ABZ shows a broadspectrum of activity in domestic animals and was subsequently licensed for human use in 1982.[6,8] Because of its effectiveness, safety andlow price, ABZ is one of the main drugs used in PC programs.[6,9]. The excellent safety record of ABZ is related to its mechanism of action, which involves selective binding to tubulin and disruption of microtubule polymerization.[10] However, to the best of our knowledge, the exact manner how ABZ binds 4 tubulin is unclear.[11] Nevertheless, there are several drawbacks associated with its use, such as poor drug absorption and the lack of water solubility.[12] In recent years, there has been an upsurge in microbial infections, notably nosocomial infections, which has led to the widespread use of anti-pathogen medications. Moreover, a number of illnesses acquired widespread antibiotic resistance [13]. Computational approaches have the potential to change drug design while also speeding up drug discovery and lowering costs. Many strategies are utilised to discover novel compounds during the medication development process, which is aided and accelerated by rational drug design (RDD). One such strategy is the docking of the drug molecule with the receptor (target) [14]. At every stage of the discovery process, when the number of potential compounds is large but access to physical samples is limited, drug development and discovery include evaluating ADME (absorption, distribution, metabolism, and excretion). Computer models are suitable substitutes for experimentation in such cases. The ten compounds were virtually screened with the protein target (PDB Code: 7ERI) to find potential lead candidates based on docking scores and residual interactions using molecular docking experiments. Lastly, the compounds' physicochemical characteristics were created in order to investigate their drug-likeness and pharmacokinetic profiles [15].

2. MATERIAL AND METHODS

2.1 Preparation of Ligand and Receptor (Protein)

The Chemdraw 12 Software was employed to create the ligand. For docking, the Protein Data Bank (PDB)'s beginning three-dimensional (3D) structure with ID: 7ERI (www.rcsb.org/pdb) was used. After the ligand and receptor production, alterations to the molecules were made, such as the removal of the water molecule, the insertion of polar hydrogen, and the addition of collaman charges. After the simulation was finished, it was turned into a pdbqt file for more research.

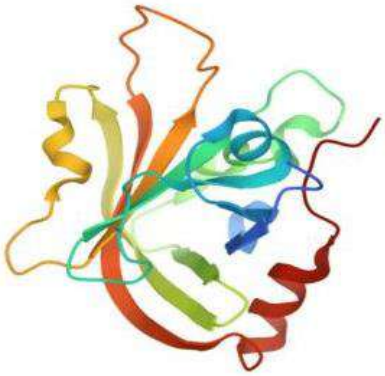


Fig.1 3D Structure of Prepared Protein(PDB:7ERI)

2.2 Determination of the Data of ADME and Lipinski Rule

The chosen medications were checked against the SwissADME online database (http://www.swissadme.ch) prior to the molecular docking investigation. For assessing how well they satisfied the Lipinski criterion. These were chosen for a molecular docking investigation after fully satisfying the Lipinski criteria. Additionally, the online databases made SAR (http://lmmd.ecust.edu.cn/admetsar2) and Molinspiration (https://www.molinspiration.com/cgibin/properties) were used to complete the ADMET properties (http://www.swissadme.ch/index.php), which is the most reliable database for predicting the AMDE (absorption, distribution, metabolism, and excretion) parameter [15].

2.3 Protein Structure Prediction

The correctness of a chosen protein structure may be assessed using a Ramchandran plot. The Ramchandran plot is generated using a variety of programmes and servers, including the PDBsum server, Molprobity, and others.

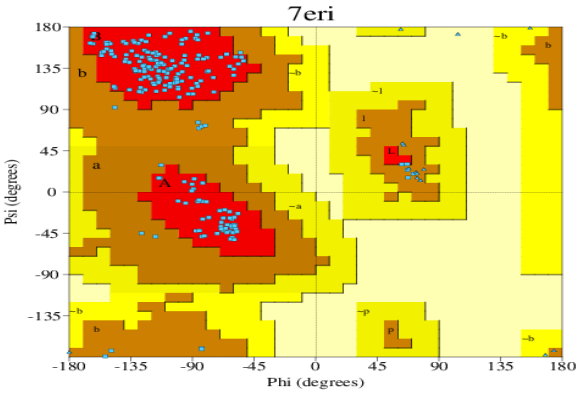


Fig no. 2 Ramchandran Plot

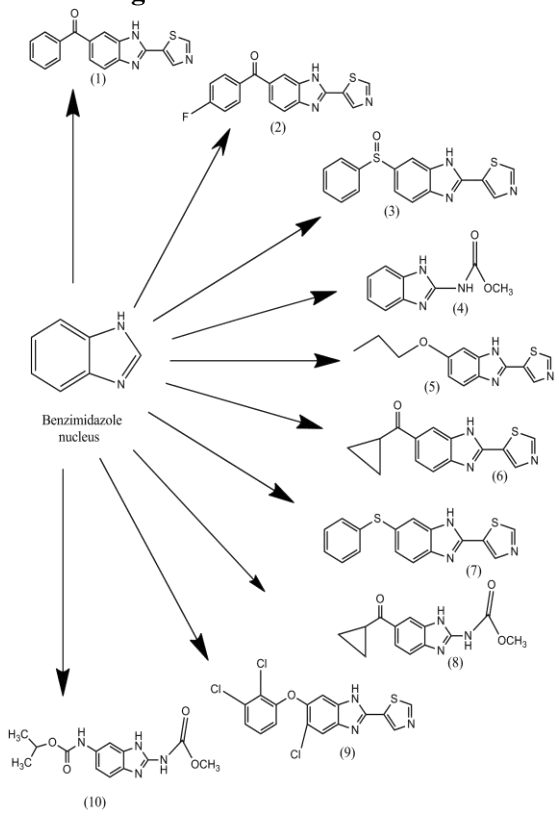


Fig. 3 Various benzimidazole Derivatives (1 to 10)

4. RESULTS AND DISCUSSION

4.1 Docking evaluation

Table 3 shows the numerical figures for cavity volume, hydrophobicity, and total energy minimization. The interaction of hydrophilic and electrostatic bonds with amino acids is compared to that of drugs of reference. The protein structure was docked with all of the commonly used drugs and ligands, and the molecules with the best docking were chosen based on their MolDock 2 score, cavity volume, hydrogen bond strength, and binding affinity, as shown in Tables 3 and 4. Figures 7–9 show how the best two ligands interact with the receptor in comparison to the conventional medication [16, 17]. The amino acids around the active site, including LEU89, LEU94, HIS118, PRO164, CYS184, ASP185, TYR187, LYS189, THR190, GLY191, VAL192, GLU194, and ARG196 (Table 3), interact with the estimated active molecule, which is shown in Figs. 7 and 8.

4.2 Toxicity analysis of the selected compounds and standards

Using ADMET prediction, the chosen compounds' toxicity, total surface area, and relative polar surface area were examined. None of the chosen chemicals pose a toxicity concern. (Table 4)

4.3 ADMET drug likeness evaluation

Microbial for pharmaceuticals should, ideally, be non-toxic and have favourable ADME characteristics. The produced compounds were examined for their ADME profile using the SwissADME service, which includes metrics like drug-likeness, partition coefficient, solubility, and numerous others (Table 1). Additionally, the chosen drug's toxicity was foreseen [16]. The bioavailability radar plots (Figure 6) provided a graphical representation of the drug-likeness and demonstrated the oral accessibility of our suggested bioactive substances.

Mol.	HBD	HBA	NBR	TPSA ($Å^2$)	Log P_o/w	Log Kp ($cm\ s^{-1}$)	Lipinski rule		MW g/mol	BS
							Result	Violation		
a	2	4	23	128.90$Å^2$	2.12	- 6.13	Yes	0	328.35	0.55
b	2	3	22	92.31$Å^2$	2.60	- 5.93	Yes	0	313.37	0.56
c	2	2	21	83.08$Å^2$	3.24	- 5.50	Yes	0	317.79	0.55

d	2	2	20	83.08Å^2	2.71	- 5.73	Yes	0	283.35	0.55
e	2	3	21	83.08Å^2	2.93	- 5.77	Yes	0	301.34	0.51
f	2	2	21	83.08Å^2	2.97	- 5.56	Yes	0	297.37	0.60
g	2	2	21	83.08Å^2	3.19	- 5.50	Yes	0	317.79	0.55
h	2	2	21	83.08Å^2	2.95	- 5.56	Yes	0	297.37	0.55
i	2	5	24	83.08Å^2	3.77	- 5.52	Yes	0	351.35	0.54
j	2	4	23	128.90Å^2	2.16	- 6.13	Yes	0	328.35	0.55
ABZ (Ref drug)	2	5	24	74.57Å^2	2.24	-9.09	Yes	0	331.34	0.55

Table 1 Data of Lipinski Rule, Pharmacokinetics and drug-likeness (a-j)

Mol.	GIA	BBB	Pgp substrate	CYP1A2 inhibitor	CYP2C19 inhibitor	CYP2C9 inhibitor	CYP2D6 inhibitor	CYP3A4 inhibitor
a	High	No	Yes	No	Yes	Yes	Yes	Yes
b	High	No	No	No	Yes	Yes	Yes	Yes
c	High	No	No	No	Yes	Yes	Yes	Yes
d	High	No	No	No	Yes	Yes	Yes	Yes
e	High	No	Yes	No	Yes	Yes	Yes	Yes
f	High	No	Yes	No	Yes	Yes	Yes	Yes
g	High	No	No	No	Yes	Yes	Yes	Yes
h	High	No	No	No	Yes	Yes	Yes	Yes
i	High	No	No	No	Yes	Yes	Yes	Yes
j	High	No	Yes	No	Yes	Yes	Yes	Yes
ABZ (Ref drug)	High	No	No	No	Yes	Yes	Yes	Yes

Table 2 In Silico ADME prediction of molecules

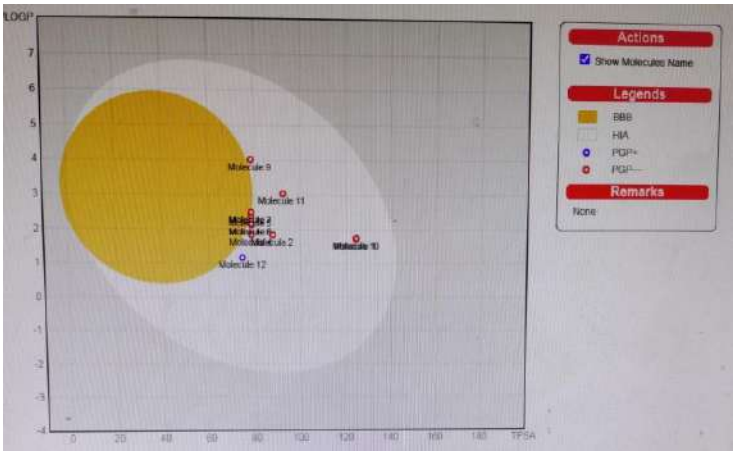
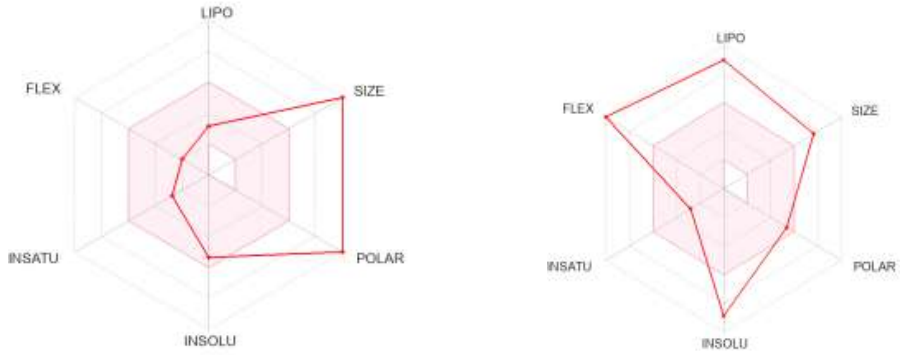


Fig no. 4 Pharmacokinetic distribution of benzimidazole analogs in a brain or intestinal estimated permeation (BOILED)-egg diagram.



A **B**

Fig no. 5 Bioavailability Radar of (A) Molecule a, and (B) Molecule i generated from SWISS ADME

Complex	Binding affinity (Kcal/mol))	Cavity volume ($Å^3$)	Hydrophobic, electrostatic and other interactions
a	**-7.7**	1500	LEU89 LEU94 HIS118 PRO164 CYS184 ASP185 ASP186 TYR187 LYS189 THR190 GLY191 VAL192 GLU194 ARG196
b	-7.0	5640	GLU80 THR124 GLY125 LYS128 MET129 LYS222 LYS223 TYR224 ASN225 GLN226 ILE227 ASN228 LEU229
c	-7.5	5640	GLU80 GLY125 LYS128 MET129 LYS222 LYS223 TYR224 ASN225 GLN226 ILE227 ASN228 LEU229
d	-7.0	5640	GLU80 GLY125 LYS128 MET129 LYS222 LYS223 TYR224 ASN225 GLN226 ILE227 ASN228 LEU229
e	-7.1	1500	LEU89 LEU94 HIS118 PRO164 THR183 CYS184 ASP185 ASP186 TYR187 LYS189 GLY191 VAL192 GLU194 ARG196
f	-7.1	1500	LEU89 LEU94 HIS118 PRO164 THR183 CYS184 ASP185 ASP186 TYR187 VAL192 TRP193 GLU194 ARG196
g	-7.0	5640	GLU80 THR124 GLY125 LYS128 MET129 LYS222 LYS223 TYR224 ASN225 GLN226 ILE227 ASN228 LEU229
h	-7.5	5640	GLU80 GLY125 LYS128 MET129 LYS222 LYS223 TYR224 ASN225 GLN226 ILE227 ASN228 LEU229
i	**-7.8**	5640	GLU80 THR124 GLY125 LYS128 MET129 LYS222 LYS223 TYR224 ASN225 GLN226 ILE227 ASN228 LEU229
j	-7.2	1500	PRO164 THR183 CYS184 ASP185 ASP186 TYR187 GLU188 LYS189 THR190 GLY191 VAL192 TRP193 GLU194 LYS195 ARG196
Albendazole (Ref.)	-7.2	1500	GLU80 GLY125 LYS128 MET129 LYS222 LYS223 TYR224 ASN225 GLN226 ILE227 ASN228

Table 3 Interactions and amino acid residues between the target protein and some designed

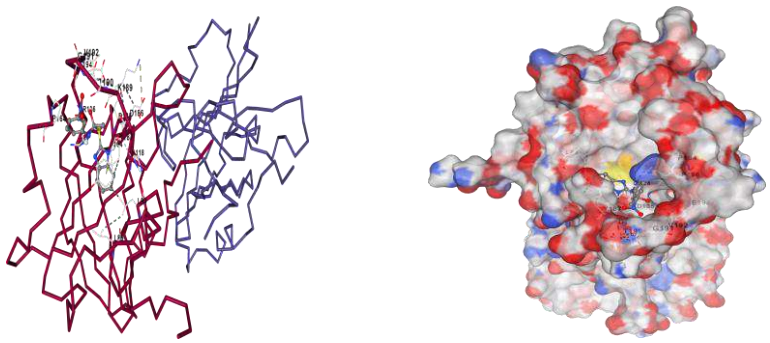


Fig no.6 2D & 3D Structure of molecule a

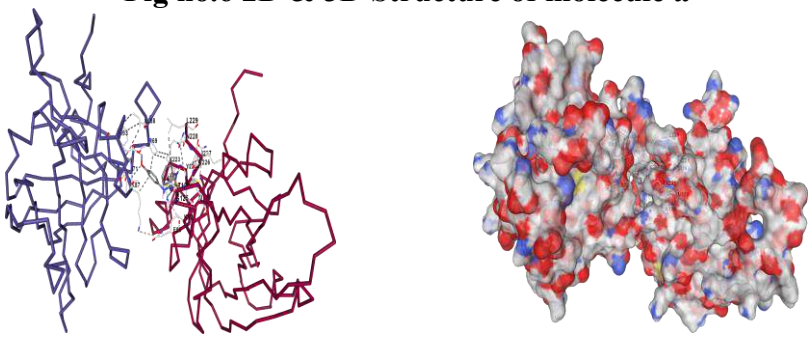


Fig no 7. 2D & 3D Structure of molecule i

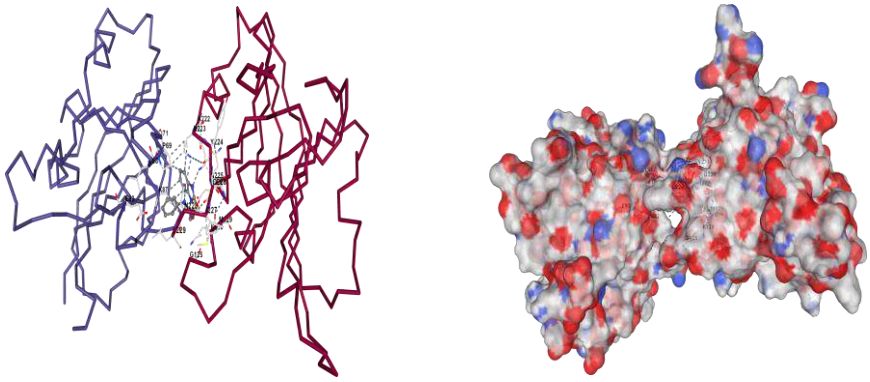


Fig. 8 2D & 3D structure of Albendazole

Some newly design compounds		
Toxicity Properties	**Molecule a**	**Molecule i**
AMES toxicity	No	No
hERG inhibitors	Yes	No
Carcinogenicity	No	No
Hepatotoxicity	No	No
Skin sensitization	No	No
Fish Toxicity	Yes	Yes

Table 4 Toxicity study of Molecule a and i

CONCLUSION

Because of the ongoing misuse of medications, the pace at which antihelmintics resistance develops among helminthes species is increasing. We created and refined several analogues, utilizing virtual screening and molecular docking studies to

find and develop novel benzimidazole derivatives, and compared them to Albendazole, the standard reference medication. We found two analogues that were strong candidates and outperformed Albendazole. In silico activity against β-tubulin polymerization. Compounds a and i were identified as the best analogues after analyzing all parameters, including ADME properties (highest binding affinity of -7.8 Kcal/mol and -7.7 Kcal/mol). To validate the efficacy of antibacterial activity demonstrated by this chemical, further manufacture and assessment of this analogue in in vitro tests is required.

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