IJPSR (2025), Volume 16, Issue 8 (Research Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 07 March 2025; received in revised form, 19 March 2025; accepted, 23 March 2025; published 01 August 2025

DESIGN, SYNTHESIS, *IN-SILICO* STUDIES AND EVALUATION OF *IN-VITRO* ANTIDIABETIC ACTIVTY OF SOME NOVEL BENZIMIDAZOLE DERIVATIVES

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Keywords:

Benzimidazole, Docking, Antidiabetic activity, α-amylase

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ABSTRACT: New Benzimidazole derivatives were designed and synthesized. To explain the activity of new derivatives, we have explored the binding affinity of the compounds against α-amylase (PDB ID: 4W93), the target enzyme for the antidiabetic activity. α-amylase is considered as primary target because it converts starch into maltose, which is followed by the production and transportation of the glucose into the blood. Docking study strongly enhanced the activity of these compounds as new discovered hits. The drug likeness score established the compounds to be pharmacokinetically active. All the reactions were monitored by TLC one spot technique, melting point analysis and the structures of the synthesized compounds were confirmed by UV, IR, proton NMR spectra. The inhibitory activity of all the derivatives against alpha amylase enzyme showed moderate activity in comparison to standard drug acarbose. Among all the derivatives, BM-1emerged with potent inhibitory activity. Compounds BM-2, BM-3 and BM-4 exhibited moderateinhibitoryactivity.BM-5was found to be the least potent derivative.

INTRODUCTION: The prevalence of diabetes is increasing globally, with a faster rise in low- and middle-income countries compared to high-income nations. Diabetes is a leading cause of serious health issues such as blindness, kidney failure, heart attacks, and strokes. This highlights the urgent need to develop new antidiabetic drugs. Benzimidazole, a heterocyclic aromatic organic compound that contains nitrogen, is one such promising structure. It consists of a fused benzene and imidazole ring, making it an important pharmacophore and a privileged structure in medicinal chemistry.

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.16(8).2259-66

This article can be accessed online on www.ijpsr.com

DOI link: https://doi.org/10.13040/IJPSR.0975-8232.16(8).2259-66

Benzimidazole has shown a range of therapeutic activities, including antiulcer, antihypertensive, analgesic, antiviral, antifungal, anticancer, and antihistaminic effects. Diabetes is a major and increasingly widespread global health issue, currently impacting over 400 million people worldwide. This figure represents a dramatic rise from just 30 million in 1985. By 2040, the global prevalence is expected to rise even further, with an estimated 640 million people affected, which means that 10% of all adults will be living with diabetes.

Alpha amylase is a key enzyme involved in breaking down starch into maltose, which is further converted into glucose. By inhibiting this enzyme, glucose production can be reduced without disrupting other bodily processes. As a result, alpha amylase has been chosen as a target for developing anti-diabetic drugs [1]. Computer docking techniques are crucial in drug design and discovery, as well as

in studying the mechanisms of drug action. This technique involves placing a molecule into the binding site of a target macromolecule in a non-covalent manner. It helps predict the binding geometry, the hydrogen bonds formed with surrounding amino acids, and the overall interaction between the ligand and receptor. These factors together contribute to the docking score, which indicates how well the molecule binds to the target. Building on these insights, the goal of this study was to design and develop new anti-diabetic agents using computational methods. The primary focus was to identify and synthesize benzimidazole compounds as potential anti-diabetic drugs. One effective approach to managing diabetes is by inhibiting the activity of the α-amylase enzyme, which plays a crucial role in converting starch into maltose and producing glucose. As a result, α-amylase was chosen as the drug target for this study. The research aims to evaluate the ability of the synthesized benzimidazole derivatives to inhibit α-amylase, a key enzyme involved in carbohydrate breakdown [2-4].

MATERIAL AND METHODS:

Chemistry: All solvents and reagents used in the study were of analytical grade. The purity of the target compounds was checked using thin layer chromatography (TLC) on glass plates coated with silica gel 60 F254, with chloroform: methanol (9:1) as the mobile phase. UV light at 254 nm was employed for detection. Melting points were measured using a visual melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded using a FT-IR PerkinElmer spectrophotometer, and proton NMR spectra were obtained on a Bruker spectrophotometer with $CDCl_3$ as the solvent.

Synthetic Procedure:

Synthesis of Benzimidazole: Equal molar amounts (0.05 M) of o-phenylenediamine and phenoxyacetic acid were combined and dissolved in 50 ml of 4N HCl. The reaction mixture was then refluxed for 4 hours using a heating mantle. After cooling to room temperature, the mixture was slowly poured into 400 ml of ice-cold water while stirring continuously. Ammonia (NH_3) solution was added drop wise to neutralize the mixture. The resulting precipitate was filtered, washed, and dried. It was then recrystallized from ethanol, and the progress of the reaction was monitored using thin layer chromatography.

Synthesis of Mannich Bases of Benzimidazole: Equal molar amounts (10 mmol) of benzimidazole, formaldehyde (HCHO), and secondary amines, along with 4-5 drops of concentrated hydrochloric acid, were dissolved in DMF. The reaction mixture was stirred at room temperature for 1 hour and then refluxed for 3 hours. After cooling, the resulting precipitate was filtered, washed, and dried. It was recrystallized from ethanol, and the reaction completion was monitored using thin layer chromatography.

BM – 11 - [(4-methylpiperazin – 1 - yl) methyl] - 2- (phenoxymethyl) - 1*H* - benzimidazole: C20H25N4O, M. W.336.44, M. P(^{0}C):161-169, 79.62%, R_f:0.77, λ_{max}:274,IR (KBr cm^{-1}): C-H stretch – 3741.90, C-N stretch – 1311.59, C= N stretch-1589.34, -CH_3stretch- 2769.78, C-O-C stretch – 1072.42, C=C stretch – 1489.05, NMR (δ ppm)- 5.38 (d, 2H, CH_2), 6.95-7.64 (m, 17H, Ar-H)

BM-22-(phenoxy methyl)-1-(pyrrolidin-1-yl)-1*H*-benzimidazole: C19H22N4O, M. W.307.40, M. P(^{0}C):185-190, 86.21%, R_f:0.98, λ_{max}:272,IR (KBr cm^{-1}): C-N stretch – 1384.26, C= N stretch-1493.98, C-O-C stretch – 1072.42, C=C stretch – 1489.05, NMR (δ ppm) - 4.39 (d, 2H, CH_2), 7.25-7.84 (m, 17H, Ar-H).

BM-31-[2-(phenoxy methyl)-1*H*-benzimidazol-1-yl]pyrrolidin-2-one: C19H20N3O2, M. W.321.38, M. P(^{0}C):174-179, 68.20%, R_f:0.92, λ_{max}:254,IR (KBr cm^{-1}): C-N stretch -1218.61 C= N stretch- 1389.04, C-O-C stretch-1091.71 C=C stretch – 1413.45 C=O stretch -1678.24NMR (δ ppm) - 4.65 (d, 2H, CH_2), 7.25-7.84 (m, 15H, Ar-H).

BM-41-[(morpholin-4-yl) methyl] – 2 - (phenoxy methyl)-1*H*-benzimidazole: C19H21N3O2, M. W.323.40, M. P(^{0}C):191-198, 71.59%, R_f:1, , λ_{max}:272, IR (KBr cm^{-1}): C-N stretch -1346.91 C= N stretch- 1298.02, C-O-C stretch-1043.51 C=C stretch – 1473.45 C=O stretch -1636.54NMR (δ ppm) - 4.92 (d, 2H, CH_2), 7.75-8.53 (m, 17H, Ar-H).

BM-5*N*, *N*-dimethyl-1-[2-(phenoxymethyl)-1*H*-benzimidazol-1-yl]methanamine: $C_{17}H_{20}N_3O$, M.

W.281.36, M. P(^{0}C):164-170, 61.94%, R_f:0.86, IR (KBr cm^{-1}): 257,IR (KBr cm^{-1}): C-N stretch - 1357.89 C= N stretch- 1589.34, -CH_3 stretch-3417.86, C-O-C stretch - 1080.14 C=C stretch – 1489.05NMR (δ ppm) - 4.17 (d, 2H, CH_2), 7.75-8.77 (m, 9H, Ar-H).

***In-silico* Studies:**

Selection of Target: The α-amylase enzyme (PDB ID: 4W93) facilitates the conversion of starch into maltose, which is subsequently converted into glucose and transported into the bloodstream. The PDB file of the enzyme, serving as the receptor, was obtained from the RCSB Protein Data Bank (PDB code 4W93) and utilized as a rigid molecule in the study.

Selection of Lead: Virtual screening was performed using iGEMDOCK v.2, where benzimidazole was identified as the lead compound from a library of fifteen potential α-amylase **(**PDB ID: 4W93) enzyme inhibitors. The small molecule library was sourced from the ZINC database.

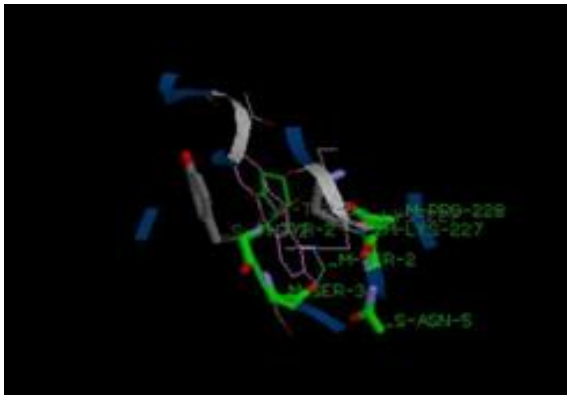


FIG. 1: BINDING OF LIGANDS

The virtual screening results indicated that the benzimidazole scaffold could serve as a promising inhibitor of α-amylase (PDB ID: 4W93). Among the 15 α-amylase inhibitors screened, benzimidazole emerged as the lead compound, with its binding interactions shown in **Fig. 1.**

Lead Optimization: Lead optimization was carried out using the Molinspiration server to enhance the ligands' oral bioavailability. The optimization aimed to improve both the efficacy and safety of the compounds. The study results showed that all 8 derivatives had favorable drug-likeness scores. The compounds were further evaluated using Lipinski's Rule of Five, and it was found that none of the compounds violated the rules, indicating good potential for oral absorption.

Docking: In this study, we utilized the AutoDock 4.2 software package to assess the binding affinity of the synthesized compounds to the binding pocket of the 4W93 enzyme. The enzyme's PDB file (PDB code: 4W93) was obtained from the RCSB Protein Data Bank and used as a rigid receptor molecule.

Docking studies are computational methods used to explore the potential binding modes of a ligand to a specific receptor, enzyme, or binding site. Here, AutoDock 4.2 was employed to evaluate the binding energy of the ligands within the known 3D structure of the target enzyme. The most optimal docked structures should exhibit binding energies lower than the standard. The binding sites and active sites are shown in the snapshots, and the binding energy of the compounds was found to be roughly similar when compared to the standardand shown in **Fig. 2-6.**

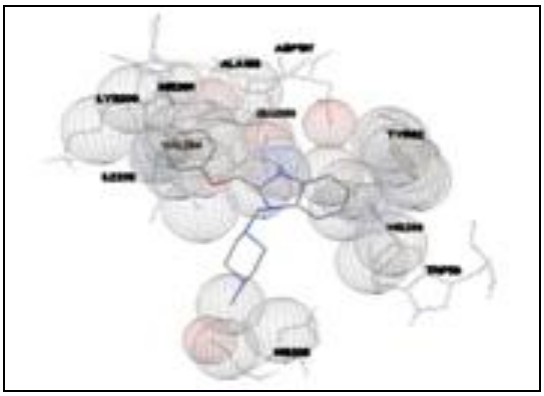


FIG. 2: BINDING INTERACTION OF BM-1 WITH ALPHA AMYLASE ENZYME

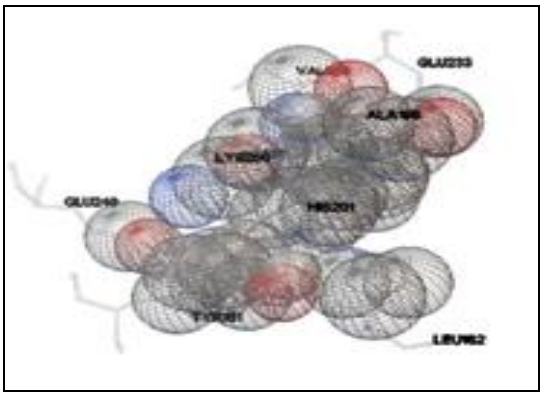


FIG. 3: BINDING INTERACTION OF BM-1 WITH ALPHA AMYLASE ENZYME

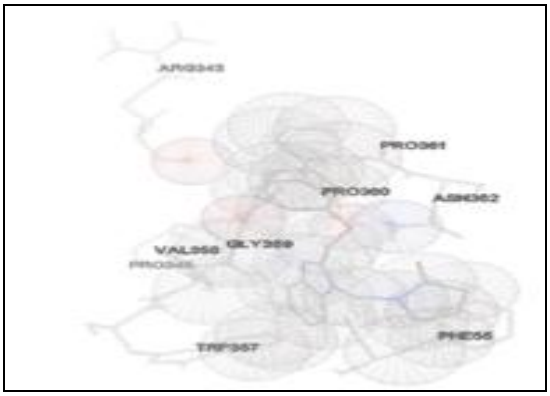


FIG. 4: BINDING INTERACTION OF BM-1 WITH ALPHA AMYLASE ENZYME

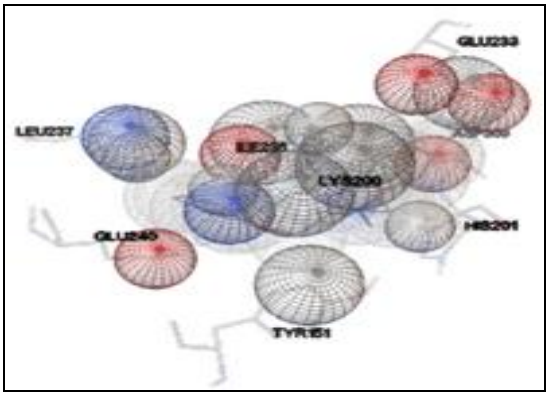


FIG. 5: BINDING INTERACTION OF BM-1 WITH ALPHA AMYLASE ENZYME

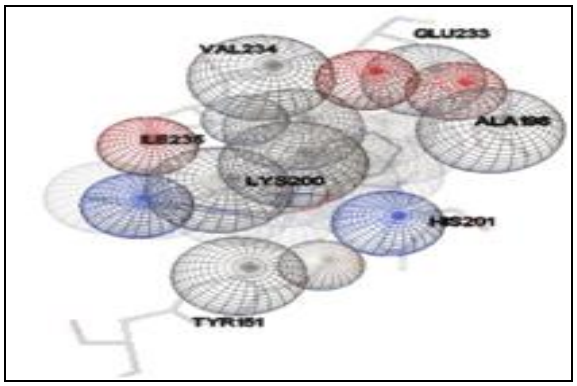


FIG. 6: BINDING INTERACTION OF BM-1 WITH ALPHA AMYLASE ENZYME

With Alpha amylase receptor, the binding energy was found to be best for 5 compounds BM-1 (-7.51Kcal/mol), BM-2(-7.11 Kcal/mol), BM-3(-7.1 Kcal/mol), BM-4(-7.27 Kcal/mol), BM-5(-6.65 Kcal/mol), Acarbose (-5.09 kcal/mol) and were interacting well with the key residues TYR 304, GLU 438, LEU 484.

***In-vitro* Anti-diabetic Studies:**

Preparation of Phosphate Buffer: Phosphate buffier (20 mM) of pH 6.9 (prepared with sodium phosphate monobasic and sodium chloride).

Preparation of Starch Solution: Starch solution (1.0%) prepared with phosphate buffer by boiling.

Preparation of Coloring Reagents: The coloring reagent is prepared by gradually adding a sodium potassium tartrate solution (made by dissolving 12 g of solid in 8 ml of 2M sodium hydroxide) to 20 ml of a 96 mM 3,5-dinitrosalicylic acid solution (prepared in distilled water). The mixture is then diluted to a final volume of 40 ml with distilled water [5-7].

Preparation of Enzyme Solution: Enzyme solution, alpha amylase (0.5 mg/ml) prepared with phosphate buffer pH 6.9.

Procedure: Different concentrations (10-320 µg/ml) of benzimidazole derivatives were prepared from a 1 mg/ml stock solution by adding a few drops of ethanol and adjusting the volume with water. To the prepared solution, 1 ml of alpha-amylase was added and incubated for 10 minutes at room temperature. Then, 1 ml of 1.0% starch solution was added and incubated for an additional 10 minutes. Following this, 1 ml of the coloring reagent was added to the reaction mixture, which was then heated in a boiling water bath for 15 minutes. After cooling, 10 ml of distilled water was added to dilute the mixture. A blank was prepared for each concentration of the test sample by replacing the enzyme solution with buffer. Control incubations representing 100% enzyme activity were prepared by substituting the test drug with water. The absorbance of the colored solutions was measured at 540 nm. The inhibition of alpha-amylase was expressed as a percentage of inhibition, and the IC_{50} values were determined by linear regression plots, correlating the varying concentrations of the synthesized benzimidazole derivatives to the percentage of inhibition [8-10].

Percentage inhibition = (C-T / C × 100)

All analyses were performed in triplicate, and the results were expressed as mean ± SD. The inhibitory activity of all the benzimidazole derivatives against the alpha-amylase enzyme showed moderate activity when compared to the standard drug, acarbose. Among the derivatives, BM-1 demonstrated the most potent inhibitory activity. Compounds BM-2, BM-3, and BM-4 showed moderate inhibitory effects, while BM-5 was found to be the least potent. The dose-response curve is shown in **Fig. 7.**

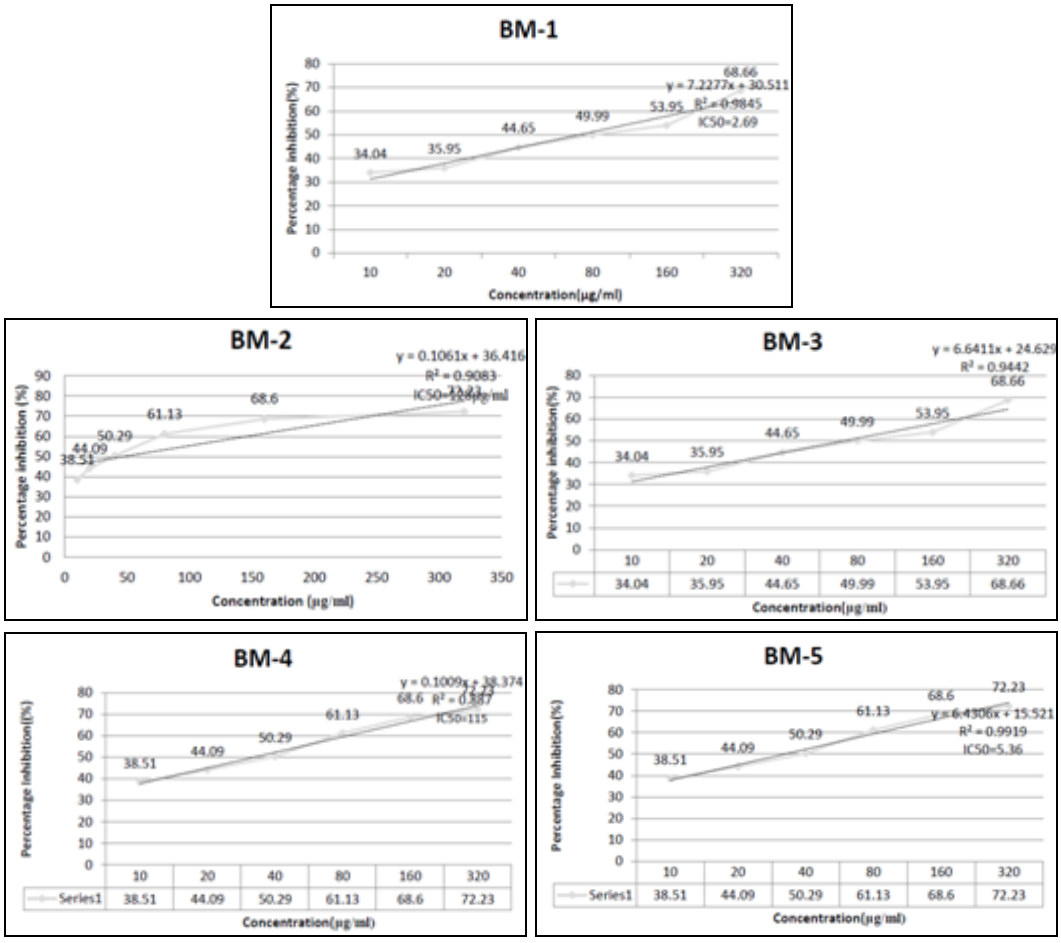


FIG. 7: DOSE – RESPONSE CURVE

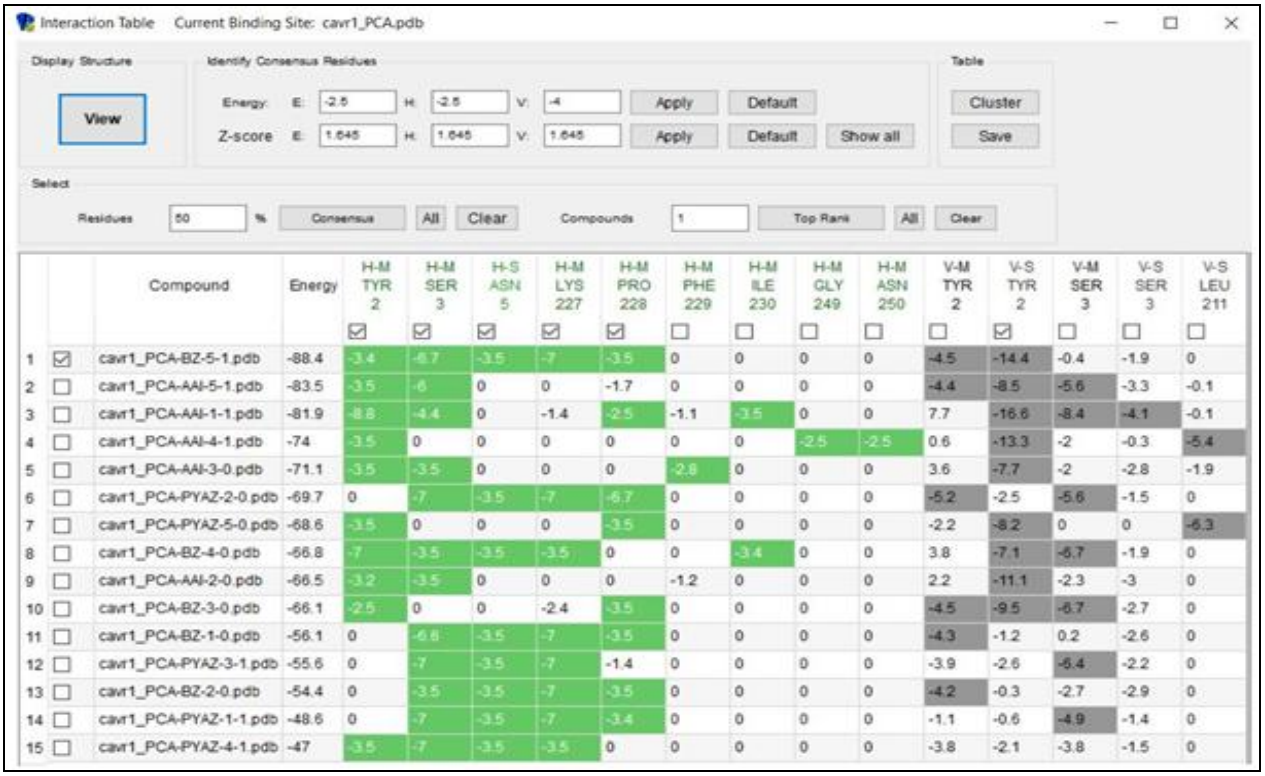
RESULTS AND DISCUSSION: To understand the promising antimicrobial activity of benzimidazole derivatives, molecular docking was performed by placing the discovered compounds within the binding pocket of α-amylase (PDB ID: 4W93), which was selected as the target from the RCSB Protein Data Bank. Virtual screening was conducted using iGEMDOCK v.2, and the results highlighted the benzimidazole scaffold as a promising inhibitor. Among the compounds screened, benzimidazole was identified as the lead compound. Fitness value is tabulated in **Table 1** and the interaction profile of the compounds are tabulated in **Table 2**. Lead optimization was carried out using the Molinspiration server to improve the ligands' oral bioavailability. The results showed that all eight derivatives had favorable drug-likeness scores, which are summarized in **Table 3**. The designed compounds were evaluated using Lipinski's Rule of Five, and it was found that none of the compounds violated the rules, indicating good potential for oral absorption. The binding energy of the ligands within the known 3D structure of the target enzyme was assessed using AutoDock 4.2.

The binding energies for the top five compounds were as follows: BM-1 (-7.51 Kcal/mol), BM-2 (-7.11 Kcal/mol), BM-3 (-7.1 Kcal/mol), BM-4 (-7.27 Kcal/mol), and BM-5 (-6.65 Kcal/mol), while Acarbose had a binding energy of -5.09 Kcal/mol. These compounds interacted effectively with key residues such as TYR 304, GLU 438, and LEU 484.

TABLE 1: FITNESS VALUE OF DOCKED COMPOUNDS

S. no.	Compound code	Fitness value
1.	BZ-1	-57.44
2.	BZ-2	-59.65
3.	BZ-3	-82.41
4.	BZ-4	-83.72
5.	BZ-5	-92.58
6.	AH-1	-81.92
7.	AH -2	-66.46
8.	AH -3	-71.00
9.	AH -4	-73.96
10.	AH -5	-83.53
11.	PYZ-1	-58.39
12.	PYZ-2	-68.29
13.	PYZ-3	-66.42
14.	PYZ-4	-67.96
15.	PYZ-5	-77.13

TABLE 2: INTERACTION TABLE OF DOCKED COMPOUNDS



		Compound	Energy	H-M TYR 2	H-M SER 3	H-S ASN 5	H-M LYS 227	H-M PRO 228	H-M PHE 229	H-M ILE 230	H-M GLY 249	H-M ASN 250	V-M TYR 2	V-S TYR 2	V-M SER 3	V-S SER 3	V-S LEU 211
1	☑	cavr1_PCA-BZ-5-1.pdb	-88.4	-3.4	-6.7	-3.5	-7	-3.5	0	0	0	0	-4.5	-14.4	-0.4	-1.9	0
2	☐	cavr1_PCA-AAI-5-1.pdb	-83.5	-3.5	-6	0	0	-1.7	0	0	0	0	-4.4	-8.5	-5.6	-3.3	-0.1
3	☐	cavr1_PCA-AAI-1-1.pdb	-81.9	-8.8	-4.4	0	-1.4	-2.5	-1.1	-3.5	0	0	7.7	-16.6	-8.4	-4.1	-0.1
4	☐	cavr1_PCA-AAI-4-1.pdb	-74	-3.5	0	0	0	0	0	0	-2.5	-2.5	0.6	-13.3	-2	-0.3	-5.4
5	☐	cavr1_PCA-AAI-3-0.pdb	-71.1	-3.5	-3.5	0	0	0	-2.9	0	0	0	3.6	-7.7	-2	-2.8	-1.9
6	☐	cavr1_PCA-PYAZ-2-0.pdb	-69.7	0	-7	-3.5	-7	-6.7	0	0	0	0	-5.2	-2.5	-5.6	-1.5	0
7	☐	cavr1_PCA-PYAZ-5-0.pdb	-68.6	-3.5	0	0	0	-3.5	0	0	0	0	-2.2	-8.2	0	0	-6.3
8	☐	cavr1_PCA-BZ-4-0.pdb	-66.8	-7	-3.5	-3.5	-3.5	0	0	-3.4	0	0	3.8	-7.1	-6.7	-1.9	0
9	☐	cavr1_PCA-AAI-2-0.pdb	-66.5	-3.2	-3.5	0	0	0	-1.2	0	0	0	2.2	-11.1	-2.3	-3	0
10	☐	cavr1_PCA-BZ-3-0.pdb	-66.1	-2.5	0	0	-2.4	-3.5	0	0	0	0	-4.5	-9.5	-6.7	-2.7	0
11	☐	cavr1_PCA-BZ-1-0.pdb	-56.1	0	-6.8	-3.5	-7	-3.5	0	0	0	0	-4.3	-1.2	0.2	-2.6	0
12	☐	cavr1_PCA-PYAZ-3-1.pdb	-55.6	0	-7	-3.5	-7	-1.4	0	0	0	0	-3.9	-2.6	-6.4	-2.2	0
13	☐	cavr1_PCA-BZ-2-0.pdb	-54.4	0	-3.5	-3.5	-7	-3.5	0	0	0	0	-4.2	-0.3	-2.7	-2.9	0
14	☐	cavr1_PCA-PYAZ-1-1.pdb	-48.6	0	-7	-3.5	-7	-3.4	0	0	0	0	-1.1	-0.6	-4.9	-1.4	0
15	☐	cavr1_PCA-PYAZ-4-1.pdb	-47	-3.5	-7	-3.5	-3.5	0	0	0	0	0	-3.8	-2.1	-3.8	-1.5	0

TABLE 3: DRUG LIKENESS SCORE

S. no	Compound Code	Log P	TPSA	No. of atoms	Molecular weight	No. of ON	No. of OHNH	No. of violations	No. of rotational bonds
1.	BM-1	3.16	33.54	25	336.44	5	0	0	5
2.	BM-2	3.67	30.30	23	307.40	4	0	0	5
3.	BM-3	3.0	47.37	24	321.38	5	0	0	5
4.	BM-4	3.12	39.53	24	323.40	5	0	0	5
5.	BM-5	3.27	30.30	21	281.36	4	0	0	5
6.	BM-6	5.85	27.74	30	399.54	4	1	1	6
7.	BM-7	4.14	27.74	23	311.43	4	1	0	7
8.	BM-8	4.29	27.74	24	323.44	4	1	0	5

The details of interacting amino acids with lead molecules is tabulated in **Table 4**. Physico-chemical parameters of the synthesized compounds are tabulated in **Table 5**, solubility parameters in **Table 6,** anti-diabetic activity data in **Table 7** and list of compounds synthesized in **Table 8.**

TABLE 4: INTERACTION OF COMPOUNDS WITH AMINO ACIDS

S. no.	Compound code	Binding energy Kcal/mol	Interacting amino acids
1.	BM-1	-7.51	ALA 106, ASP 107, GLU 233, HIS 201, ILE 235, LYS 206, TRP 58, TYR 62, VAL 204
2.	BM-2	-7.11	ALA 193, GLU 233, GLU 240, GLU 23, HIS 201, LEU 162, TYR 131, VAL 132
3.	BM-3	-7.10	ARG 343, ASN 362, GLY 359, PHE 55, TRP 357, VAL 358
4.	BM-4	-7.27	ASP 300, GLU 233, GLU 240, HIS 201, ILE 235, LEU 237, LYS 200, TYR 151, PRO 360, PRO 361
5.	BM-5	-6.65	ALA 198, GLU 233, HIS 201, ILE 235, LYS 200, TYR 151, VAL 234
6.	BM-6	-6.83	ALA 195, ASP 197, ASP 300, HIS 101, HIS 201, HIS 305, ILE 235, LEU 162, LYS 200, TYR 151
7.	BM-7	-6.52	GLU 240, HIS 201, ILE 235, LEU 237, LYS 200, TYR 151
8.	BM-8	-5.82	ALA 198, ASP 300, GLU 240, HIS 201, ILE 235, LYS 200, TYR 151, VAL 234
9.	ACARBOSE	-16.67	ASN273, TYR59, GLN63, GLN126, ASP212, LEU142, GLU208

TABLE 5: PHYSICO-CHEMICAL PARAMETERS OF SYNTHESIZED COMPOUNDS

S. no.	Compound code	Molecular Formula	Molecular weight (gm)	M. P(^{0}C)	% yield (w/w)
1.	BM-1	$C_{20}H_{25}N_4O$	336.44	161-169	79.62
2.	BM-2	$C_{19}H_{22}N_4O$	307.40	185-190	86.21
3.	BM-3	$C_{19}H_{20}N_3O_2$	321.38	174-179	68.20
4.	BM-4	$C_{19}H_{21}N_3O_2$	323.40	191-198	71.59
5.	BM-5	$C_{17}H_{20}N_3O$	281.36	164-170	61.94

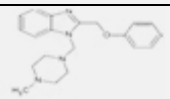
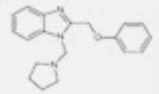
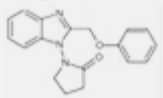
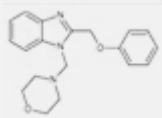
TABLE 6: SOLUBILITY PARAMETERS OF SYNTHESIZED COMPOUNDS

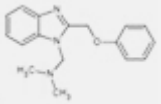
Compound code	Solvents				
	Water	Benzene	Chloroform	Ethanol	DMSO
BM-1	Insoluble	Soluble	Freely Soluble	Soluble	Freely Soluble
BM-2	Insoluble	Soluble	Freely Soluble	Soluble	Freely Soluble
BM-3	Insoluble	Soluble	Freely Soluble	Soluble	Freely Soluble
BM-4	Insoluble	Soluble	Freely Soluble	Soluble	Freely Soluble
BM-5	Insoluble	Soluble	Freely Soluble	Soluble	Freely Soluble

TABLE 7: ANTI-DIABETIC ACTIVITY DATA OF SYNTHESIZED COMPOUNDS

Compound code	10µg/ml	20µg/ml	40µg/ml	80µg/ml	160µg/ml	320µg/ml	IC_{50}
BM-1	38.51	44.09	50.29	61.13	68.60	72.23	39
BM-2	32.16	35.95	44.65	49.99	53.95	68.66	52
BM-3	34.04	38.95	44.07	52.89	53.37	71.62	62
BM-4	33.30	39.62	43.32	53.14	56.17	68.73	62
BM-5	22.46	27.93	36.24	40.19	46.12	55.04	190
Standard (Acarbose)	44.26	28.88	37.79	46.48	57.84	69.67	25

TABLE 8: LIST OF SYNTHESIZED COMPOUNDS

Compound code	Structure	IUPAC Nomenclature
BM-1		1-[(4-methylpiperazin-1-yl) methyl]-2-(phenoxymethyl)-1H-benzimidazole
BM-2		2-(phenoxy methyl)-1-(pyrolidin-1-yl)-IH-benzimidazole
BM-3		1-[2-(phenoxy methyl)-1H-benzimidazol 1-ylpyrrolidin-2-one
BM-4		1-[(morpholin-4-yl) methyl]-2-(phenoxy methyl)-1H-benzimidazole

BM-5		NN-dimethyl-1-[2-(phenoxymethyl)-1H benzimidazol-1-ylmethananine

CONCLUSION: New benzimidazole derivatives were designed and synthesized, and molecular docking studies were performed to examine their interactions with the active site of α-amylase (PDB ID: 4W93), the primary target. The computational predictions were highly consistent with experimental findings, highlighting the significance of this molecular docking study. The drug-likeness scores indicated that the compounds have favourable pharmacokinetic properties. The inhibitory activity of all the derivatives against α-amylase showed moderate activity compared to the standard drug acarbose. Among the derivatives, BM-1 exhibited the most potent inhibitory activity, while BM-2, BM-3, and BM-4 showed moderate inhibition. BM-5 was the least potent derivative. These compounds show promise as lead molecules for further development as potential anti-diabetic agents.

ACKNOWLEDGEMENT: The authors would like to express their gratitude to the Management and Principal of Sri Ramakrishna Institute of Paramedical Sciences, Coimbatore, for their continuous support throughout the duration of this work

CONFLICTS OF INTEREST: The authors have no conflicts of interest regarding this study.

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How to cite this article:
Beena KP and Akelesh T: Design, synthesis, *in-silico* studies and evaluation of *in-vitro* antidiabetic activty of some novel benzimidazole derivatives. Int J Pharm Sci & Res 2025; 16(8): 2259-66. doi: 10.13040/IJPSR.0975-8232.16(8).2259-66.