IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Human Journals
Research Article
January 2021 Vol.:20, Issue:2
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Design and Synthesis of Novel 2-Methyl Benzimidazole Bearing Thiazolidin-4-One Derivatives as Anti-Diabetic Agents

IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

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Submitted: 10 December 2020
Revised: 30 December 2020
Accepted: 20 January 2021

www.ijppr.humanjournals.com

Keywords: Benzimidazole derivatives, Molecular docking, Conventional synthesis, *In vitro* antidiabetic activity

ABSTRACT

The present work aims to design and synthesize novel 2-methyl benzimidazole bearing thiazolidin-4-one derivatives and to perform *in vitro* evaluation of their antidiabetic activity. *In silico* modeling of benzimidazole bearing thiazolidin-4-one derivatives were carried out using various software such as ACD Lab Chemsketch 12.0, Molinspiration, PASS (Prediction of activity spectra for substances), and AutoDock Vina. Ten derivatives (BT-4a, BT-4b, BT-4c, BT-4d, BT-4e, BT-4f, BT-4g, BT-4h, BT-4i, BT-4j) were designed. From the designed derivatives, five derivatives with required physicochemical properties, drug-likeness, obeying Lipinski's rule of five, and high docking score was selected for the synthesis. The synthesized derivatives were subjected to TLC, melting point determination, FTIR, ^{1}H NMR, and Mass spectroscopic studies. As per the PASS score and docking score, the derivatives were selected for *in vitro* antidiabetic evaluation by the PPARγ ELISA study. All the tested derivatives exhibited optimum activity.

INTRODUCTION

The disease burden related to diabetes is high and rising in every country. Diabetes mellitus is a chronic condition associated with an abnormally high level of glucose in the blood[1]. Several pathogenic processes are involved in the development of diabetes. There are three types of diabetes mellitus. Type 1 diabetes mellitus is a chronic autoimmune condition in which the pancreas produces little or no insulin (insulin-dependent). Type 2 diabetes mellitus is a chronic condition that affects the way the body processes blood glucose. It begins with insulin resistance and lack of insulin may also develop (insulin-independent). Type 3 diabetes mellitus or Gestational diabetes is any degree of glucose intolerance that was first recognized during pregnancy [2]. Currently available therapies for diabetes mellitus include anti-diabetic agents such as Sulfonylureas (glimepiride), Biguanides (metformin), Meglitinides (repaglinide), GLP-1 agonists (lixisenatide, liraglutide), DPP-4 inhibitors (sitagliptin, saxagliptin), Thiazolidinediones (pioglitazone), and alpha-glucosidase inhibitors (acarbose). But these drugs had various side effects such as severe joint pain and heart failure (DPP-4 inhibitors), kidney dysfunction (metformin), hypoglycemia (sulfonylureas), liver disease, and weight gain (thiazolidinediones), diarrhea, and bloating (acarbose)[3,4,5].

Peroxisome proliferator-activated receptor gamma (PPARγ) also known as the glitazone receptor regulates the genes important for cell differentiation and various metabolic processes especially lipid and glucose homeostasis. Activation of PPARγ causes insulin sensitization and enhances glucose metabolism[6,7].

Designing of new hetero derivatives are done by incorporating heterocyclic moiety into a lead molecule. The nucleus selected for the present work is the combination of two heteroaromatic molecules benzimidazole and thiazolidinedione.

Benzimidazole is one of the oldest known nitrogen-containing heterocyclic aromatic compounds. This bicyclic compound is the fusion of benzene and imidazole nucleus. Benzimidazole nucleus explores a variety of therapeutic uses including antitumor, antifungal, antidiabetic, analgesic, and anti-inflammatory activity[8].

Thiazolidinone is a five-membered heterocyclic compound containing one nitrogen, one sulfur, and three carbon atom, with a carbonyl group. It having variety of biological activities such as antidiabetic, anti-inflammatory, antihistaminic, antifungal, anthelmintic, and CNS stimulants[9].

The present work aims to design and synthesize novel 2-methyl benzimidazole bearing thiazolidin-4-one derivatives and to perform *in vitro* evaluation of their antidiabetic activity. *In silico* molecular modeling studies are the most important step in drug design. The *in silico* modeling of all the proposed derivatives was carried out by using different computational Softwares to predict the physiological and biological parameters[10]. The software used for *in silico* studies includes ACD Lab Chemsketch12.0, Molinspiration, PASS, and AutoDock Vina. The designed derivatives were synthesized by the conventional method and were subjected to TLC, melting point determination, FTIR, ^{1}H NMR, and Mass spectroscopic studies. As per the PASS score and docking score, the derivatives were selected for antidiabetic evaluation.

MATERIALS AND METHODS

ACD Lab Chemsketch 12.0: Used for drawing chemical structures, 3D optimization, and calculating various physicochemical properties of the proposed derivatives. The values obtained for the novel derivatives were compared with the standard drug (Pioglitazone). About 10 derivatives were designed for molecular descriptor analysis and docking studies[11].

Molinspiration: It is used to calculate the molecular properties and bioactivity for the prediction of Lipinski's rule of five. Lipinski's rule of five or rule of thumb helps to determine whether the compound is likely to have the physical and chemical properties to be orally bioavailable[12].

PASS Online: PASS software is designed as a tool for the evaluation of general biological potential in the molecule under study. The approach used in PASS is based on the suggestion that Activity = f (structure). Thus, by comparing the structure of a new compound with the structure of a well-known biologically active substance, it is possible to estimate if a new compound may have a particular effect[13].

Molecular docking: Docking is the prediction of affinity and activity of derivatives to suitable protein targets. AutoDock Vina, an open-source docking program was selected for docking studies. *PyMOL* was used for protein preparation and visualization. *PyRx* was used for docking analysis[14].

Crystallographic structures of the targets of interest were obtained from PDB (Protein Data

Bank) and saved in standard 3D coordinate format. The targets used for the present study is peroxisome proliferator-activated receptor gamma (PDB ID: 1PRG)[15,16].

Procedure for Synthesis

Step 1: Synthesis of Ethyl (2-methyl-1*H*-benzimidazol-1-yl)acetate (1)

To a mixture of 2-methylbenzimidazole (0.01mol) and anhydrous potassium carbonate (2g) in dry acetone, ethylchloroacetate (0.01mol) was added dropwise within 5-10 minutes by stirring. The mixture was refluxed for 18 hours, and then it was poured onto ice-cold water and stirred to dissolve potassium carbonate. The solid ester obtained was filtered, washed with water, dried, and recrystallized using absolute ethanol. TLC was carried out using ethanol: chloroform(1:4).

Step 2: Synthesis of 2-(2-methyl-1*H*-benzimidazol-1-yl)acetohydrazide (2)

Ethyl (2-methyl-1*H*-benzimidazol-1-yl)acetate (0.01mol) and hydrazine hydrate (0.02mol, 0.9 mL) in ethanol (20 mL) were mixed well and refluxed for 7hours. After cooling, the resulting solid was filtered, dried, and recrystallized from ethanol. TLC was carried out using ethanol: chloroform(1:4).

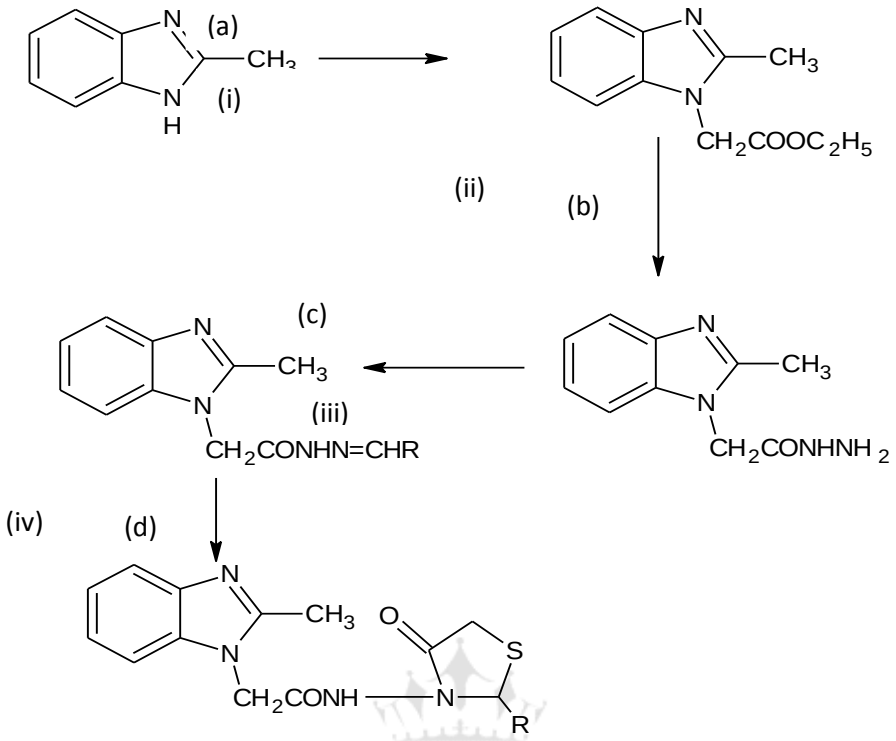
Step 3: Synthesis of 2-(2-methyl- 1*H*-benzimidazol-1-yl)- *N*'-[phenyl methylidene] acetohydrazide (3)

A mixture of 2-(2-methyl-1*H*-benzimidazol-1-yl)acetohydrazide (0.01mol), respective aldehyde (0.01mol), and 2-3 drops of glacial acetic acid in ethanol (20mL) was refluxed on a water bath for about 7 hours. After completion of the reaction, the mixture was poured into ice-cold water and the solid precipitate so formed was filtered, washed with ice water, dried, and recrystallized from absolute ethanol. TLC was carried out using ethanol: chloroform(1:4).

Step 4: Synthesis of 2-(2-methyl-1*H*-benzimidazol-1-yl)-*N*-(4-oxo-2-phenyl-1,3-thiazolidin-3-yl)acetamide (4)

To the mixture of 2-(2-methyl- 1*H*-benzimidazol-1-yl)- *N*'-[(*E*)- phenyl methylidene] acetohydrazide (0.01mol) in DMF (30 (mL) was added mercaptoacetic acid (0.01mol) and $ZnCl_2$ (1g) and the reaction mixture was refluxed for 9hours. Then cooled and poured into

crushed ice, the separated solid was filtered and washed with 10% sodium bicarbonate. The crude product was dried and recrystallized from DMF to obtain the desired product. TLC was carried out using ethanol: chloroform(1:4)[17,18,19].

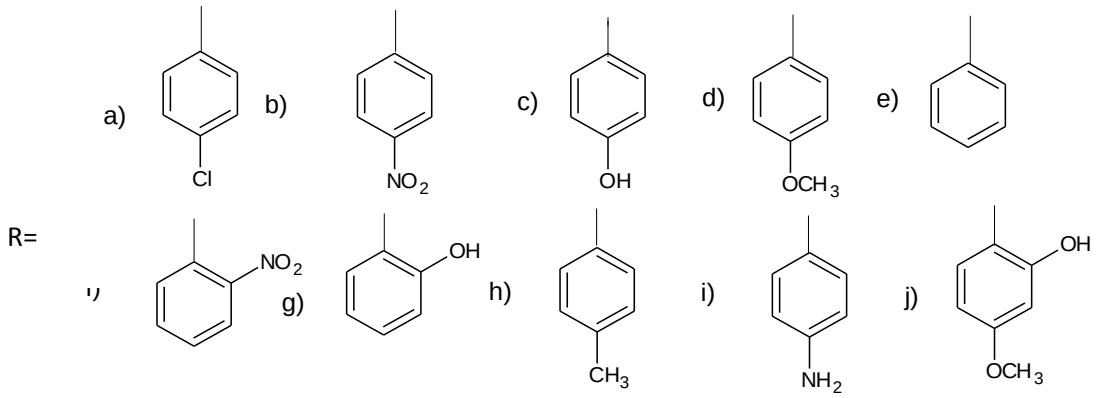


(a) $ClCH_2COOC_2H_5$, K_2CO_3, $(CH_3)_2CO$ (b) EtOH, $NH_2.NH_2.H_2O$

(i) 18 hours, 90°C (ii) 7 hours, 70°C

(c) R-CHO, EtOH, CH_3COOH (d) $SHCH_2COOH$, DMF, $ZnCl_2$

(iii) 7 hours, 70°C (iv) 9 hours, 70°C



Scheme 1: Synthetic pathway to generate benzimidazole bearing thiazolidinone derivatives

Characterization

The synthesized 2-substituted benzimidazole analogs were characterized by various analytical techniques like Melting point determination, Thin Layer Chromatography (TLC), Vibrational Spectroscopy (IR), ^{1}H NMR spectroscopy, and MASS spectroscopy (MS).

The derivatives with good docking score and PASS score were selected for antidiabetic evaluation. The designed benzimidazole bearing thiazolidinone derivatives were selected for antidiabetic studies were compared with the standard drug for any violation of Lipinski rule of five and drug-likeness score. Lipinski‟s rule of five that describes the drugability of a determinate molecule. This rule helps to determine if a biologically active chemical is likely to have the chemical physical properties to be orally bioavailable[20].

Drug likeness may be defined as a complex balance of various molecular properties and structural features which determine whether particular molecule is similar to the known drugs [21].

***In vitro* antidiabetic activity**

ELISA study

The principle used in this study is Sandwich-ELISA. Standards or samples are added to the micro ELISA plate wells and combined with the specific antibody. Then a biotinylated detection antibody specific for Human PPAR-γ and Avidin-Horseradish Peroxidase (HRP) conjugate are added successively to each microplate well and incubated. Free components are washed away. The substrate solution is added to each well. Only those wells that contain Human PPAR-γ, biotinylated detection antibody, and AvidinHRP conjugate will appear blue. The enzyme-substrate reaction is terminated by the addition of stop solution and the color turns yellow. The optical density (OD) is measured spectrophotometrically at a wavelength of 450 nm. The OD value is proportional to the concentration of Human PPAR-γ.

Sample collection

Cell lysates: For adherent cells, gently wash the cells (MIA PaCa-2) with a moderate amount of pre-cooled PBS and dissociate the cells using trypsin. Collect the cell suspension into a centrifuge tube and centrifuge for 5 min at 1000×g. Discard the medium and wash the

cells 3 times with pre-cooled PBS. For every 1×106 cells, add 150-250 µL of pre-cooled PBS to keep the cells suspended. Repeat the freeze-thaw process several times or use an ultrasonic cell disrupter until the cells are fully lysed. Centrifuge for 10min at 1500×g at 4℃. Remove the cell fragments, collect the supernatant to carry out the assay.

Reagent preparation

- Bring all reagents to room temperature (18~25℃) before use.

- Wash Buffer: Dilute 30 mL of Concentrated Wash Buffer with 720 mL of deionized or distilled water to prepare 750 mL of Wash Buffer.

- Standard working solution: Centrifuge the standard at 10,000×g for 1 min. Add 1.0 mL of Reference Standard &Sample Diluent, let it stand for 10 min, and invert it gently several times. After it dissolves fully, mixes it thoroughly with a pipette. This reconstitution produces a working solution of 10 ng/mL. Then make serial dilutions as needed. The recommended dilution gradient is as follows: 10, 5, 2.5, 1.25, 0.63, 0.32, 0.16, 0 ng/mL.

- Biotinylated Detection Ab working solution: Calculate the required amount before the experiment (100 µL/well). In preparation, slightly more than calculated should be prepared. Centrifuge the stock tube before use, dilute the 100× Concentrated Biotinylated Detection Ab to 1×working solution with Biotinylated Detection Ab Diluent.

- Concentrated HRP Conjugate working solution: Calculate the required amount before the experiment (100 µL/well). In preparation, slightly more than calculated should be prepared. Dilute the 100× Concentrated HRP Conjugate to 1× working solution with Concentrated HRP Conjugate Diluent.

Procedure

- Add the Standard working solution to the first two columns: Each concentration of the solution is added in duplicate, to one well each, side by side (100 µL for each well). Add the samples to the other wells (100 µL for each well). Cover the plate with the sealer provided in the kit. Incubate for 90 min at 37℃.

- Remove the liquid out of each well, do not wash. Immediately add 100 µL of Biotinylated Detection Ab working solution to each well. Cover with the Plate sealer. Gently mix up. Incubate for 1 hour at 37°C.

- Aspirate or decant the solution from each well, add 350 µL of wash buffer to each well. Soak for 1-2 min and aspirate or decant the solution from each well and pat it dry against clean absorbent paper. Repeat this wash step 3 times. Note: a microplate washer can be used in this step and other wash steps.

- Add 100 µL of HRP Conjugate working solution to each well. Cover with the Plate sealer. Incubate for 30 min at 37°C.

- Aspirate or decant the solution from each well, repeat the wash process five times as conducted in step 3.

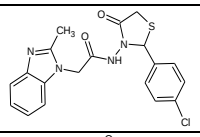
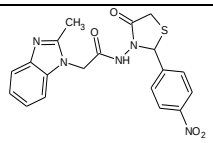
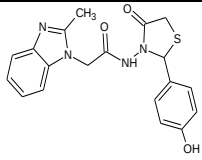
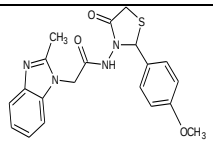
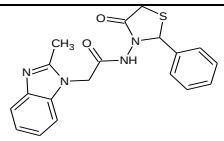
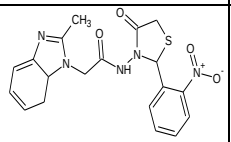
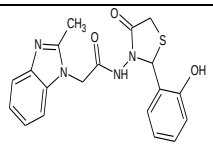
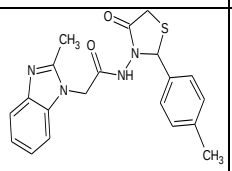
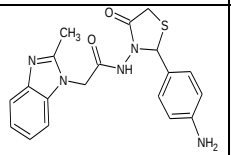
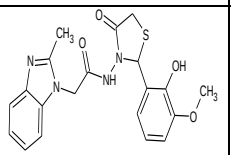
- Add 90 µL of Substrate Reagent to each well. Cover with a new plate sealer. Incubate for about 15 min at 37°C. Protect the plate from light. Add 50 µL of Stop Solution to each well. Determine the optical density (OD value) of each well at once with a micro-plate reader set to 450 nm[38].

$$\text{Percentage expression} = \frac{\text{test} - \text{control}}{\text{control}} \times 100$$

RESULTS

In the present study, *in silico* design of the proposed derivatives was carried out by using different software. 3D drawing, optimizing, and calculating various molecular descriptors of the proposed derivatives were done using ACD labs chemsketch 12.0. The results are shown in Table 1.

Table No. 1: Structure and molecular descriptors of derivatives

Compound code	Structure	Parachor (cm^3)	Molar volume (cm^3)	Molar refractivity (cm^3)	Surface tension (dyne/cm)
BT-4a		758.6 ±8.0	272.8±7.0	108.93±0.5	59.8±7.0
BT-4b		775.3± 8.0	268.1±7.0	104.11±0.5	63.2±7.0
BT-4c		735.5±8.0	260.7±7.0	104.11±0.5	63.2±7.0
BT-4d		780.0±8.0	288.1±7.0	109.0±0.5	63.4±7.0
BT- 4e		729.8± 8.0	263.5±7.0	103.26±0.5	58.8±7.0
BT-4f		775.3± 8.0	268.7±7.0	104.11±0.5	63.2±7.0
BT-4g		735.5± 8.0	260.7±7.0	108.92±0.5	60.2±7.0
BT-4h		760.9± 8.0	278.7±7.0	107.86±0.5	55.7±7.0
BT-4i		737.7± 8.0	260.2±7.0	104.11±0.5	61.3±7.0
BT-4j		785.7± 8.0	284.4±7.0	107.68±0.5	63.7±7.0

With the help of Molinspiration software the log P values, any violation of Lipinski rule of five, and drug-likeness were studied by comparing with the existing standard drug. The results are shown in Tables 2 and 3.

Table No. 2: Analysis of Lipinski rule of five of derivatives and standard drug

Compound code	Log P	M W(g)	nON	NOHNH	nrotb	n Vio
BT-4a	2.65	400.89	6	1	4	0
BT-4b	1.93	411.44	9	1	5	0
BT-4c	1.49	382.44	7	2	4	0
BT-4d	2.03	396.97	7	1	5	0
BT-4e	1.97	366.45	6	1	4	0
BT-4f	2.07	413.26	9	1	5	0
BT-4g	1.91	382.44	7	2	4	0
BT-4h	2.42	380.47	6	1	4	0
BT-4i	1.05	381.26	7	3	4	0
BT-4j	1.52	412.47	8	2	5	0
pioglitazone	3.07	356.45	5	1	7	0

Table No. 3: Analysis of drug-likeness of derivatives and standard drug

Compound code	GPCR ligand	Ion channel modulator	Kinase inhibitor	Nuclear receptor ligand	Protease inhibitor	Enzyme inhibitor
BT-4a	-0.22	-0.33	-0.81	-0.93	-0.36	-0.36
BT-4b	-0.34	-0.36	-0.86	-0.93	-0.43	-0.40
BT-4c	-0.18	-0.29	-0.76	-0.78	-0.31	-0.28
BT-4d	-0.25	-0.38	-0.80	-0.89	-0.56	-0.35
BT-4e	-0.23	-0.34	-0.82	-0.94	-0.33	-0.34
BT-4f	-0.10	-0.25	-0.88	-0.86	-0.18	-0.28
BT-4g	-0.24	-0.41	-0.74	-0.67	-0.35	-0.34
BT-4h	-0.25	-0.38	-0.82	-0.93	-0.36	-0.36
BT-4i	-0.18	-0.28	-0.70	-0.96	-0.25	-0.25
BT-4j	-0.26	-0.41	-0.71	-0.73	-0.41	-0.36
pioglitazone	-0.25	-0.51	-0.61	-0.64	-0.09	-0.05

Docking studies of derivatives were carried out using AutoDock Vina with protein 1PRG. The docking score of derivatives and standard pioglitazone with protein 1PRG is shown in Table 4.

Table No. 4: Docking score of derivatives and standard (Pioglitazone) with 1PRG

Sl. No	Compound code	Docking score (Kcal/mol)
1	BT-4a	-9.0
2	BT-4b	-8.7
3	BT-4c	-8.9
4	BT-4d	-8.5
5	BT-4e	-8.1
6	BT-4f	-7.9
7	BT-4g	-7.9
8	BT-4h	-8.0
9	BT-4i	-8..0
10	BT-4J	-7.9
11	Pioglitazone	-9.5

Schematic 2D representation of the docked complex of selected 5 derivatives and standard (pioglitazone) with protein 1PRG was visualized using *PyMOL* (Figure 1).

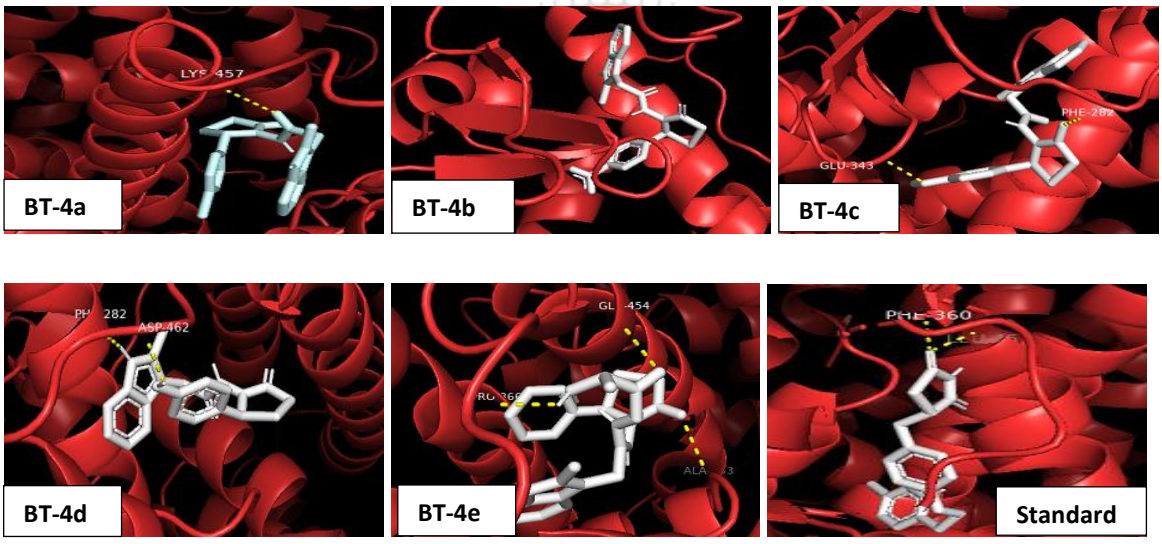


Figure No. 1: Docked images of derivatives and pioglitazone (white) with protein 1PRG (red). Hydrogen bonds are shown as yellow.

The results obtained from Lipinski's rule of five, drug-likeness, and docking score, five derivatives (BT-4a, BT-4b, BT-4c, BT-4d, and BT-4e) were synthesized and the Purity of

the derivatives was ascertained by TLC and melting point determination. The results are shown in Table 5.

Table No. 5: Melting point and R_f value of the synthesized derivatives

Compound code	Molecular formula	% yield & color	M P (°C)	R_f value
BT-4a	$C_{19}H_{18}ClN_4O_2S$	60% Yellow	243-244	0.83
BT-4b	$C_{19}H_{17}N_5O_4S$	60% Yellow	231-233	0.71
BT-4c	$C_{19}H_{18}N_4O_3S$	50% Brown	220-221	0.75
BT-4d	$C_{20}H_{20}N_4O_3S$	40% yellow	225-227	0.81
BT-4e	$C_{19}H_{18}N_4O_2S$	40% Brown	208-210	0.78

Characterization of synthesized derivatives was done by IR, NMR, and Mass spectral analysis and was shown in Tables 6, 7, and 8. Characteristic absorption peaks of derivatives were confirmed from IR spectroscopy and a total number of protons was obtained from ^1H NMR spectroscopy.

Table No. 6: Characteristic IR peaks of synthesized derivatives

Compound code	IR (KBr υ cm^{-1})
BT-4a	3370.43 NH stretch, 2978.71 Ar-CH stretch, 3208.31 Ar-NH stretch, 1681.84 C=O stretch, 1521.47 CONH stretch, 1424 CH_3 bending, 738. 63 Ar-Cl stretch, 715 C-S-C stretch
BT-4b	3382.22 NH stretch, 2979.96 Ar-CH stretch, 1682.35 C=O stretch, 1587.21 CONH stretch, 1420.97 CH_3 bending, 1518.27 Ar-NO_2 stretch, 735 C-S-C stretch
BT-4c	3498.84 NH stretch, 3061.13 Ar-NH stretch, 2980.22 Ar-CH stretch, 3181.81 Ar-OH stretch 1672.39 C=O stretch, 1603.63 CONH stretch, 1448.48 CH_3 bending, 736.01 C-S-C stretch
BT-4d	3389.45 NH stretch, 2980.49 Ar-CH stretch, 2837.42 Ar-OCH_3 stretch, 1681.48 C=O stretch, 1603.63 CONH stretch, 1457.37 CH_3 bending, 744.82 C-S-C stretch
BT-4e	3368.63 NH stretch, 2919.84 Ar-CH stretch, 1673.51 C=O stretch, 1579.86 CONH stretch, 1465.86 CH_3 bending, 735 C-S-C stretch

Table no 7: Characteristic ^{1}H NMR spectral values of synthesized derivatives

Compound Code	Solvent	^{1}H NMR (δ ppm)
BT-4a	DMSO	2.507 (s, Ar-CH_3, 3H), 5.455 (s, -N-CH_2 -, 2H) 8.084 (s, -NH-, 1H), 7.725 (d, -S-CH_2 -, 2H) 7.136 (t, Ar-H, 2H), 7.151 (d, Ar-H, 6H), 7.745 (s, -S-CH-, 1H)
BT-4b	DMSO	2.470 (s, Ar-CH_3, 3H), 5.455 (s, -N-CH_2 -, 2H) 8.084 (s, -NH-, 1H), 7.725 (d, -S-CH_2 -, 2H) 7.144 (t, Ar-H, 2H), 7.157 (d, Ar-H, 6H), 7.745 (s, -S-CH-, 1H)
BT-4c	DMSO	2.471(s, Ar-CH_3, 3H), 5.432 (s, -N-CH_2, 2H) 8.166 (s, -NH-, 1H), 7.431 (d, Ar-H, 6H), 7.547 (d, -S-CH_2 -, 2H) 7.136 (t, Ar-H, 2H), 7.527 (s, -S-CH-, 1H),4.984(s, Ar-OH, 1H)

Table No. 8: Mass spectral data of synthesized derivatives

Compound Code	Molecular ion peak	Parent peak
BT-4a	400.1186	327.1026
BT-4b	412.1123	327.1028

Based on the PASS score and Docking score, BT-4a, BT-4b, and BT-4c were selected for *in-vitro* antidiabetic evaluation by PPARγ ELISA study.

Table No. 9: Different concentration of standard with their optical density

Sample	Concentration (ng/ml)	OD at 450nm
Standard	10	0.797
	5	0.493
	2.5	0.286
	1.25	0.135
	0.625	0.073
	0.3125	0.029
	0.15625	0.014
Blank	-	0.0055

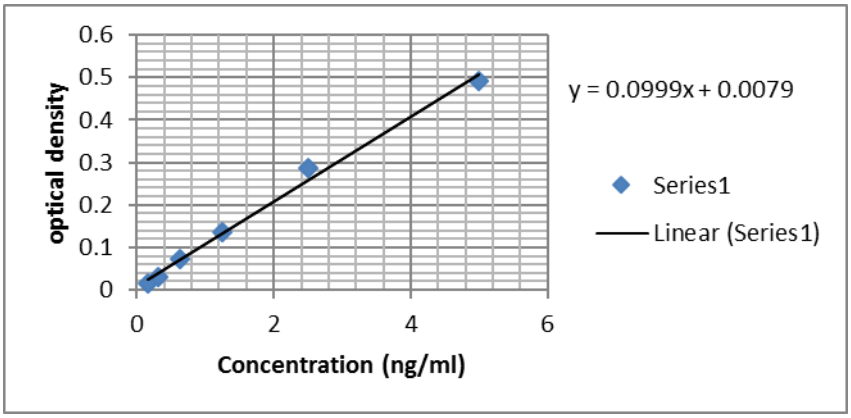


Figure No. 2: Standard curve for PPARγ

Table No. 10: Percentage expression of PPARγ by synthesized derivatives

Sample	Optical density (OD)	PPARγ (ng/ml)	Total protein(mg/ml) (by BCA method)	PPARγ ng/mg protein	Percentage expression (%)
Control	0.47	4.68	0.35	13.38	-
BT-1 (5µg/ml)	0.411	4.08	0.19	21.47	60.48
BT-2 (5µg/ml)	0.385	3.81	0.22	17.31	29.37
BT-3 (5µg/ml)	0.381	3.77	0.23	16.39	22.49

DISCUSSION

In silico design of all the proposed derivatives was carried out using ACD Labs Chemsketch 12.0, Molinspiration, PASS, and AutoDock Vina. The compounds were synthesized by the conventional method and were characterized by TLC, melting point determination, FTIR, NMR, and MASS. The synthesized derivatives were screened for the biological activities based on Pass and docking score.

The *in vitro* antidiabetic screening of all the selected derivatives exhibited better activity. Compound BT-4a exhibited high percentage expression of PPARγ than BT-2 and BT-3.

As the above results show a good significance in anti-diabetic therapy, the derivative BT-4a can be subjected to detailed *in-vivo* pharmacological screening and derivatization with other heterocycles and non–heterocycles and the utility of this compound as an anti-diabetic agent can be undoubtedly established.

CONCLUSION

In summary, the main objective of the present work was to design and synthesize novel 2-methyl benzimidazole bearing thiazolidin-4-one derivatives as antidiabetic agents. Various benzimidazole-bearing thiazolidinone derivatives were synthesized and characterized by spectral studies. In the *in vitro* antidiabetic screening, compound BT-4a exhibited significant expression of PPARγ.

ACKNOWLEDGEMENT

The authors are thankful to everyone who assisted in this work.

CONFLICT OF INTEREST: Nil

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