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Research Article

IN SILICO MODELLING, SYNTHESIS, AND ANTI-DIABETIC EVALUATION OF BENZOTHIAZOLE SUBSTITUTED OXADIAZOLE DERIVATIVES

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ABSTRACT

Objective: The study contemplates *in silico* modeling, synthesis and *in-vitro* anti-diabetic evaluation of benzothiazole substituted oxadiazole derivatives. [{5-[(1, 3-benzothiazol-2-ylsulfanyl) methyl]-1, 3, 4-oxadiazol-2-yl} sulfanyl) methyl] derivatives were synthesized by a conventional method.

Methods: All the newly synthesized derivatives were characterized by determining their melting point, retention factor from thin-layer chromatography, and spectral methods (Infrared, ^{1}H NMR spectroscopy, ^{13}C NMR spectroscopy, Mass spectroscopy) and evaluated for their anti-diabetic activity.

Results: [{5-[(1, 3-benzothiazol-2-ylsulfanyl) methyl]-1, 3, 4-oxadiazol-2-yl} sulfanyl) methyl] derivatives have been made and characterized using physical and spectral methods. The *in-vitro* anti-diabetic screening study revealed that BZT1 and BZT4 exhibited high inhibition against glucose uptake assay and alpha-amylase enzyme. But only the derivative BZT4 showed inhibition against alpha-glucosidase enzyme.

Conclusion: Various benzothiazole substituted oxadiazole derivatives were synthesized, characterized by spectral studies. The anti-diabetic studies revealed that the synthesized derivatives have significant anti-diabetic properties and further structure-activity relationship studies may develop more potent and less toxic molecules.

Keywords: Diabetes mellitus, Benzothiazole, Oxadiazole, Anti-diabetic.

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INTRODUCTION

Diabetes mellitus is a critical metabolic disorder characterized by high blood glucose levels and impairment in insulin action or both [1]. It has many sub-classifications including type-1, type-2, gestational diabetes, and other specific types. Type-1 diabetes is mainly due to autoimmune destruction of pancreatic β cells through T- cell-mediated inflammatory response as well as humoral response. Type- 2 may range from predominant insulin deficiency to secretory defect with insulin resistance [2]. The chronic hyperglycemia of diabetes is associated with long-term microvascular complications affecting the eyes, kidneys, and nerves, as well as an increased threat for cardiovascular disease. Currently, available drugs for the treatment of diabetes include Sulphonylureas (Tolbutamide and Glibenclamide), Biguanides (Metformin), Thiazolidinediones (Pioglitazone), Meglitinide derivatives (Repaglinide and Nateglinide), α- glucosidase inhibitors (Acarbose and Voglibose), DPP-4 inhibitors (Sitagliptin) [3].

Peroxisome proliferator-activated receptors (PPARs) constitute a group of nuclear receptors (NRs) that play crucial roles in the regulation of several physiological processes such as cellular differentiation and development, whole-body energy homeostasis (carbohydrate, lipid, and protein metabolism) [4]. PPARs are ligand-activated transcription factors and encompass a DNA binding domain in its N-terminus and ligand binding area in C-terminus [5]. The family of PPARs accommodates three isoforms: PPAR-α, PPAR-β, PPAR-γ. Among these subtypes, PPAR-γ agonist shows a prominent role in the orally effective anti-hyperglycemic agent. Thiazolidinediones act *via* PPAR- γ influences free fatty acid reflux, reduction of insulin resistance, and blood glucose level. Hence, they are widely used in the treatment of Diabetes mellitus [6].

A heterocyclic compound having nitrogen, oxygen, sulfur show wide applications in fields of medicinal chemistry. Benzothiazole is a privileged bicyclic ring system. The versatile biological functions exhibited by the benzothiazole nucleus include anti-diabetic, anti-microbial, analgesics, anti-convulsant, anti-inflammatory, etc. [7]. Oxadiazole is recognized as a promising class of bioactive heterocycle. Thereby it is considered as an important construction motif for the drug discovery and development process [8].

METHODS

ACD Lab Chemsketch ver 12.0 was used to draw chemical structures including organics, organometallics, polymers, and also for the calculation of molecular properties [9].

Molinspiration molecular viewer allows the visualization of molecules which is encoded as SMILES or SD file for the calculation of important molecular descriptors as well as prediction of bioactivity score of important drug targets [10].

Pharmacokinetic study by Swiss ADME

Swiss ADME revealed pharmacokinetic properties, drug-likeness (Table 1) of a potent molecule through predictive models such as BOILED-Egg (Fig. 1) iLOGP, and Bioavailability Radar (Fig. 2) [11].

PASS online

Prediction of Activity Spectra for Substances (PASS) is a computer program that allows to estimating the probable profile of biological activity of a drug-like organic compound based on its structural formula [12].

Protein data bank (PDB)

PDB provided three-dimensional structural data for large biological molecules such as proteins, and nucleic acids. Each structure published PDB receives a four-character alphanumeric identifier called PDB ID,

for example.,: 4YT1 (Human PPAR-γ ligand-binding domain in complex with Gamma Selective Synthetic Partial Agonist MEKT76) [13].

Molecular docking

Molecular docking is achieved by Autodock Vina(Table 2). The 3D crystallographic structures of proteins were uncovered from the (PDB ID- 4YT1). PyMOL produces a high-quality 3D image of protein as well as its visualization. PyRx is for docking analysis (Fig. 3) [14,15,16].

Synthetic procedure

STEP 1: Synthesis of ethyl (1, 3-benzothiazol-2-ylsulfanyl) acetate

A mixture of 2-mercaptobenzothiazole (0.01 mol) and ethyl-2-chloroacetate (0.01 mol) in dry acetone in the presence of anhydrous potassium carbonate (2 g) was allowed to reflux with stirring for 5 h at 70°C. Then it poured into ice-cold water with rapid stirring. The solid residue obtained is filtered and washed with water, dried, and recrystallized using absolute ethanol. Thin-layer chromatography (TLC) was carried out using ethyl acetate: petroleum ether (1:4). Spots visualized using ultraviolet cabinet.

STEP 2: Synthesis of 2-(1, 3-benzothiazol-2-ylsulfanyl) acetohydrazide

A solution of ethyl (1, 3-benzothiazol-2-ylsulfanyl) acetate (0.01 mol) and hydrazine hydrate 99% (0.02 mol) in ethanol (20 mL) was stirred well and refluxed for 8 h. The cooled product was filtered, dried, and recrystallized from methanol. TLC was carried out using ethyl acetate: petroleum ether (1:4).

STEP 3: Synthesis of 5-[(1,3-benzothiazol-2-ylsulfanyl)methyl]-1,3,4-oxadiazole-2-thiol

2-(1, 3-benzothiazol-2-ylsulfanyl) acetohydrazide (0.02mol) in solution of potassium hydroxide (0.22g) in ethanol (20 mL) of carbon disulphide (2 mL) with stirring. It is then refluxed at 40°C for 4 h. The filtrate is then neutralized with dilute hydrochloric acid and the solid residue is filtered, dried, and recrystallized with ethanol. TLC was carried out using ethyl acetate: petroleum ether (1:4).

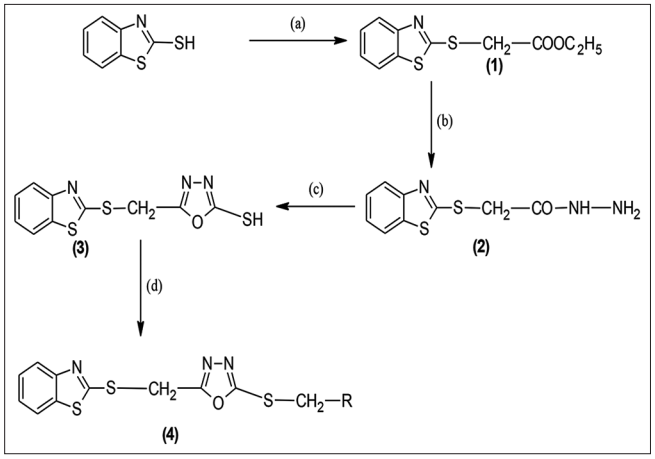
STEP 4: Synthesis of [{5-[(1,3-benzothiazol-2-ylsulfanyl)methyl]-1,3,4-oxadiazol-2yl}sulfanyl)methyl] derivatives

A mixture of 5-[(1, 3-benzothiazol-2-ylsulfanyl) methyl]-1,3,4-oxadiazole-2-thiol (0.01 mol) in dioxane and absolute ethanol (1:1, 20 mL), formaldehyde 37% (0.05 mol) was refluxed for 1–6 h at 30°C. To this solution, primary or secondary amine (0.01 mol) in absolute ethanol (5 mL) was added dropwise. The obtained product is filtered, dried, and recrystallized with ethanol. TLC was carried out using ethyl acetate: petroleum ether (1:4).

The synthetic scheme is given below:

Characterization

The synthesized benzothiazole substituted oxadiazole derivatives were characterized by various analytical techniques are as follows:



1. Melting point determination
2. TLC
3. Spectroscopy (Infrared, ^{1}H NMR, ^{13}C NMR, MASS)

R= NH-C_6H_5-Cl, -N-C_4H_9O, -N-C_5H_{11}, - NH-C_6H_5-CH_3, -NH-$C_6H_5NO_2$

(a) $ClCH_2COOC_2H_5$, anhydrous K_2CO_3, Dry Acetone, 70°C, 5 h reflux

(b) $NH_2NH_2.H_2O$, EtOH, 80°C, 8 h reflux

(c) CS_2, KOH, EtOH, 40°C, 4 h reflux

(d) HCHO, R-NH_2, EtOH, 1,4-dioxane, 30°C, 6 h reflux

***In vitro* anti-diabetic evaluation**

Glucose uptake assay

Glucose uptake activity in L6 cells was estimated by the methods described by Guptha *et al*. with slight modifications. Cells were cultured on 12 well plates and incubated for 24 h at 37°C in a CO_2 incubator. When a semi-confluent monolayer was formed, the culture was renewed with serum-free DMEM containing 0.2% BSA and incubated for 18 h at 37°C in the CO_2 incubator. After 18 h, the medium was discarded and cells were washed with phosphate buffer solution (pH 7.4) buffer once and treated with 1000 µg/mL glucose along with test compound (25, 50, and 100 µg/mL) and insulin standard (2.35, 4.7 and 9.4 µg/mL) for 1 h. The cells treated only with 1000 µg/mL glucose were kept as control. Glucose uptake was calculated as the difference between the initial (1000 µg/mL) and final glucose content in the incubated medium. The final glucose concentration was estimated by the anthrone method with the aid of a glucose standard graph. The glucose uptake in L6 cells treated with test compounds was compared with that of control cells (untreated). If the treated cells showed improved glucose uptake compared to control cells indicates the compound has medicinal value [17].

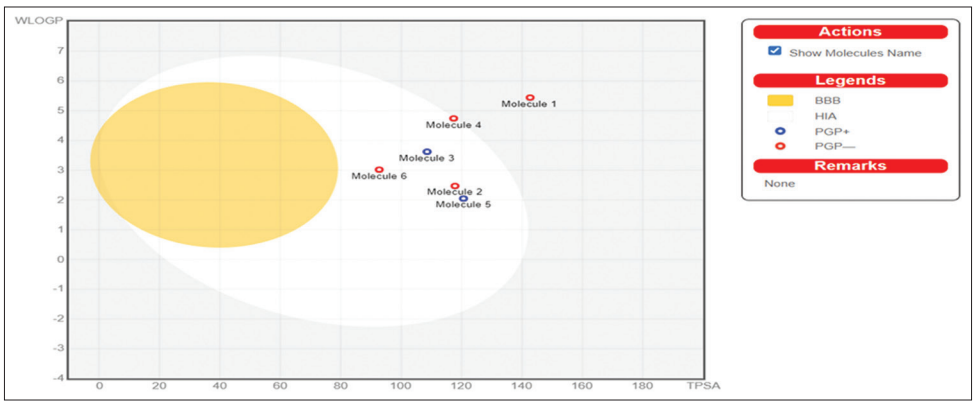


Fig. 1: BOILED Egg model to predict Passive diffusion by Swiss ADME

Table 1: Pharmacokinetic study by SWISS ADME

Comp Code	GI Absorption (High/Low)	BBB Permeant (Yes/No)	P-gp Substrate (Yes/No)	PAINS (alert)
BZT_1	Low	No	No	0
BZT_2	High	No	No	0
BZT_3	High	No	Yes	0
BZT_4	High	No	No	0
BZT_5	High	No	Yes	0
STD	High	No	No	0

Table 2: Docking score of derivatives and standard (Pioglitazone) with protein 4YT1

S. No.	Comp Code	Docking score (kcal/mol)	Aminoacid interactions
1.	BZT_1	–8.7	LYS-336, MET-364, PHE-374, ARG-443
2.	BZT_2	–8.3	HIS-323, PHE-363, ALA-371, VAL-446
3.	BZT_3	–8.1	LYS-275, PHE-287, PRO-366, LEU-442
4.	BZT_4	–8.4	ARG-357, GLN-415, PHE-432
5.	BZT_5	–8.1	LYS-301, GLU-369, THR-440, HIS-449
6.	Standard (Pioglitazone)	–8.6	ASP-441, PHE-370, ARG-443, ILE-325, MET-439

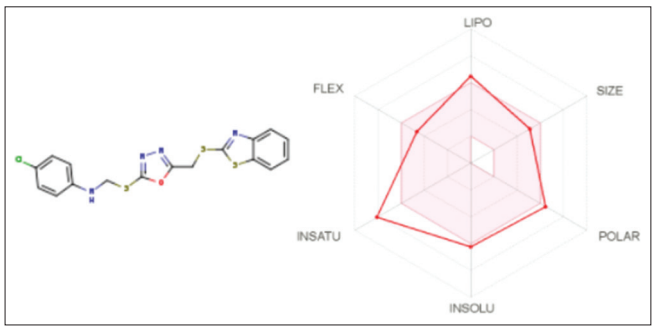


Fig. 2: Bioavailability radar of BZT_1

$$\% \text{ Glucose uptake} = \frac{\text{OD of test} - \text{OD of control}}{\text{OD of test}} \times 100$$

OD: Optical density

Alpha-glucosidase inhibitory assay

The effect of the sample on α-glucosidase activity was determined according to the method described by Shai *et al.*, (2011) with slight modification. 400 µL of α-glucosidase (0.067 U/mL) was preincubated with different concentrations of the sample for 30 min. Then 200 µL of 3.0 mM (*p*NPG) used as substrate dissolved in 0.1M sodium phosphate buffer (pH 6.9) was then added to start the reaction. The reaction mixture was incubated at 37°C for 30 min and stopped by adding 2 mL of 0.1 M Na_2CO_3. The α-glucosidase activity was determined by measuring the yellow-colored *para*-nitrophenol released from *p*NPG at 400 nm. The results were expressed as percentage of inhibition. The same procedure was done with Acarbose (1 mg/ml stock) which was used as standard [18].

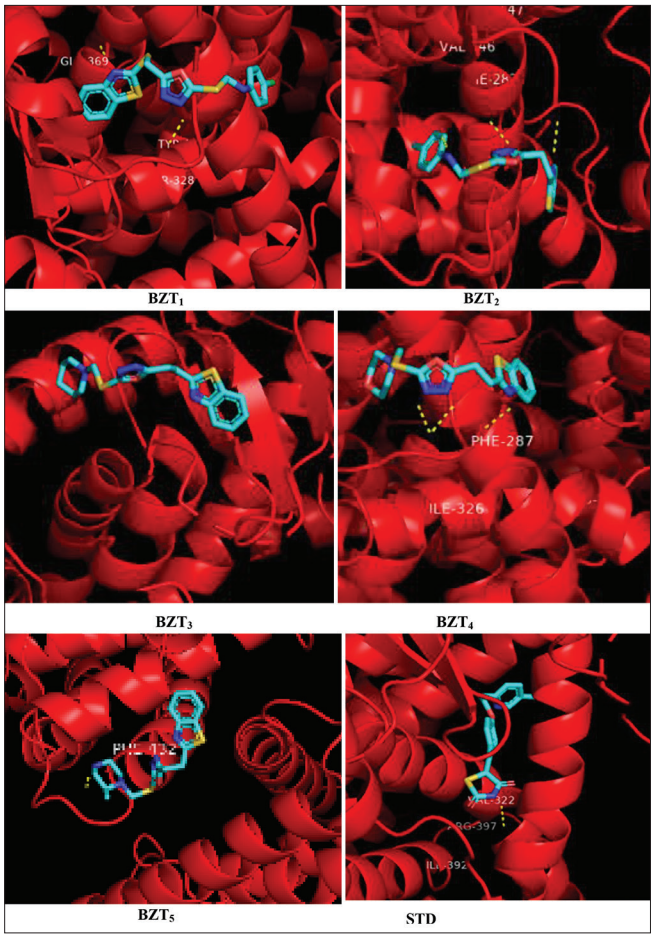


Fig. 3: Docking images of derivatives and standard (Pioglitazone) with protein 4YT1

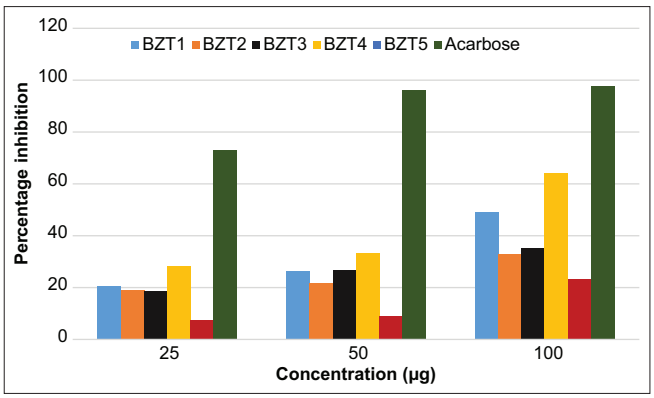
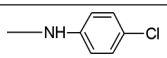
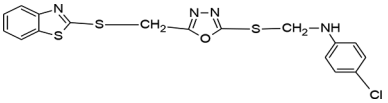
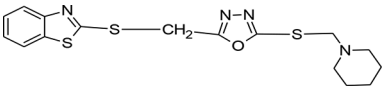
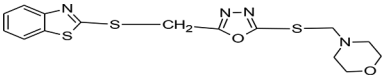
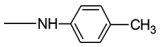
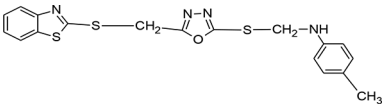
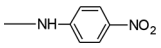
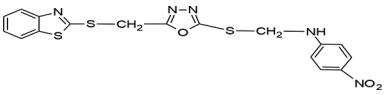


Fig. 4: Graphical representation of the alpha-glucosidase inhibitory assay

Table 3: Synthesis of benzothiazole substituted oxadiazole derivatives

Comp code	Substitution	Final product
BZT_1		
BZT_2		
BZT_3		
BZT_4		
BZT_5		

*Comp code: Compound code

Table 4: Analysis of Lipinski's rule of five by Molinspiration

Comp code	MW (g/mol)	HA	HD	LogP	nrotb	Violations
BZT_1	420.97	5	1	4.46	6	0
BZT_2	362.48	6	0	2.17	6	0
BZT_3	360.51	5	0	3.24	7	0
BZT_4	382.51	5	1	4.23	6	0
BZT_5	375.52	6	1	1.96	6	0
STD (Pioglitazone)	367.8	5	1	4.12	7	0

MW: Molecular weight, HD: Hydrogen bond Donors, Nrotb: No. of rotatable bonds, HA: Hydrogen bond Acceptor

Table 5: Drug- likeness score evaluation by molinspiration

Comp code	Gpcr ligand	Ion channel modulator	Kinase inhibitor	Nuclear receptor ligand	Protease inhibitor	Enzyme inhibitor
BZT_1	−0.82	−1.35	−0.28	−0.88	−0.45	−0.50
BZT_2	−0.55	−0.90	−0.04	−1.13	−0.20	−0.31
BZT_3	−0.46	−0.80	−0.07	−1.09	−0.16	−0.26
BZT_4	−0.59	−0.68	−0.13	−1.06	−0.20	−0.28
BZT_5	−0.64	−0.79	−0.22	−1.05	−0.26	−0.30

Table 6: Physical characterization of synthesized compounds

Compound code	Molecular formula	Melting point (°C)	R_f value
BZT_1	$C_{17}H_{13}ClN_4OS_3$	189–192	0.58
BZT_2	$C_{16}H_{18}N_4OS_3$	185–188	0.63
BZT_3	$C_{15}H_{16}N_4O_2S_3$	158–161	0.74
BZT_4	$C_{18}H_{16}N_4OS_3$	164–167	0.57
BZT_5	$C_{17}H_{13}N_5O_3S_3$	148–152	0.61

$$\% \text{ inhibition} = \frac{\text{OD of Test} - \text{OD of Control}}{\text{OD of test}} \times 100$$

Alpha- amylase inhibitory assay

Screening of alpha-amylase inhibitors was performed using Xiao *et al.* method in test tubes with slight modifications based on the starch iodine test. The assay mixture was about 120 µL of 0.02M sodium phosphate buffer (pH 6.9), 1.5 mL of salivary alpha amylase, and plant extracts at a concentration from 0.5 to 1.5 mg/mL incubated at 37°C for 10 min. After that, soluble 1% starch was added to each reaction mixture and incubated at 37°C for 15 min. Then 60 µL of 1 M HCl was added to the reaction mixture to stop the enzymatic reaction and immediately 300 µL of iodine reagents was added. If any color change was noted and at 625 nm the absorbance was read. Inhibition [19,20]. The absorbance was measured at 625 nm and the percentage inhibitory activity was calculated using the following equation:

$$\% \text{ inhibition} = \frac{\text{OD of test} - \text{OD of control}}{\text{OD of test}} \times 100$$

RESULTS AND DISCUSSION

The benzothiazole substituted oxadiazole derivatives synthesized were depicted in Table 3. The estimation of molecular descriptors and pharmacokinetic parameters of the proposed derivatives were done by ACD Lab Chemsketch ver. 12.0 and Molinspiration Online Software, respectively. From all these parameters enlisted in Table 4, the compounds obeying Lipinski's rule of five were selected for docking studies. The drug-likeness score which is used to determine their

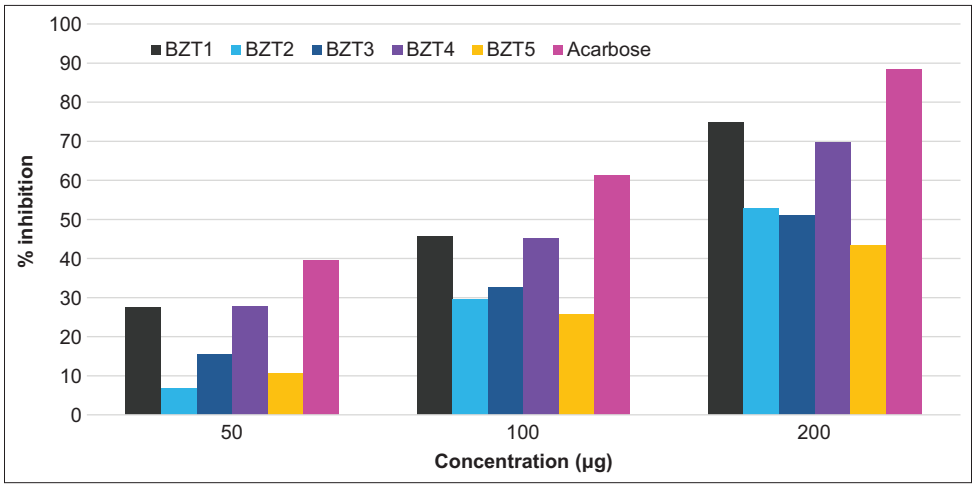


Fig. 5: Graphical representation of the alpha-amylase inhibitory assay

Table 7: Characteristic IR peaks of derivatives

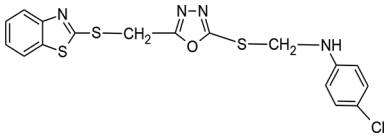
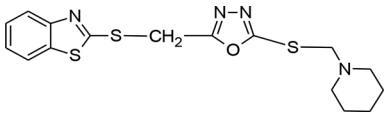
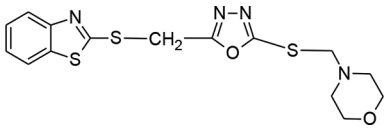
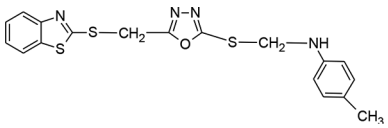
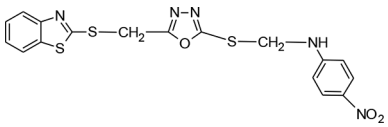
Compound code	Structure	IR (KBr υ/cm)
BZT_1		1591.95 Aromatic C=C stretch, 1810.24 N-Nstretch ,1655.04Ar C=N stretch, 1310.26 C-O stretch, 2919.7 Aliphatic C-H stretch, 696.08 C-S-C stretch, 3198.36 Ar-NH stretch, 848.64 Ar-Cl stretch
BZT_2		3198.36 Ar-CH_2 stretch, 1309.01 C-C stretch, 2591.86 Ar-SH stretch, 1557.24 C-O stretch, 1663.3 C=N stretch, 710.25 C-S-C stretch, 1264.83 C-N stretch, 3316.54 Ar-N stretch
BZT_3		1507.20 C=C stretch 1589.06 C=N stretch, 1112.32 C-O stretch, 957.23 Aromatic C-C stretch, 1857.4 N-N stretch, 1265.81 C-N stretch 637.8 C-S-C stretch, 3192.58 N-H stretch 1265.81 C-O stretch
BZT_4		2922.59 Aliphatic C-H stretch, 1658.48 Aromatic C-H stretch, 1611.23 C=N stretch, 3200.29 N-H stretch, 740.03 C-S-C stretch, 3061.44 N-H stretch (2º amine), 1430.92 C=C stretch, 905.41 C-C stretch
BZT_5		1371.14 C-H bending, 2894.66 Ar-SH stretch, 1283.63 C-O stretch, 938.54 C-C stretch, 608.12 Aliphatic C-H stretch 755.07 C-S-C stretch, 1638.23 C=C stretch, 1589.06 Ar-NO_2

Table 8: ^{1}H NMR spectral values of synthesized derivatives

Compound code	^{1}H NMR (ppm)
BZT_1	7.418 (d, Ar-H, 1H), 7.421 (t, Ar-H, 1H), 7.830 (d, Ar-H, 1H), 7.752 (d, Ar-H, 1H), 4.161 (s, S-CH_2, 2H), 4.263 (s, -NH_2, 2H), 7.850 (t, -NH, 1H)
BZT_2	7.936 (t, Ar-H, 1H), 7.825 (d, Ar-H, 1H), 7.440 (d, Ar-H, 1H), 7.409 (d, Ar-H, 1H), 4.441 (s, S-CH_2, 2H), 9.579 (d, S-H, 1H)
BZT_3	7.803 (d, Ar-H, 2H), 7.337 (d, Ar-H, 2H), 4.153 (s, S-CH_2, 2H), 4.441 (s, S-CH_2, 2H), 2.264 (d, Ar-C, 4H),3.370 (d, Ar-C, 4H)
BZT_4	7.312 (d, Ar-H, 2H), 7.804 (d, Ar-H, 2H), 4.150 (s, S-CH_2, 2H), 4.466 (s, S-CH_2, 2H), 7.993 (s, -NH, 1H), 6.925 (d, Ar-H, 2H), 6.998 (d, Ar-H, 2H), 2.166 (s, Ar-CH_3, 3H)
BZT_5	7.012 (d, Ar-H, 2H), 7.194 (d, Ar-H, 2H), 4.218 (s, S-CH_2, 2H), 4.473 (s, S-CH_2, 2H), 8.113 (s, -NH, 1H), 7.79 (d, Ar-H, 2H), 8.071 (d, Ar-H, 2H)

affinity toward certain receptors is shown in Table 5. All the proposed derivatives showed a high score for NR ligand. The biological activity of derivatives was predicted by PASS as an anti-diabetic with a $p<0.5$. Pharmacokinetic prediction of the derivatives by Swiss ADME is illustrated in Table 5. All the derivatives exhibited high gastrointestinal absorption except BZT_1. All the derivatives were found to be non-permeant of the Blood-brain barrier and zero alert for PAINS. Docking results revealed a high negative docking score (Table 6). It indicates very good interaction and affinity with the binding site of protein 4YT1. The designed derivatives and standard exhibited polar interaction such as hydrogen bonding with amino acids.

Synthetic methodology

[{5-[(1, 3-benzothiazol-2-ylsulfanyl) methyl]-1, 3, 4-oxadiazol-2-yl} sulfanyl) methyl] derivatives were synthesized through a four-step conventional method. Five synthesized derivatives were named as BZT_1, BZT_2, BZT_3, BZT_4, and BZT_5. The characterization of synthesized derivatives carried out by TLC and melting point determination is presented in Table 6. Spectral characterization was done by Infrared,

Table 9: ^{13}C NMR Spectral values of synthesized derivatives

Compound code	^{13}C NMR (ppm)
BZT_1	a (122.28-1C, s), b (128.95-1C, s), c (152.87-1C, s), d (135.38-1C, s), e (165.27-1C, s), f (36.11-1C, s), g (153.17-1C, s), h (159.17-1C, s), i (52.14-1C, s), j (135.14-1C, s), k (121.83-1C, s), l (128.95-1C, s), m (129.07-1C, s)
BZT_2	a (121.83-1C, s), b (126.93-1C, s), c (152.91-1C, s), d (135.20-1C, s), e (165.47-1C, s), f (35.37-1C, s), g (158.79-1C, s), h (161.37-1C, s), i (40.39-1C, s), j (40.59-1C, s), k (27.20-1C, s), l (39.34-1C, s)
BZT_3	a (122.35-1C, s), b (126.93-1C, s), c (152.89-1C, s), d (135.35-1C, s), e (165.48-1C, s), f (34.89-1C, s), g (158.84-1C, s), h (180.58-1C, s), i (50.09-1C, s), j (40.55-1C, s), k (66.62-1C, s)
BZT_4	a (122.18-1C, s), b (128.95-1C, s), c (152.87-1C, s), d (135.14-1C, s), e (165.27-1C, s), f (36.11-1C, s), g (159.17-1C, s), h (148.17-1C, s), i (52.14-1C, s), j (135.38-1C, s), k (119.08-1C, s), l (129.07-1C, s), m (147.51-1C, s), n (27.11-1C, s)
BZT_5	a (119.45-1C, s), b (131.76-1C, s), c (147.85-1C, s), d (131.96-1C, s), e (66.99-1C, s), f (39.30-1C, s), g (107.70-1C, s), h (67.11-1C, s), i (40.55-1C, s), j (111.96-1C, s), k (116.44-1C, s), l (116.23-1C, s), m (147.23-1C, s)

Table 10: Mass spectral values of synthesized derivatives

Compound code	Molecular mass	Molecular ion peak	Parent peak
BZT_1	420.97	420.95	279.950
BZT_4	382.51	382.74	279.950

Table 11: Percentage of glucose uptake of synthesized derivatives and pioglitazone

Sample	Concentration (µg)	OD at 630 nm	% Glucose uptake
Blank	-	0.0591	-
BZT_1	25	0.8943	23.73
	50	0.7471	51.27
	100	0.6150	89.07
BZT_2	25	0.9158	20.52
	50	0.8806	25.87
	100	0.8243	35.46
BZT_4	25	0.8057	38.97
	50	0.7455	51.69
	100	0.6369	81.54
Pioglitazone	25	0.7723	45.73
	50	0.7105	60.15
	100	0.6619	83.68

Table 12: Alpha-glucosidase inhibitory activity of synthesized derivatives and acarbose

Sample	IC_{50} (µg)
BZT_1	58.11
BZT_2	72.13
BZT_3	81.03
BZT_4	48.80
BZT_5	92.48
Acarbose	39.15

Table 13: Alpha-amylase inhibitory activity of synthesized derivatives and acarbose

Sample	IC_{50} (µg)
BZT_1	51.46
BZT_2	100.08
BZT_3	100.66
BZT_4	63.74
BZT_5	101.72
Acarbose	28.47

^{1}H NMR, ^{13}C NMR, and Mass spectroscopy. The results are shown in Tables 7-10. Based on the docking score, all the synthesized derivatives were selected for *in vitro* anti-diabetic screening.

Anti-diabetic evaluation

The result obtained from the glucose uptake assay depicted in Table 11 showed that BZT_1 and BZT_4 exhibited a dose-dependent increase in uptake of glucose when compared with standard (Pioglitazone). In case of the alpha-glucosidase enzyme inhibitory assay, BZT_4 showed significant inhibition for the alpha-glucosidase enzyme (Fig. 4). The compound exhibited high percentage inhibition (64.06%) and the IC_{50} value of BZT_4 was found to be 48.8µg (Table 12) which is adjacent to the IC_{50} of standard (Acarbose).

In the alpha-amylase inhibitory assay, derivatives BZT_1 and BZT_4 revealed high percentage inhibition at concentration 200 µg (Fig. 5). From IC_{50} values in Table 13, we can elucidate that compounds BZT_1 and BZT_4 possess good alpha-amylase inhibitory activity at the lowest concentration.

CONCLUSION

The present study was conducted by in silico modeling and synthesis of benzothiazole substituted oxadiazole derivatives. These derivatives were characterized using physical and spectral analytical studies. All the derivatives evaluated for in-vitro biological assay methods. BZT1 and BZT4 showed high percentage glucose uptake and inhibition against alpha-amylase. But only BZT4 has excellent inhibition against alpha-glucosidase.

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AUTHORS CONTRIBUTIONS

We hereby declare that 1st and 2nd authors contributed to the entire work and drafted manuscript. The 3rd author participated in *in-vitro* studies.

CONFLICTS OF INTEREST

The author confirms that the content of the article has no conflict of interest.

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