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Synthesis, Molecular Docking, and *In-Vitro* Evaluation of Novel 2 - Amino Substituted Benzothiazole Derivatives as Alpha -Glucosidase Inhibitors for Antidiabetic Activity

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ABSTRACT

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder characterized by persistent hyperglycemia resulting from impaired insulin secretion and insulin resistance. Inhibition of α-glucosidase is an effective therapeutic strategy for reducing postprandial blood glucose levels. In the present study, a series of novel benzothiazole–thiazolidinedione derivatives were synthesized and evaluated for their potential as α-glucosidase inhibitors through molecular docking and in vitro enzymatic assays. The target compounds were synthesized via a multistep synthetic route and characterized using standard physicochemical and spectroscopic techniques. Molecular docking studies were performed against the α-glucosidase enzyme (PDB ID: 3A4A) using AutoDockVina to investigate binding affinity and interactions within the enzyme active site. The synthesized compounds were subsequently evaluated for their α-glucosidase inhibitory activity using the p-nitrophenyl-α-D-glucopyranoside (pNPG) assay, with acarbose employed as the reference standard. Several derivatives exhibited favorable binding affinities and established significant hydrogen bonding and hydrophobic interactions with key catalytic amino acid residues. The in vitro studies demonstrated promising α-glucosidase inhibitory activity, with selected compounds showing inhibition comparable to that of acarbose. The correlation between molecular docking and biological evaluation suggests that the synthesized benzothiazole–thiazolidinedione derivatives possess considerable potential as lead molecules for the development of novel antidiabetic agents. Further pharmacological and in vivo investigations are warranted to establish their therapeutic efficacy and safety.

Keywords: Benzothiazole; Thiazolidinedione; α-Glucosidase; Molecular docking; Antidiabetic activity; Type 2 diabetes mellitus.

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INTRODUCTION

Diabetes mellitus (DM) is one of the most prevalent chronic metabolic disorders worldwide and represents a major public health challenge due to its increasing incidence and associated complications. Type 2 diabetes mellitus (T2DM) accounts for approximately 90–95% of all diabetes cases and is characterized by insulin resistance, progressive pancreatic β-cell dysfunction, and persistent hyperglycemia. Uncontrolled blood glucose levels contribute to the development of severe microvascular and macrovascular complications, including nephropathy, retinopathy, neuropathy, and cardiovascular diseases, resulting in increased morbidity and mortality. Consequently, the development of safe and effective therapeutic agents for glycemic control remains a priority in diabetes management.[1,2]

Postprandial hyperglycemia is a significant contributor to the progression of T2DM and is recognized as an independent risk factor for diabetic complications. One of the established therapeutic strategies for controlling postprandial glucose levels involves the inhibition of intestinal carbohydrate-hydrolyzing enzymes, particularly α-glucosidase. This enzyme, located in the brush-border membrane of the small intestine, catalyzes the hydrolysis of oligosaccharides and disaccharides into absorbable glucose molecules. Pharmacological inhibition of α-glucosidase delays

carbohydrate digestion, reduces glucose absorption, and attenuates postprandial blood glucose excursions. Clinically available α-glucosidase inhibitors, including acarbose, miglitol, and voglibose, have demonstrated efficacy in glycemic control; however, their long-term use is frequently associated with gastrointestinal adverse effects such as flatulence, abdominal discomfort, and diarrhea. These limitations have stimulated the search for novel α-glucosidase inhibitors possessing improved efficacy and safety profiles.[3–5]

Heterocyclic compounds continue to play an indispensable role in medicinal chemistry owing to their structural diversity and broad spectrum of biological activities. Among them, benzothiazole has emerged as a privileged scaffold because of its favorable physicochemical characteristics and remarkable pharmacological potential. Benzothiazole derivatives have exhibited antimicrobial, anticancer, anti-inflammatory, antioxidant, antiviral, anticonvulsant, and antidiabetic activities. Structural modification of the benzothiazole nucleus has enabled the development of compounds with enhanced biological activity through improved interactions with specific therapeutic targets. Consequently, benzothiazole-based molecules have gained considerable attention as promising candidates for drug discovery against metabolic disorders, including diabetes mellitus.[6–8]

Similarly, thiazolidinedione is another pharmacologically significant heterocyclic scaffold extensively investigated in antidiabetic drug development. The thiazolidinedione nucleus is capable of interacting with multiple biological targets associated with glucose metabolism and insulin sensitivity. Incorporation of thiazolidinedione into hybrid molecular frameworks has been reported to improve biological activity by enhancing hydrogen-bonding interactions and increasing binding affinity toward enzymatic targets. Molecular hybridization of benzothiazole and thiazolidinedione pharmacophores therefore represents a rational approach for designing novel antidiabetic agents with improved therapeutic potential.[9–11]

Computer-aided drug design has become an integral component of modern medicinal chemistry by facilitating the identification and optimization of biologically active molecules. Molecular docking enables prediction of ligand orientation, binding affinity, and intermolecular interactions within the active site of target proteins, thereby providing valuable insights into structure–activity relationships before biological evaluation. Integration of molecular docking with experimental enzymatic assays significantly improves the efficiency of lead identification and supports the rational design of enzyme inhibitors.[12,13]

Considering the therapeutic significance of α-glucosidase inhibition and the promising pharmacological properties of benzothiazole and thiazolidinedione scaffolds, the present study was undertaken to synthesize a series of novel benzothiazole–thiazolidinedione derivatives and evaluate their potential as α-glucosidase inhibitors. The synthesized compounds were characterized using standard analytical techniques, and their binding interactions with α-glucosidase (PDB ID: 3A4A) were investigated through molecular docking studies using AutoDockVina. Furthermore, the compounds were evaluated for in vitro α-glucosidase inhibitory activity using acarbose as the reference standard. The combined computational and experimental approach adopted in this study is expected to provide valuable insights into the development of potent benzothiazole-based antidiabetic agents with improved inhibitory activity against α-glucosidase.

MATERIALS AND METHODS

Chemicals and Reagents

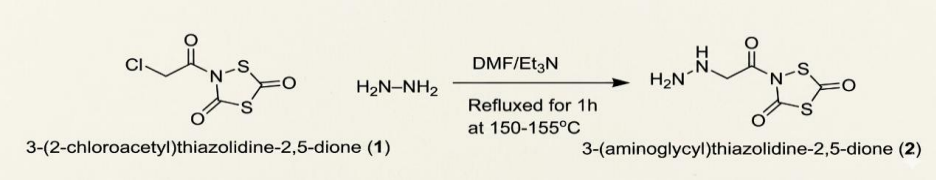
All chemicals and reagents used in the present study were of analytical reagent (AR) grade and used without further purification. Thiazolidine-2,5-dione, 2-chloroacetamide, hydrazine hydrate, substituted benzoic acids, N,N-dimethylformamide (DMF), triethylamine (TEA), 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDC·HCl), hydroxybenzotriazole (HOBt), potassium carbonate, ethanol, ethyl acetate, sodium bicarbonate, and other solvents were procured from Sigma-Aldrich (St. Louis, MO, USA) and Merck (Darmstadt, Germany). Acarbosewas used as the reference standard for the α-glucosidase inhibition assay. Thin-layer chromatography (TLC) was performed on silica gel 60 F254 precoatedaluminum plates (Merck), and the spots were visualized under ultraviolet light (254 nm).

General Experimental Procedure

Melting points were determined using a digital melting point apparatus and are uncorrected. The progress of the reactions was monitored by TLC using silica gel 60 F254 plates with *n*-hexane:ethyl acetate as the mobile phase. Purification of synthesized compounds was achieved by recrystallization from ethanol. All reactions were performed under standard laboratory conditions.

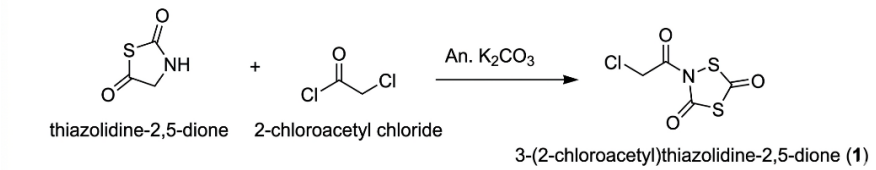
Synthesis of 3-(2-Chloroacetyl) thiazolidine-2,5-dione (Compound 1)

Thiazolidine-2,5-dione (1.0 g, 0.011 mol) was dissolved in acetone, followed by the addition of potassium carbonate (0.24 g, 0.0179 mol). The reaction mixture was stirred at room temperature for 15 min. Subsequently, 2-chloroacetamide (0.242 g, 0.0143 mol) was added gradually, and the reaction mixture was stirred continuously for 4–12 h. The reaction progress was monitored by TLC using *n*-hexane:ethyl acetate (1:2–1:6) as the developing solvent. After completion of the reaction, the precipitated product was filtered, washed with cold water, dried, and recrystallized from ethanol to obtain 3-(2-chloroacetyl)thiazolidine-2,5-dione as a pure solid.[12]



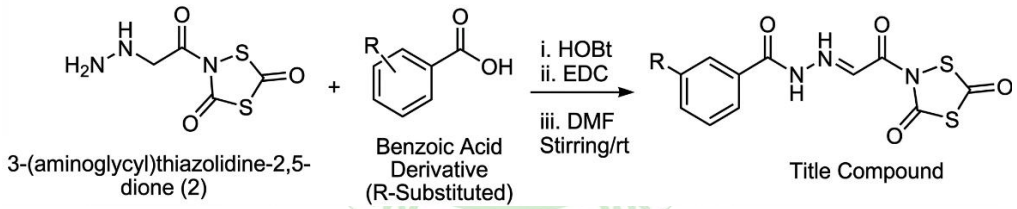
Synthesis of 3-(Aminoglycyl) thiazolidine-2,5-dione (Compound 2)

Compound 1 (0.01 mol) was dissolved in DMF (40 mL), and hydrazine hydrate was added slowly with continuous stirring. The reaction mixture was refluxed at 150–155°C for approximately 1 h until completion, as confirmed by TLC. After cooling to room temperature, the resulting precipitate was filtered, washed thoroughly with distilled water, and recrystallized from ethanol to obtain 3-(aminoglycyl) thiazolidine-2,5-dione.[13]



General Procedure for the Synthesis of Benzothiazole–Thiazolidinedione Derivatives

The synthesized intermediate 3-(aminoglycyl)thiazolidine-2,5-dione (0.0014 mol) was dissolved in DMF (15 mL), followed by the addition of the appropriate substituted benzoic acid (0.0014 mol) and HOBt (0.0029 mol). The reaction mixture was cooled to 0°C, and EDC·HCl (0.0029 mol) was added slowly with continuous stirring. The reaction mixture was gradually allowed to attain room temperature and stirred until completion of the reaction as monitored by TLC using *n*-hexane:ethyl acetate (1:4). The reaction mixture was quenched with saturated sodium bicarbonate solution and extracted three times with ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude products were purified by recrystallization from ethanol to obtain the desired substituted benzothiazole derivatives.[14]



Molecular Docking Studies

Protein Preparation

The three-dimensional crystal structure of α-glucosidase (PDB ID: 3A4A) was retrieved from the Protein Data Bank (https://www.rcsb.org). Water molecules and co-crystallized ligands were removed, and polar hydrogen atoms together with Kollman charges were added using AutoDock Tools. The prepared protein structure was saved in PDBQT format for molecular docking.[15,16]

Ligand Preparation

The chemical structures of the synthesized compounds and acarbosewere drawn using ChemDraw and converted into three-dimensional conformations. Geometry optimization was performed, and the structures were saved in MOL2 format. The optimized ligands were converted into PDBQT format using Open Babel before docking analysis.[17]

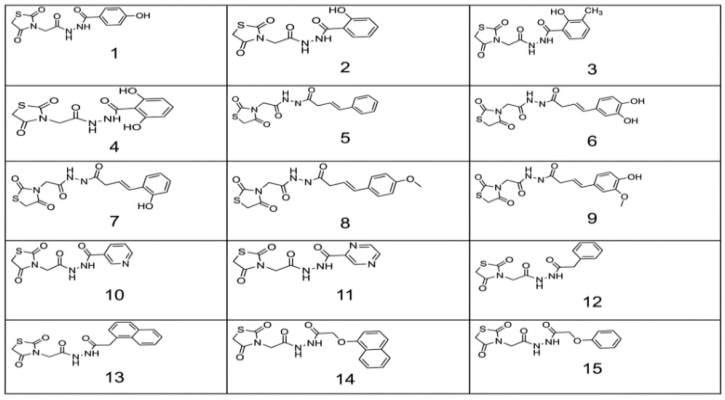


Figure 1: Structure of Synthesised compounds

Binding Site Prediction

The active binding pocket of α-glucosidase was identified using the Computed Atlas of Surface Topography of Proteins (CASTp 3.0) server. The amino acid residues within the largest active-site pocket were selected to define the docking grid.[18]

Molecular Docking

Molecular docking studies were carried out using AutoDockVina. Grid box dimensions were centered on the predicted active site of α-glucosidase. Binding affinities were expressed as binding energies (kcal/mol), and the docking poses were ranked according to the lowest binding energy. The best binding conformations were selected for further interaction analysis.[19]

Visualization of Protein–Ligand Interactions

The docked complexes were visualized using BIOVIA Discovery Studio Visualizer to identify hydrogen bonds, hydrophobic interactions, π–π stacking, and other non-covalent interactions between the synthesized compounds and the amino acid residues present in the active site of α-glucosidase.[20]

In Vitro α-Glucosidase Inhibitory Assay

The α-glucosidase inhibitory activity of the synthesized compounds was determined spectrophotometrically using p-nitrophenyl-α-D-glucopyranoside (pNPG) as the substrate. The assay mixture consisted of α-glucosidase enzyme (0.1 U/mL) prepared in 0.1 M phosphate buffer (pH 6.8) and different concentrations of the test compounds. Following incubation at 37°C for 15 min, pNPG (1.25 mM) was added to initiate the enzymatic reaction. After incubation for an additional 30 min at 37°C, the absorbance of the released p-nitrophenolwas measured at 405 nm using a UV–Visible spectrophotometer. Acarbose served as the positive control, while DMSO was used as the negative control. Each experiment was performed in triplicate.[21,22]

The percentage inhibition of α-glucosidase activity was calculated using the following equation:

$$\% \text{ Inhibition} = \frac{\text{A control} - \text{A sample}}{\text{A control}} X100$$

where*A*control represents the absorbance of the control reaction and *A*sample represents the absorbance in the presence of the test compound. The IC_{50} values were determined from concentration–response curves using GraphPad Prism software.[23]

Statistical Analysis

All experiments were carried out in triplicate, and the results are expressed as mean ± standard deviation (SD). Statistical analysis was performed using GraphPad Prism (version 9.0). Differences between groups were analyzed using one-way analysis of variance (ANOVA) followed by Tukey's multiple comparison test. A p value < 0.05 was considered statistically significant.[24]

RESULTS

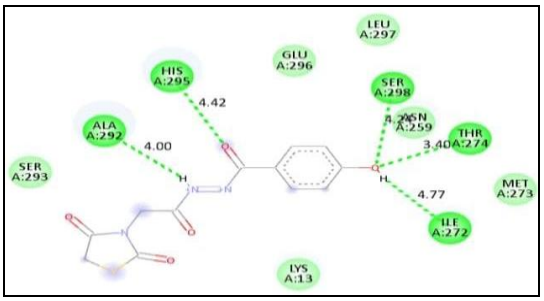
Molecular Docking Studies

Molecular docking was performed to evaluate the binding affinity of the synthesized benzothiazole derivatives against α-glucosidase (PDB ID: 3A4A). The docking scores are presented in Table 1**.** All synthesized compounds exhibited favorable binding affinities, ranging from −6.1 to −7.2 kcal/mol**,** indicating their potential interaction with the enzyme active site. Among the synthesized derivatives, compounds 9d and 13d showed the highest binding affinity **(**−7.2 kcal/mol**),** followed by compound 4d **(**−7.0 kcal/mol**)** and compound 15d **(**−6.9 kcal/mol**).** The standard inhibitor, acarbose, exhibited a docking score of −7.3 kcal/mol**.**

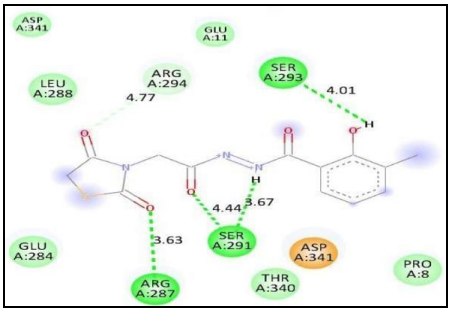
The results suggest that compounds 9d and 13dpossess binding affinities comparable to acarbose, indicating their potential as effective α-glucosidase inhibitors. The variation in docking scores among the synthesized derivatives may be attributed to differences in the nature and position of substituent groups on the benzothiazole scaffold, which influence ligand–protein interactions. Overall, the molecular docking study demonstrated that the synthesized benzothiazole derivatives have promising binding characteristics toward α-glucosidase and warrant further in vitro evaluation to validate their antidiabetic potential.

Table 1: Docking score of designed compounds

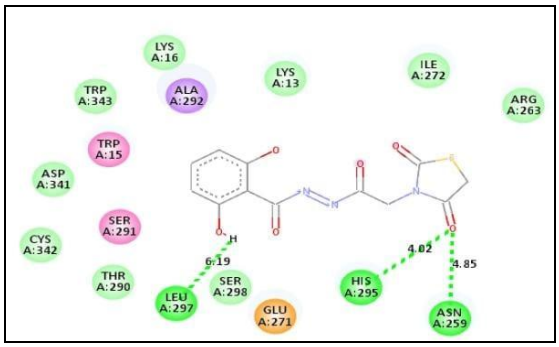
Compound	Binding affinity (kcal/mol)
1d	−6.5
2d	−6.2
3d	−6.7
4d	−7.0
5d	−6.5
6d	−6.1
7d	−6.5
8d	−6.6
9d	**−7.2**
10d	−6.7
11d	−6.3
12d	−6.2
13d	**−7.2**
14d	−6.3
15d	−6.9
Acarbose	**−7.3**



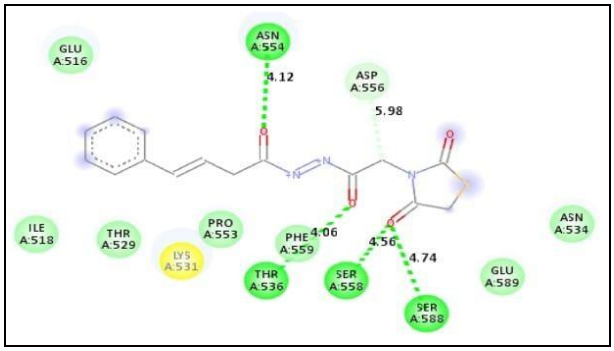
1d



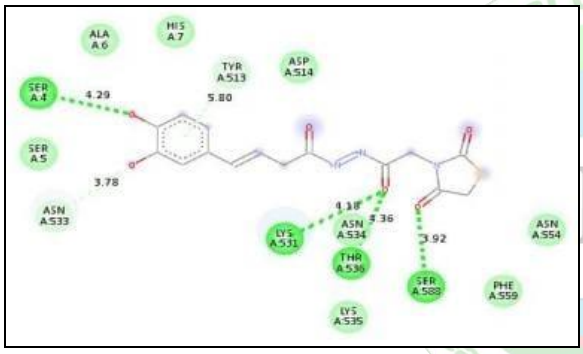
3d



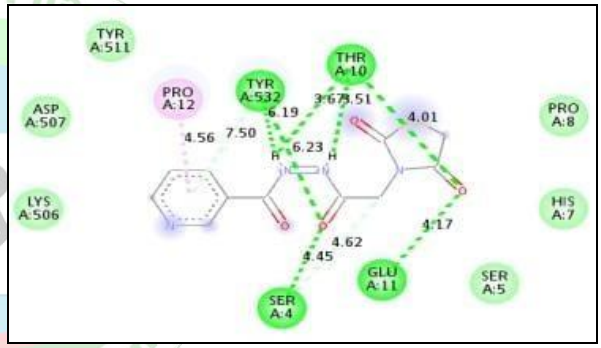
4d



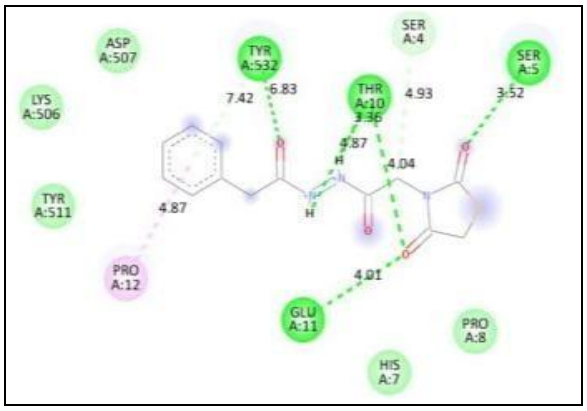
5d



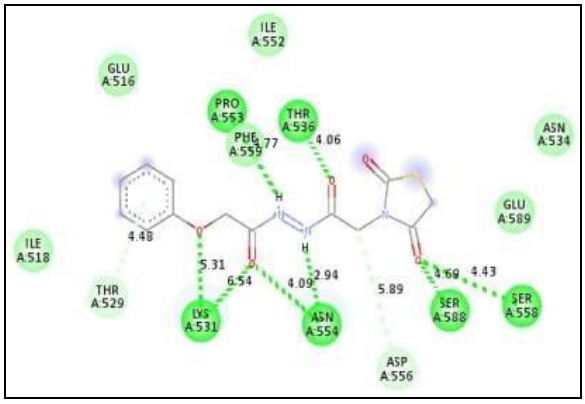
6d



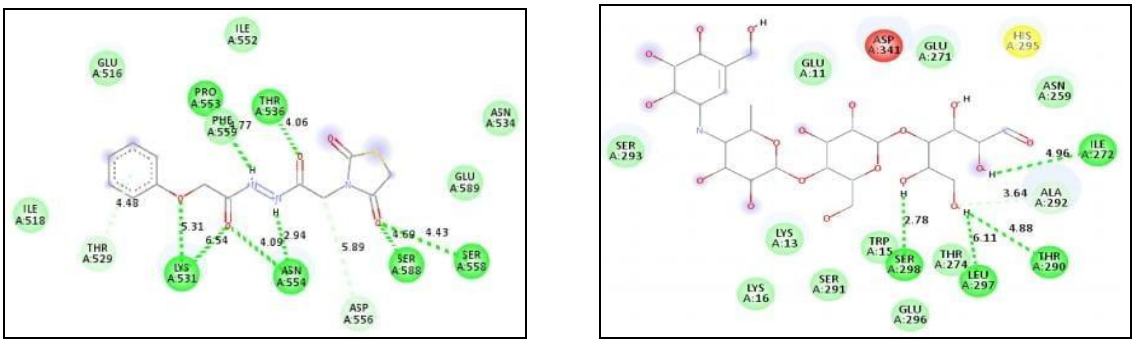
10d



12d



14d



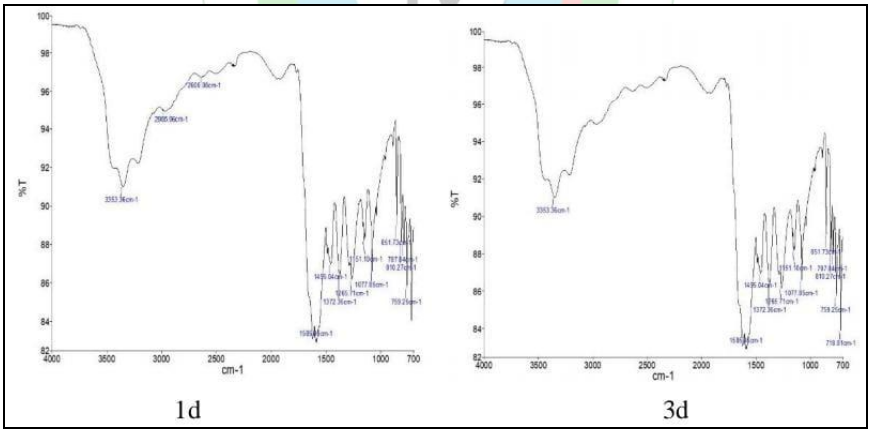
15d acarbose

Figure 2: Protein and ligands interaction

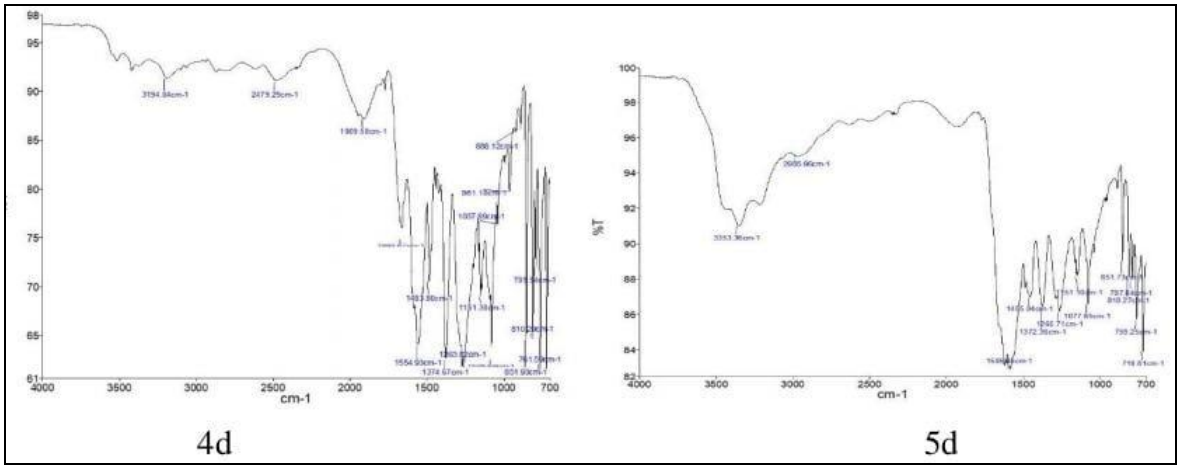
Among the docked compounds, compound 15d possesses significant docking score 9.2 K/cal when compared to standard drug Adriamycin. The compound 24d shows 5 hydrogen bonds between the amino acids GLN94, SER111, ALA117 and ALA 269. The compound 1d shows a significant docking score of - 9.1 K/cal along with 3 hydrogen bonds with amino acids GLN94, PHE96, and ASN267. The remaining docked compound shows a docking score range from 7 to 9 K/cal along with one or two hydrogen bond interactions. Based on the docking score the derivatives 1d, 3d,4d, 5d, 6d, 8d, 10d, 2d, 23d and 24d are selected for the synthesis by conventional method.

Synthetic work

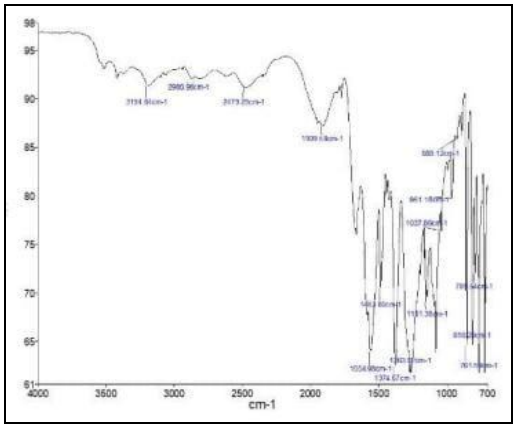
The substituted benzothiazole derivatives are prepared by the reaction of 2 Hydrazino-1,3-benzothiazole and hydroxy-benzotriazole, added to substituted benzoic acid in N,N-dimethylformamide (DMF). On cooled in an ice bath with stirring and then 1-ethyl-3-(3-dimethylaminopropyl) carbodiimde hydrochloride was added and all the compounds and intermediates were purified by successive recrystallization from ethanol. The IR spectrum of the final synthesized compounds showed absorption bands around 2850 – 2950 shows the presence of CH stretching alkane group, the peak 2030 shows presence of CH stretching aromatic and the peak at 1489–1464 cm-1 for CH2, 1379 1344 cm-1 for CH3, and 800–700 cm-1 for aromatic rings.



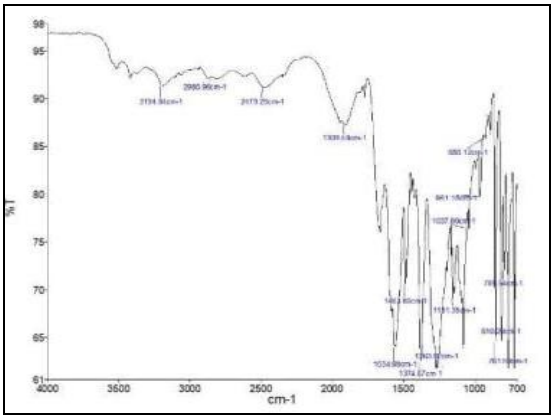
1d 3d



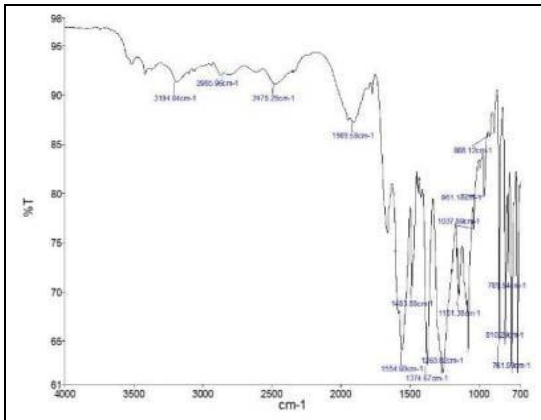
4d 5d



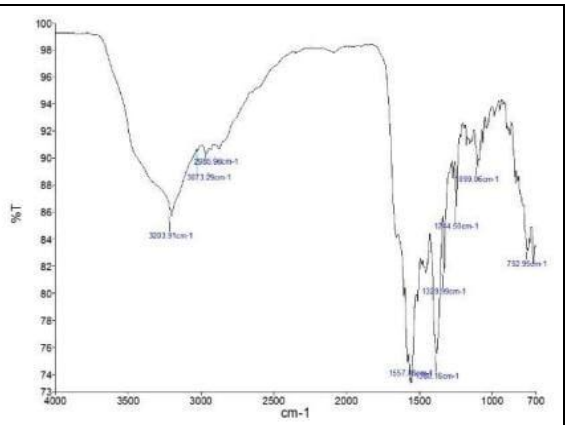
6d



8d



10d



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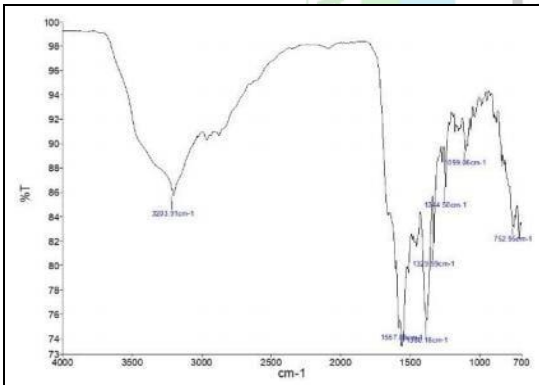
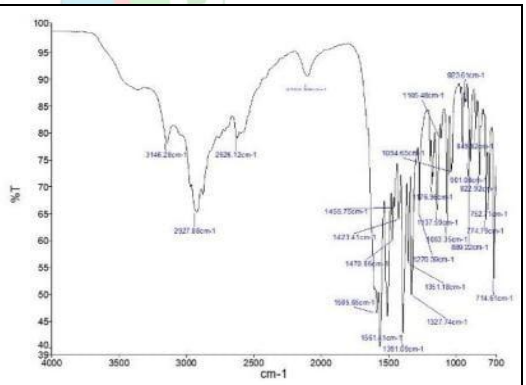


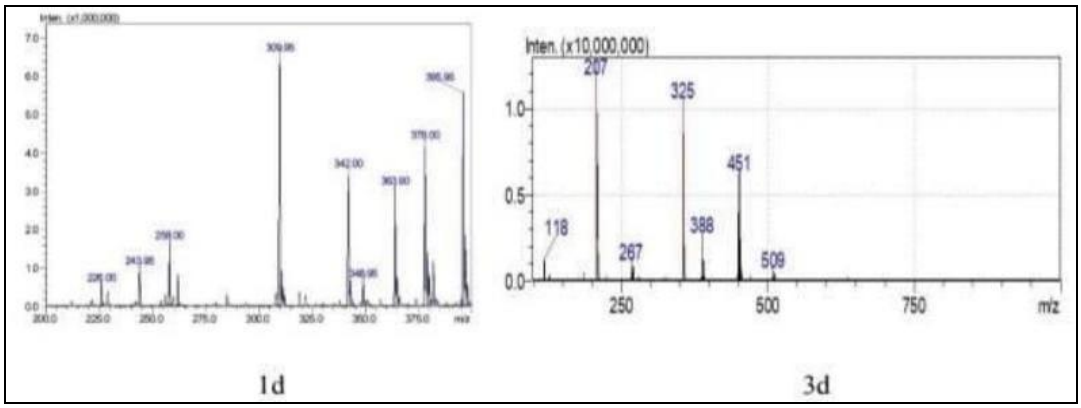
14d



15d

Figure 3: IR Spectrum of compounds

The corresponding molecular ion peak in the LC-MS spectra were in conformity with the assigned structure.



1d 3d

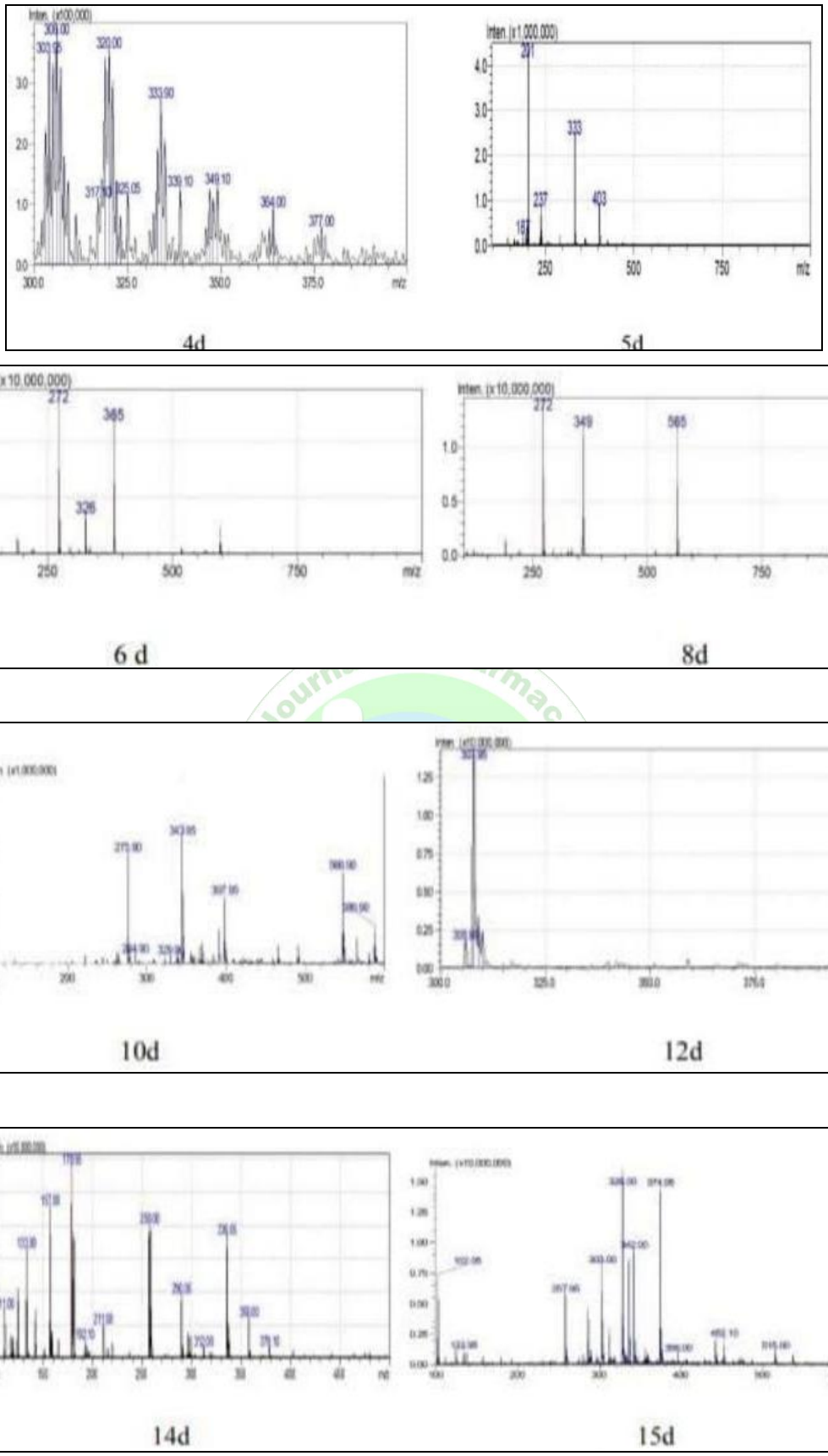
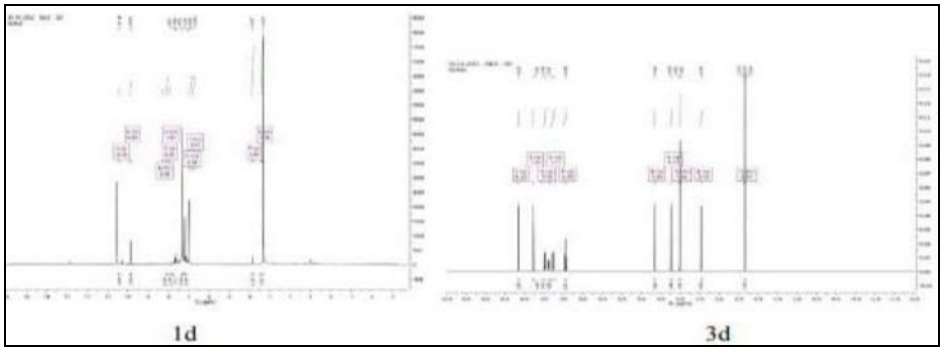
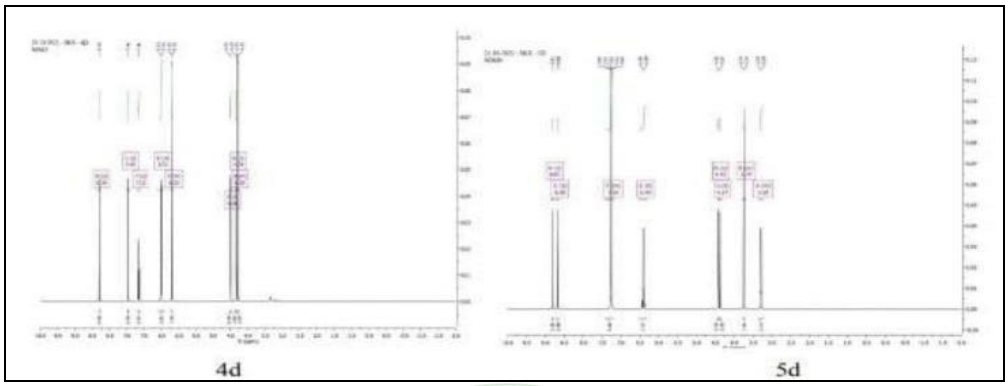
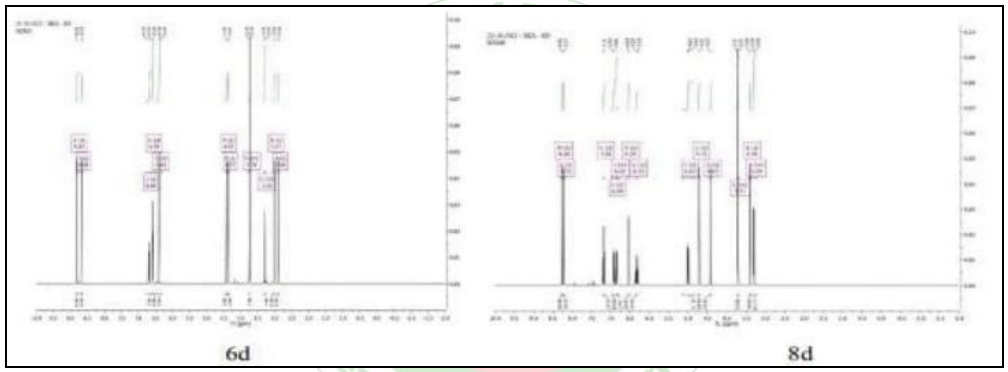


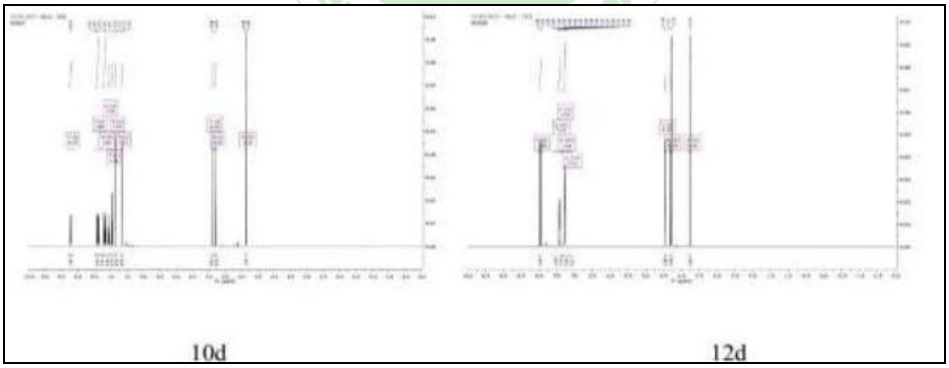
Figure 4: Mass spectra for compound

These compounds also exhibited appropriate peaks at corresponding ppm in their H NMR spectra. The H NMR spectra of the synthesized compounds revealed a singlet signal a signal at 7.5-8.5 for H of aromatic ring. The ^{13}C NMR spectra of synthesized compounds revealed a signal at 160-175 for carbonyl carbon and a signal at 120-145 for aromatic carbon.









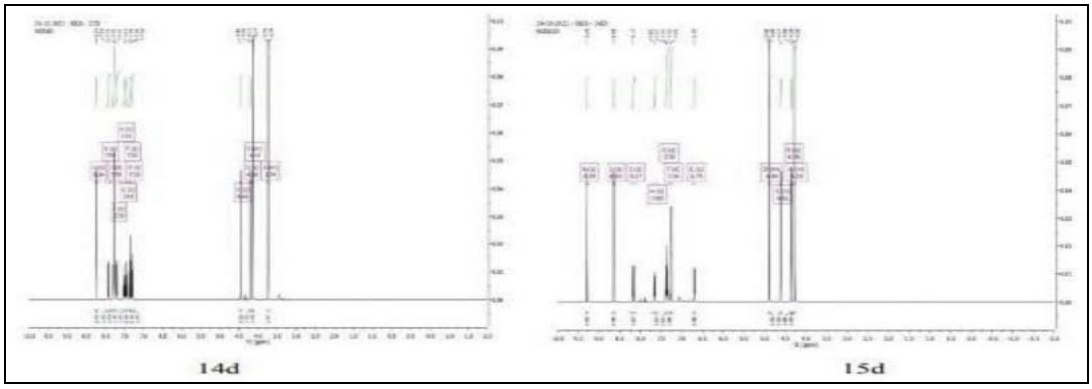


Figure 5: H NMR Spectra for compounds

In-Vitro Antidiabetic Activity

Results of antidiabetic activity of the compounds were expressed as IC50 values which were determined by plotting the percentage cell viability versus concentration of sample on a logarithmic graph and reading off the control. The experiments were performed in triplicates, and then, the final IC50 values were calculated by taking average of triplicate results. The results of in-vitro anti-diabetic activity expressed in IC50 (µg/mL) are expressed in table 2 and were compared to Acrabose. Among the tested compounds, several derivatives exhibited significant inhibitory activity. Compound 10d showed the highest activity with an IC_{50} value of 5.44 ± 0.13 µM, indicating strong inhibition of Alpha-glucosidase. This was followed by compound 5d (IC_{50} = 6.57 ± 0.17 µM) and compound 4d (IC_{50} = 7.93 ± 0.18 µM), which also demonstrated potent inhibitory effects. Compounds 3d (17.18 ± 0.15 µM) and 1d (20.85 ± 0.22 µM) showed moderate activity, while compounds 14d and 15d exhibited comparatively lower inhibition with IC_{50} values of 39.81 ± 0.36 µM and 35.79 ± 0.25 µM, respectively.

Table 2: In vitro α-glucosidase inhibitory activity of synthesized benzothiazole derivatives and the reference standard

S. No.	Compound	IC_{50} (µM)
1	1d	20.85 ± 0.22
2	3d	17.18 ± 0.15
3	4d	7.93 ± 0.18
4	5d	6.57 ± 0.17
5	10d	**5.44 ± 0.13**
6	13d	7.72 ± 0.16
7	14d	39.81 ± 0.36
8	15d	35.79 ± 0.25
9	Acarbose (Standard)	817.38 ± 6.27

The enhanced activity observed for compounds 10d, 5d, and 4d may be attributed to the presence of favorable aromatic substituents on the benzothiazole scaffold, which can facilitate stronger hydrogen bonding and hydrophobic interactions with the active site residues of Alpha-glucosidase. These interactions improve the binding affinity of the compounds toward the enzyme and consequently enhance their inhibitory activity. When compared with the standard drug Acarbose (IC_{50} = 817.38 ± 6.27 µM), the synthesized benzothiazole derivatives exhibited remarkably stronger inhibitory activity, suggesting that the benzothiazole scaffold plays an important role in enhancing antidiabetic potential.

DISCUSSION

A series of novel benzothiazole derivatives were successfully synthesized using a straightforward synthetic approach with good yields and satisfactory purity. The structures of the synthesized compounds were confirmed by FT-IR, ^1H NMR, and LC-MS spectral analyses, which were consistent with the proposed molecular structures. Molecular docking studies demonstrated that all synthesized derivatives exhibited favorable binding affinities toward α-glucosidase, with compounds 9d and 13d showing docking scores comparable to the standard inhibitor, acarbose. The *in vitro* α-glucosidase inhibitory assay further revealed that several compounds exhibited potent inhibitory activity, particularly 10d**,** 5d**,** 13d**,** and 4d, which showed lower IC_{50} values than the reference standard. The enhanced activity may be attributed to the presence of suitable aromatic substituents capable of forming favorable hydrogen-bonding and hydrophobic interactions within the enzyme active site. Overall, the findings suggest that structural modification of the benzothiazole scaffold significantly influences α-glucosidase inhibition, and the synthesized derivatives represent promising lead molecules for the development of novel antidiabetic agents.

CONCLUSION

A series of novel benzothiazole derivatives were successfully synthesized and evaluated for their α-glucosidase inhibitory potential through molecular docking and *in vitro* studies. The synthesized compounds exhibited favorable binding affinities toward α-glucosidase, with compounds 9d and 13dshowing docking scores comparable to the reference drug acarbose. Among the tested derivatives, compound 10d demonstrated the most potent *in vitro* α-glucosidase inhibitory activity, followed by compounds 5d**,** 13d, and 4d. The enhanced activity observed for these derivatives suggests that appropriate aromatic substitutions on the benzothiazole scaffold contribute to improved enzyme inhibition. Overall, the findings indicate that benzothiazole derivatives represent promising lead molecules for the development of novel α-glucosidase inhibitors with potential antidiabetic activity. Further in vivo pharmacological studies and toxicity evaluations are warranted to establish their therapeutic efficacy and safety.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest

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