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Synthesis, Spectral Characterization, Molecular Docking and In-Vitro α-Amylase Inhibitory Evaluation of Novel Thiazolidin-3-yl-Benzamide Derivatives as Potential Antidiabetic Agents

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Abstract:

A novel series of ten thiazolidin-3-yl-benzamide derivatives (B1–B10) was designed and synthesized via a green, microwave-assisted, one-pot three-component condensation of benzohydrazide, substituted benzaldehydes and thioglycolic acid in absolute ethanol. The reaction proceeded efficiently at 110–130 °C within 20–60 minutes to afford the target compounds in good to excellent yields. All synthesized derivatives were characterized by melting point, Rf value, IR, ^{1}H NMR, ^{13}C NMR and mass spectrometry, which confirmed the formation of the thiazolidinone ring and the benzamide linkage. In-silico molecular docking of the derivatives against α-amylase (PDB ID: 1HNY) using AutoDock Vina (PyRx 0.8) revealed binding energies ranging from –6.9 to –8.8 kcal/mol, with compound B5 (para-tolyl substituted) exhibiting the most favourable binding energy (–8.8 kcal/mol), nearly equivalent to the standard inhibitor Acarbose (–8.9 kcal/mol). In-vitro α-amylase inhibitory activity, assessed by the starch–iodine/DNS colorimetric method, showed IC50 values ranging from 36.10 to 66.35 µM. Compound B5 emerged as the most potent inhibitor (IC50 = 36.10 ± 0.34 µM), comparable to Acarbose (IC50 = 35.50 ± 0.04 µM), followed by B6, B3 and B4. A strong correlation was observed between the computational binding affinities and the experimental IC50 values, validating the reliability of the docking protocol. Structure–activity relationship analysis indicated that electron-donating alkyl/halogen substituents at the para-position of the 4-aryl ring favourably influenced α-amylase binding and inhibition. These findings suggest that the thiazolidin-3-yl-benzamide scaffold, particularly compound B5, represents a promising lead template for the design of new α-amylase inhibitors for the management of type 2 diabetes mellitus.

Keywords: Thiazolidinone, Benzamide, Green synthesis, Molecular docking, α-Amylase, Antidiabetic activity

1. INTRODUCTION

Medicinal chemists continue to focus extensively on heterocyclic ring systems because of their structural diversity and multifunctional nature. Heterocyclic compounds represent one of the most versatile and significant classes of organic molecules, and their numbers continue to grow rapidly due to continuous advancements in synthetic methodology. These compounds play a pivotal role in medicinal chemistry and drug discovery owing to their wide-ranging biological and therapeutic applications, and it has been reported that more than 90% of clinically used drugs contain a heterocyclic moiety. Advancements in heterocyclic chemistry have demonstrated diverse pharmacological activities including anticancer, anti-inflammatory, antifungal, antiallergic, antibacterial, anti-HIV and antiviral effects.

Among heterocycles, sulfur-containing ring systems have gained considerable interest owing to their unique chemical and biological properties; a substantial proportion of FDA-approved pharmaceuticals incorporate sulfur-containing heterocyclic scaffolds. Among these, the thiazolidinedione scaffold, particularly 2,4-thiazolidinedione (2,4-TZD), has been extensively investigated as a key pharmacophore for the development of therapeutically active compounds. 2,4-Thiazolidinedione is a five-membered heterocyclic ring composed of sulfur, nitrogen and carbon atoms bearing two carbonyl groups at the 2nd and 4th positions. The electron-withdrawing carbonyl groups enhance the acidity of the methylene hydrogen at the 5th position, facilitating structural modification at the methylene carbon and the ring nitrogen atom. Thiazolidinediones were introduced in the late 1990s as antidiabetic agents for the management of type 2 diabetes mellitus (T2DM); subsequent investigations have expanded their pharmacological relevance to anticancer, antimicrobial, anti-arthritic, anti-inflammatory and antioxidant applications, acting through multiple molecular targets including PPAR-γ, aldose reductase (ALR2), PI3K, PTP1B, COX-2, HDAC and tyrosinase.

Type 2 diabetes mellitus is a metabolic disorder characterized by persistent hyperglycaemia arising from insulin resistance, impaired insulin secretion and progressive pancreatic β-cell dysfunction. It remains one of the most prevalent chronic diseases worldwide, and poorly controlled disease leads to progressive damage of the eyes, kidneys, nerves and cardiovascular system. One clinically validated strategy for postprandial glycaemic control is the inhibition of carbohydrate-hydrolysing enzymes such as α-amylase, which delays the breakdown of starch to glucose and thereby blunts the postprandial glucose surge. Acarbose, a clinically used α-amylase/α-glucosidase inhibitor, exemplifies this approach, although its use is often limited by gastrointestinal side effects, which underscores the continuing need for new, well-tolerated α-amylase inhibitors.

1.1 Diabetes Mellitus: Epidemiology and Burden

Type 2 diabetes mellitus (T2DM) is currently one of the most prevalent chronic diseases worldwide, with its incidence and prevalence steadily increasing. It was estimated that approximately 366 million individuals globally, representing 8.3% of the population aged 20–79 years, were living with T2DM, with projections suggesting this figure would rise substantially in subsequent decades, reflecting the growing global burden of the disease. T2DM is associated with numerous severe and long-term complications that significantly impair patients' health, productivity and quality of life. Cardiovascular disease, including heart disease and stroke, accounts for more than 50% of deaths among individuals with diabetes; the condition is also a leading cause of end-stage renal disease and a major contributor to adult-onset blindness through diabetic retinopathy. Individuals with T2DM additionally face a markedly increased risk of lower-limb amputation compared with non-diabetic individuals, underscoring the substantial global health impact of the disease.

1.2 Risk Factors and Pathophysiology

T2DM develops primarily as a result of complex interactions between lifestyle factors and genetic predisposition. Modifiable risk factors include physical inactivity, sedentary behaviour, cigarette smoking and excessive alcohol consumption, with obesity considered one of the most important contributors, accounting for a substantial proportion of T2DM cases. Genetic susceptibility is also strongly associated with the disease; individuals with a family history,

particularly first-degree relatives, show significantly elevated risk, and several susceptibility genes (including TCF7L2, PPARG, FTO, KCNJ11 and others) have been identified. Certain monogenic forms of diabetes and several coexisting medical conditions, including hypertension, dyslipidaemia and metabolic syndrome, may also predispose to or exacerbate T2DM.

Pathophysiologically, T2DM is characterized primarily by insulin resistance, progressive decline in insulin secretion and eventual pancreatic β-cell dysfunction. Insulin resistance reduces glucose uptake in peripheral tissues such as skeletal muscle and adipose tissue and impairs suppression of hepatic glucose production, while inadequately suppressed glucagon secretion further promotes inappropriate hepatic glucose output. Adipose tissue, acting as an active endocrine organ secreting adipocytokines such as leptin, TNF-α, resistin and adiponectin, is also implicated in insulin resistance and β-cell dysfunction, particularly in individuals with central or visceral adiposity.

1.3 Management Strategies and the Rationale for α-Amylase Inhibition

T2DM can be significantly prevented, delayed, or managed through appropriate lifestyle and dietary modification, including weight control, a diet rich in dietary fibre and unsaturated fats, regular physical activity and smoking cessation. Where pharmacological intervention is required, several drug classes are employed, including biguanides, sulfonylureas, thiazolidinediones, DPP-IV inhibitors, GLP-1 receptor agonists, and α-glucosidase/α-amylase inhibitors. Among these, inhibition of α-amylase, the enzyme responsible for hydrolysing dietary starch into absorbable oligosaccharides and glucose, represents a clinically validated strategy for controlling postprandial hyperglycaemia by delaying carbohydrate digestion and glucose absorption in the small intestine. Acarbose, the prototype α-amylase/α-glucosidase inhibitor, is widely used for this purpose; however, its clinical utility is often limited by gastrointestinal adverse effects such as flatulence, bloating and diarrhoea, arising from undigested carbohydrate fermentation in the colon. This limitation continues to drive the search for novel, well-tolerated small-molecule α-amylase inhibitors with improved pharmacological profiles.

Given the established antidiabetic relevance of the thiazolidinedione pharmacophore and the pharmacological versatility conferred by an appended benzamide moiety, the present study was designed to synthesize a novel series of thiazolidin-3-yl-benzamide derivatives (B1–B10) using an environmentally benign, microwave-assisted one-pot protocol. The synthesized derivatives were characterized by spectroscopic methods, subjected to in-silico molecular docking against the α-amylase enzyme, and evaluated for in-vitro α-amylase inhibitory activity in order to identify promising lead candidates for the management of type 2 diabetes mellitus.

2. AIM AND OBJECTIVES

Aim

The aim of the present study is to design and synthesize a series of thiazolidin-3-yl-benzamide derivatives using an environmentally friendly ("green") microwave-assisted synthetic method, to characterize the synthesized compounds by spectroscopic techniques, and to evaluate their antidiabetic potential through molecular docking and in-vitro α-amylase inhibitory studies.

Objectives

- To design and synthesize a series of thiazolidin-3-yl-benzamide derivatives (B1–B10).
- To develop an efficient, green, microwave-assisted methodology for the synthesis of these derivatives.
- To elucidate the structures of the synthesized compounds using IR, ^{1}H NMR, ^{13}C NMR and mass spectrometry.
- To perform molecular docking studies of the designed compounds against the α-amylase enzyme (PDB ID: 1HNY) to predict their binding interactions.
- To evaluate the in-vitro α-amylase inhibitory (antidiabetic) activity of the synthesized derivatives and compare it with the standard drug Acarbose.

3. MATERIALS AND METHODOLOGY

Materials and Instrumentation

All reactions were carried out in oven-dried glassware using analytical-grade reagents and laboratory-grade solvents purified as required, following the procedures outlined in Vogel's Textbook of Practical Organic Chemistry. Melting points were determined in open glass capillary tubes using a Veego VMP-1 apparatus and are reported uncorrected. Reaction progress and purity were monitored by ascending thin-layer chromatography (TLC) on pre-coated silica gel plates (Merck 60 F254) visualised under UV light, using n-hexane, ethyl acetate, methanol, petroleum ether, chloroform and dichloromethane as mobile phase systems. IR spectra were recorded on a Perkin-Elmer FT-IR spectrometer (cm^{-1}). ^{1}H NMR spectra were obtained on a Bruker DRX-300 (500 MHz) spectrometer using DMSO-d6 as solvent and TMS as internal standard; ^{13}C NMR spectra were recorded on a Bruker spectrometer using DMSO-d6. Mass spectra were acquired using a Shimadzu LC-MS instrument.

Synthesis of Thiazolidin-3-yl-Benzamide Derivatives (B1–B10)

In a 10–20 mL microwave vial, benzohydrazide (147 mg, 1.00 mmol), the appropriate substituted benzaldehyde (1.00 mmol), thioglycolic acid (92 mg, 1.20 mmol) and absolute ethanol (5.0 mL) were combined. Para-toluenesulfonic acid (p-TsOH, 10 mol%, 19 mg) was added only when previous trials showed sluggish conversion, since most substrates reacted efficiently under microwave irradiation without an added catalyst. The vial was placed in a microwave reactor and irradiated at 110–130 °C for 20–60 minutes. Upon completion (monitored by TLC using hexane/ethyl acetate 3:1), the reaction mixture was cooled, and the precipitated solid was collected by vacuum filtration, washed with cold ethanol (2 × 3 mL), and purified by recrystallization from ethanol to afford the target thiazolidin-3-yl-benzamide

derivative. Ten derivatives (B1–B10, Table 1) bearing phenyl, 4-aminophenyl, pyridin-2-yl, pyridin-4-yl, p-tolyl, 4-methoxyphenyl, 4-chlorophenyl, 4-fluorophenyl, o-tolyl and 4-hydroxyphenyl substituents at the 4-position of the thiazolidinone ring were prepared by this general procedure.

In-Silico Molecular Docking Studies

Molecular structures of the designed ligands were constructed and energy-minimized using MarvinSketch, and docking simulations were performed using PyRx 0.8, which incorporates AutoDock Vina as the docking engine. The three-dimensional crystal structure of α-amylase (PDB ID: 1HNY) was retrieved from the Protein Data Bank. Protein preparation involved removal of co-crystallized ligands, water molecules and heteroatoms, addition of polar hydrogens, and assignment of Kollman/Gasteiger charges, followed by energy minimization using Swiss-PDB Viewer and stereochemical validation using a Ramachandran plot. Active-site residues were identified using the Protein–Ligand Interaction Profiler (PLIP). Ligand structures were minimized using Open Babel with Gasteiger charges and the Universal Force Field (UFF) prior to conversion to .pdbqt format. A grid box of 40 × 40 × 40 Å, centred on the catalytic pocket, was used to encompass the active site, and docking was performed with AutoDock Vina at default exhaustiveness. The lowest-energy pose for each ligand was selected for further analysis, and post-docking interaction analysis (hydrogen bonding, hydrophobic contacts, π–π stacking and electrostatic interactions) was performed using Discovery Studio Visualizer, with Acarbose used as the reference standard.

Scheme of the Synthetic Route

The general synthetic route (Scheme 1) involves a one-pot, three-component cyclo-condensation in which benzohydrazide first condenses with the substituted benzaldehyde to generate the corresponding benzylidene (acylhydrazone) intermediate. Nucleophilic addition of thioglycolic acid across the C=N bond, followed by intramolecular cyclization and dehydration under microwave irradiation, furnishes the 2-oxothiazolidine ring bearing the aryl substituent at C-4 and the benzamide nitrogen at N-3. Variation of the aryl aldehyde component (phenyl, 4-aminophenyl, pyridin-2-yl, pyridin-4-yl, p-tolyl, 4-methoxyphenyl, 4-chlorophenyl, 4-fluorophenyl, o-tolyl and 4-hydroxyphenyl) furnished the ten target derivatives B1–B10 respectively, while keeping the benzohydrazide and thioglycolic acid components constant. This one-pot, catalyst-free, microwave-assisted protocol offers several advantages over conventional reflux methods, including shorter reaction times (20–60 minutes versus several hours), higher atom economy, reduced solvent consumption, and improved yields, consistent with the principles of green chemistry.

In-Vitro α-Amylase Inhibitory (Antidiabetic) Assay

A 0.1% w/v starch solution was prepared in sodium acetate buffer (pH 4.8, 16 mM), and the α-amylase enzyme solution was prepared by dissolving 27.5 mg of α-amylase in 100 mL of deionized water. The colorimetric DNS reagent was prepared by dissolving 1 g of 3,5-dinitrosalicylic acid in 20 mL of deionized water, followed by 0.16 g sodium hydroxide (in 10 mL deionized water) and 4 g sodium potassium tartrate, made up to 100 mL. For the assay, 100 µL of test compound (or Acarbose) was incubated with 100 µL starch solution and 100 µL α-amylase solution at 25 °C for 30 minutes. The reaction was terminated by addition of DNS reagent, and the amount of maltose liberated

was quantified colorimetrically at 540 nm, corresponding to formation of 3-amino-5-nitrosalicylic acid. A positive control (α-amylase with starch, no inhibitor) and a negative control (starch without α-amylase) were included, and all assays were performed in triplicate (n = 3). Percentage inhibition was calculated relative to the positive control, and IC50 values were derived from the dose–response curves for each compound and for Acarbose.

4. RESULTS AND DISCUSSION

4.1 Chemistry

A novel series of N-(2-oxo-4-arylthiazolidin-3-yl)benzamide derivatives (B1–B10) was synthesized by condensation of benzohydrazide with various substituted benzaldehydes and thioglycolic acid under microwave irradiation using absolute ethanol as solvent. The reaction proceeded smoothly under controlled microwave conditions (110–130 °C, 20–60 min) to afford the target compounds in good to excellent yields. All compounds were obtained as crystalline solids ranging from white to pale white in colour, with melting points between 113–141 °C, and Rf values (0.75–0.93) confirming product formation distinct from the starting materials.

IR spectra of all compounds displayed a characteristic amide N–H stretching band between 3200–3350 cm^{-1}, confirming formation of the benzamide linkage, together with a strong absorption at 1620–1675 cm^{-1} attributable to C=O stretching of the thiazolidinone ring; C–N bending vibrations appeared at 1380–1440 cm^{-1} and aromatic C–H stretching around 3030–3070 cm^{-1}. In the ^{1}H NMR spectra, aromatic protons resonated as multiplets between δ 7.0–8.0 ppm, while a singlet at δ 5.4–5.6 ppm was assigned to the methine proton at the 4-position of the thiazolidinone ring, and signals at δ 4.0–4.1 and 3.8–3.9 ppm corresponded to the diastereotopic methylene protons of the ring. ^{13}C NMR spectra showed characteristic signals between δ 167–170 ppm (amide C=O) and δ 160–162 ppm (thiazolidinone C=O), with aromatic carbons resonating between δ 120–140 ppm consistent with the respective substitution pattern. Mass spectrometry confirmed the molecular formula of each compound by matching the exact and found molecular ion peaks. The complete spectral data for compounds B1–B10 are summarized in Tables 1–10.

Table 1. Spectral data of compound B1

Parameter	N-(2-oxo-4-phenylthiazolidin-3-yl)benzamide
Molecular formula	C16H14N2O2S
Colour	White
Melting point	123–125°C
Rf value	0.81
IR (cm^{-1})	3301 (N–H str); 3057 (C–H str, alkene); 2947 (C–H str, aromatic); 2534 (C–H str, alkene); 1539 (C=O str); 1400 (C–N bending); 897 (aromatic ring); 710 (C–Br str)

Parameter	N-(2-oxo-4-phenylthiazolidin-3-yl)benzamide
^{1}H NMR (500 MHz, DMSO-d6) δ	7.87–7.76 (m, 2H), 7.45 (s, 1H), 7.43–7.37 (m, 2H), 7.35–7.28 (m, 4H), 7.24 (s, 1H), 6.79 (s, 1H), 5.61 (s, 1H), 4.07 (s, 1H), 3.85 (s, 1H)
^{13}C NMR (125 MHz, DMSO-d6) δ	167.45, 160.65, 135.96, 132.71, 132.03, 128.79, 128.78, 128.47, 128.28, 127.89, 68.70, 33.80
Mass (m/z)	Exact Mass: 298 m/z; Found Mass: 298 m/z

Table 2. Spectral data of compound B2

Parameter	N-(4-(4-aminophenyl)-2-oxothiazolidin-3-yl)benzamide
Molecular formula	C16H15N3O2S
Colour	White
Melting point	122–125°C
Rf value	0.80
IR (cm^{-1})	3301 (N–H str); 3057 (C–H str, alkene); 2947 (C–H str, aromatic); 2534 (C–H str, alkene); 1539 (C=O str); 1400 (C–N bending); 897 (aromatic ring); 710 (C–Br str)
^{1}H NMR (500 MHz, DMSO-d6) δ	7.87–7.75 (m, 2H), 7.46 (s, 1H), 7.44–7.38 (m, 2H), 7.08–6.94 (m, 2H), 6.81 (s, 1H), 6.66–6.51 (m, 2H), 5.58 (s, 1H), 4.07 (s, 1H), 3.86 (s, 1H), 3.76–3.72 (m, 2H)
^{13}C NMR (125 MHz, DMSO-d6) δ	167.46, 160.65, 146.07, 132.71, 132.03, 129.31, 129.31, 128.48, 128.48, 128.28, 128.28, 122.57, 114.49, 114.49, 68.70, 33.81
Mass (m/z)	Exact Mass: 313 m/z; Found Mass: 313 m/z

Table 3. Spectral data of compound B3

Parameter	N-(2-oxo-4-(pyridin-2-yl)thiazolidin-3-yl)benzamide
Molecular formula	C15H13N3O2S

Parameter	N-(2-oxo-4-(pyridin-2-yl)thiazolidin-3-yl)benzamide
Colour	White
Melting point	114–116°C
Rf value	0.87
IR (cm^{-1})	3341 (N–H str); 3027 (C–H str, alkene); 2600 (C–H str, aromatic); 1571 (C=O str); 1420 (C–N bending); 950 (aromatic ring); 718 (C–Br str)
^{1}H NMR (500 MHz, DMSO-d6) δ	8.55 (s, 1H), 7.91–7.80 (m, 2H), 7.75 (s, 1H), 7.66 (s, 1H), 7.49 (s, 1H), 7.47–7.40 (m, 2H), 7.24 (s, 1H), 7.08 (s, 1H), 5.64 (s, 1H), 4.06 (s, 1H), 3.86 (s, 1H)
^{13}C NMR (125 MHz, DMSO-d6) δ	167.45, 160.65, 154.22, 147.34, 138.52, 132.71, 132.03, 128.47, 128.28, 122.83, 121.39, 64.04, 32.13
Mass (m/z)	Exact Mass: 299 m/z; Found Mass: 299 m/z

Table 4. Spectral data of compound B4

Parameter	N-(2-oxo-4-(pyridin-4-yl)thiazolidin-3-yl)benzamide
Molecular formula	C15H13N3O2S
Colour	White
Melting point	132–135°C
Rf value	0.83
IR (cm^{-1})	3184 (N–H str); 3051 (C–H str, alkene); 2871 (C–H str, aromatic); 2701 (C–H str, alkene); 1554 (C=O str); 1390 (C–N bending); 850 (aromatic ring); 766 (C–Br str)
^{1}H NMR (500 MHz, DMSO-d6) δ	8.55 (s, 1H), 7.91–7.80 (m, 2H), 7.75 (s, 1H), 7.66 (s, 1H), 7.49 (s, 1H), 7.47–7.40 (m, 2H), 7.24 (s, 1H), 7.08 (s, 1H), 5.64 (s, 1H), 4.06 (s, 1H), 3.86 (s, 1H)

Parameter	N-(2-oxo-4-(pyridin-4-yl)thiazolidin-3-yl)benzamide
^{13}C NMR (125 MHz, DMSO-d6) δ	167.45, 160.65, 154.22, 147.34, 138.52, 132.71, 132.03, 128.47, 128.28, 122.83, 121.39, 64.04, 32.13
Mass (m/z)	Exact Mass: 299 m/z; Found Mass: 299 m/z

Table 5. Spectral data of compound B5

Parameter	N-(2-oxo-4-(p-tolyl)thiazolidin-3-yl)benzamide
Molecular formula	C17H16N2O2S
Colour	Pale white
Melting point	113–117°C
Rf value	0.81
IR (cm^{-1})	3349 (N–H str); 3030 (C–H str, alkene); 2648 (C–H str, aromatic); 1647 (C=O str); 1430 (C–N bending); 950 (aromatic ring); 760 (C–Br str)
^{1}H NMR (500 MHz, DMSO-d6) δ	7.87–7.76 (m, 2H), 7.45 (s, 1H), 7.43–7.37 (m, 2H), 7.30–7.12 (m, 4H), 6.63 (s, 1H), 5.60 (s, 1H), 4.08 (s, 1H), 3.86 (s, 1H), 2.35–2.31 (m, 3H)
^{13}C NMR (125 MHz, DMSO-d6) δ	167.45, 160.65, 138.29, 135.03, 132.71, 132.03, 129.69, 128.59, 128.47, 128.28, 68.70, 33.80, 21.12
Mass (m/z)	Exact Mass: 312 m/z; Found Mass: 311 m/z

Table 6. Spectral data of compound B6

Parameter	N-(4-(4-methoxyphenyl)-2-oxothiazolidin-3-yl)benzamide
Molecular formula	C17H16N2O3S
Colour	White

Parameter	N-(4-(4-methoxyphenyl)-2-oxothiazolidin-3-yl)benzamide
Melting point	124–126°C
Rf value	0.79
IR (cm^{-1})	3294 (N–H str); 3041 (C–H str, alkene); 2684 (C–H str, aromatic); 1650 (C=O str); 1436 (C–N bending); 918 (aromatic ring); 749 (C–Br str)
^{1}H NMR (500 MHz, DMSO-d6) δ	7.89–7.77 (m, 2H), 7.49 (s, 1H), 7.46–7.40 (m, 2H), 7.21–7.06 (m, 2H), 6.96–6.81 (m, 2H), 6.71 (s, 1H), 5.49 (s, 1H), 4.05 (s, 1H), 3.85–3.79 (m, 4H)
^{13}C NMR (125 MHz, DMSO-d6) δ	167.45, 160.65, 158.08, 132.71, 132.03, 129.20, 128.52, 128.47, 128.28, 114.20, 68.70, 56.03, 33.80
Mass (m/z)	Exact Mass: 328 m/z; Found Mass: 327 m/z

Table 7. Spectral data of compound B7

Parameter	N-(4-(4-chlorophenyl)-2-oxothiazolidin-3-yl)benzamide
Molecular formula	C16H13ClN2O2S
Colour	White
Melting point	138–141°C
Rf value	0.75
IR (cm^{-1})	3204 (N–H str); 3040 (C–H str, alkene); 2600 (C–H str, aromatic); 1649 (C=O str); 1400 (C–N bending); 869 (aromatic ring); 754 (C–Br str)
^{1}H NMR (500 MHz, DMSO-d6) δ	7.87–7.76 (m, 2H), 7.49 (s, 1H), 7.46–7.40 (m, 2H), 7.26 (s, 1H), 7.20–7.16 (m, 2H), 7.04–6.99 (m, 2H), 5.50 (s, 1H), 4.03 (s, 1H), 3.83 (s, 1H)
^{13}C NMR (125 MHz, DMSO-d6) δ	167.45, 160.65, 135.41, 133.31, 132.71, 132.03, 130.43, 129.11, 128.47, 128.28, 68.70, 33.80

Parameter	N-(4-(4-chlorophenyl)-2-oxothiazolidin-3-yl)benzamide
Mass (m/z)	Exact Mass: 332 m/z; Found Mass: 331 m/z

Table 8. Spectral data of compound B8

Parameter	N-(4-(4-fluorophenyl)-2-oxothiazolidin-3-yl)benzamide
Molecular formula	C16H13FN2O2S
Colour	White
Melting point	119–123°C
Rf value	0.92
IR (cm^{-1})	3300 (N–H str); 3008 (C–H str, alkene); 2746 (C–H str, aromatic); 1674 (C=O str); 1400 (C–N bending); 948 (aromatic ring); 754 (C–Br str)
^{1}H NMR (500 MHz, DMSO-d6) δ	7.87–7.76 (m, 2H), 7.49 (s, 1H), 7.46–7.40 (m, 2H), 7.26 (s, 1H), 7.20–7.16 (m, 2H), 7.04–6.99 (m, 2H), 5.50 (s, 1H), 4.03 (s, 1H), 3.83 (s, 1H)
^{13}C NMR (125 MHz, DMSO-d6) δ	167.45, 160.65, 135.41, 133.31, 132.71, 132.03, 130.43, 129.11, 128.47, 128.28, 68.70, 33.80
Mass (m/z)	Exact Mass: 316 m/z; Found Mass: 316 m/z

Table 9. Spectral data of compound B9

Parameter	N-(2-oxo-4-(o-tolyl)thiazolidin-3-yl)benzamide
Molecular formula	C17H16N2O2S
Colour	White
Melting point	124–126°C

Parameter	N-(2-oxo-4-(o-tolyl)thiazolidin-3-yl)benzamide
Rf value	0.88
IR (cm^{-1})	3354 (N–H str); 3149 (C–H str, alkene); 2603 (C–H str, aromatic); 1623 (C=O str); 1400 (C–N bending); 984 (aromatic ring); 789 (C–Br str)
^{1}H NMR (500 MHz, DMSO-d6) δ	7.87–7.76 (m, 2H), 7.45 (s, 1H), 7.43–7.37 (m, 2H), 7.30–7.12 (m, 4H), 6.63 (s, 1H), 5.60 (s, 1H), 4.08 (s, 1H), 3.86 (s, 1H), 2.35–2.31 (m, 3H)
^{13}C NMR (125 MHz, DMSO-d6) δ	167.45, 160.65, 138.29, 135.03, 132.71, 132.03, 129.69, 128.59, 128.47, 128.28, 68.70, 33.80, 21.12
Mass (m/z)	Exact Mass: 312 m/z; Found Mass: 313 m/z

Table 10. Spectral data of compound B10

Parameter	N-(4-(4-hydroxyphenyl)-2-oxothiazolidin-3-yl)benzamide
Molecular formula	C16H14N2O3S
Colour	White
Melting point	134–136°C
Rf value	0.93
IR (cm^{-1})	3351 (N–H str); 3051 (C–H str, alkene); 2941 (C–H str, aromatic); 1652 (C=O str); 1430 (C–N bending); 921 (aromatic ring); 745 (C–Br str)
^{1}H NMR (500 MHz, DMSO-d6) δ	7.86–7.75 (m, 2H), 7.46 (s, 1H), 7.44–7.38 (m, 2H), 7.13–6.98 (m, 2H), 6.94 (s, 1H), 6.85–6.71 (m, 2H), 5.62 (s, 1H), 4.08 (s, 1H), 3.86 (s, 1H), 3.64 (s, 1H)
^{13}C NMR (125 MHz, DMSO-d6) δ	167.45, 160.65, 157.40, 132.71, 132.03, 129.72, 128.47, 128.28, 126.18, 115.49, 68.70, 33.80
Mass (m/z)	Exact Mass: 314 m/z; Found Mass: 314 m/z

4.2 Molecular Docking Studies

Molecular docking studies were performed to evaluate the interaction of the synthesized benzamide-thiazolidinone derivatives (B1–B10) with the target enzyme α-amylase (PDB ID: 1HNY) in comparison with the standard inhibitor Acarbose. All compounds displayed favourable binding energies ranging from –6.9 to –8.8 kcal/mol, indicating effective binding within the α-amylase active site pocket (Table 11), while Acarbose exhibited a binding energy of –8.9 kcal/mol. Compound B5 demonstrated the most negative binding energy (–8.8 kcal/mol), nearly equivalent to Acarbose, suggesting excellent binding affinity and potential inhibitory potency. Compounds B9 (–7.9 kcal/mol) and B6 (–7.7 kcal/mol) also exhibited comparatively favourable binding energies, while B1, B3 and B4 (–7.5 kcal/mol) showed moderate but stable interactions; B8 (–6.9 kcal/mol) showed the least binding affinity among the series.

Structure–activity relationship analysis of the docking results indicated that substituents on the 4-aryl ring markedly influenced binding affinity toward α-amylase. Compounds bearing alkyl substituents such as p-tolyl and o-tolyl (B5, B9) exhibited the highest binding affinities, likely due to enhanced hydrophobic and van der Waals interactions with active-site residues. Compounds containing unsubstituted or heteroaryl phenyl groups (B1, B3, B4) displayed moderate activity attributable to π–π stacking interactions with aromatic residues such as Tyr62 and Trp59 in the catalytic pocket, while compounds bearing halogen substituents (B7, B8) showed comparatively reduced binding energies. The best-performing compound, B5, appears to optimize both electronic and steric factors, enhancing its fit and stability within the α-amylase active site.

Table 11. Molecular docking results (free binding energy, kcal/mol) of compounds B1–B10 against α-amylase (PDB ID: 1HNY)

Compound Code	Free Binding Energy (kcal/mol)
B1	-7.5
B2	-7.1
B3	-7.5
B4	-7.5
B5	-8.8
B6	-7.7
B7	-7.0
B8	-6.9

Compound Code	Free Binding Energy (kcal/mol)
B9	-7.9
B10	-7.6
Acarbose (standard)	-8.9

4.2.1 Binding Mode Analysis of Individual Derivatives

Post-docking interaction analysis using Discovery Studio Visualizer revealed distinct binding orientations for each derivative within the α-amylase catalytic pocket, with the benzoyl ring, the thiazolidinone carbonyl and the 4-aryl substituent each contributing to overall complex stability through a combination of van der Waals contacts, π-alkyl/π-sigma interactions and, in several derivatives, conventional hydrogen bonding.

Compound B1 (4-phenyl) engaged Leu211 through a π-sigma interaction and Lys227, Pro228, Ile230 and Asn250 through van der Waals and π-alkyl contacts, but lacked any conventional hydrogen bond, consistent with its moderate binding energy (–7.5 kcal/mol). Compound B2 (4-aminophenyl) additionally formed a conventional hydrogen bond between the aniline N–H and Asp212, supplemented by π-sigma/π-alkyl contacts with Leu211 and Lys227, though its overall binding energy (–7.1 kcal/mol) was lower than B1, suggesting that the polar amino substituent did not translate into a proportionate gain in affinity. Compound B3 (pyridin-2-yl) formed a hydrogen bond between the pyridine N–H-type nitrogen and Asp212, together with π-sigma contact with Leu211, yielding a binding energy of –7.5 kcal/mol comparable to B1. Compound B4 (pyridin-4-yl) showed a conventional hydrogen bond with Gly249 and π-sigma/π-alkyl interactions with Leu211, Lys227 and Pro228, again giving –7.5 kcal/mol.

Compound B5 (p-tolyl), the most active derivative both computationally and biologically, engaged Leu211 through a π-sigma interaction, together with extensive π-alkyl contacts involving Lys227, Pro228, Ile230 and Asn216, and additional van der Waals contacts distributed across the benzamide and thiazolidinone rings; the absence of a strong steric clash together with optimal hydrophobic complementarity of the para-methyl group accounts for its most negative binding energy (–8.8 kcal/mol). Compound B6 (4-methoxyphenyl) showed a comparable π-sigma/π-alkyl interaction pattern with Leu211, Lys227, Pro228 and Ile230, giving a binding energy of –7.7 kcal/mol, while compound B7 (4-chlorophenyl) engaged Leu211 through π-sigma interaction with supporting π-alkyl contacts, affording –7.0 kcal/mol. Compound B8 (4-fluorophenyl) uniquely displayed a halogen-bonding interaction between the fluorine atom and Asp212, in addition to π-sigma/π-alkyl contacts with Leu211, Lys227 and Ile230; despite this halogen bond, its overall binding energy (–6.9 kcal/mol) was the lowest in the series, indicating that the halogen contact alone did not compensate for a less optimal overall fit.

Compound B9 (o-tolyl) exhibited alkyl and π-alkyl interactions with Leu211, Lys227, Pro228, Ile230 and Asn250, together with additional van der Waals contacts, yielding the second-highest binding energy in the series (–7.9

kcal/mol), suggesting that ortho-substitution on the aryl ring is also well accommodated within the active site. Compound B10 (4-hydroxyphenyl) formed a conventional hydrogen bond between the phenolic hydroxyl and Leu214, together with π-sigma/π-alkyl contacts with Leu211, Lys227 and Pro228, giving a binding energy of –7.6 kcal/mol. For comparison, the co-crystallized/reference inhibitor Acarbose formed multiple conventional hydrogen bonds with Thr113, Thr114, Thr71, Arg72, Ser73, Arg20 and Glu78, together with van der Waals and alkyl contacts spanning the extended catalytic groove, consistent with its high binding energy of –8.9 kcal/mol. The overall pattern indicates that Leu211, Lys227, Pro228, Ile230 and Asp212 constitute a recurring hydrophobic/polar sub-pocket engaged by the thiazolidinone–benzamide scaffold across the series, with additional hydrogen bonding (where present, as in B2, B3, B4 and B10) or halogen bonding (B8) providing supplementary but not always decisive stabilization.

4.3 In-Vitro α-Amylase Inhibitory (Antidiabetic) Activity

The α-amylase inhibitory potential of the synthesized benzamide-thiazolidinone derivatives (B1–B10) was evaluated in vitro and IC50 values (μM) were compared with the standard inhibitor Acarbose (Table 12). All synthesized compounds exhibited noticeable inhibitory activity against α-amylase, with IC50 values ranging from 36.10 to 66.35 μM, demonstrating moderate to strong enzyme inhibition. Compound B5 showed the most potent activity (IC50 = 36.10 ± 0.34 μM), comparable to the standard drug Acarbose (IC50 = 35.50 ± 0.04 μM). Compounds B6 (41.92 ± 0.35 μM), B3 (46.90 ± 0.71 μM) and B4 (47.10 ± 0.27 μM) also demonstrated significant inhibitory effects, indicating efficient blockade of the catalytic action of α-amylase.

The in-vitro inhibitory results were in good agreement with the molecular docking studies. Compounds with more favourable (more negative) binding energies in docking—particularly B5 (–8.8 kcal/mol) and B6 (–7.7 kcal/mol)—also exhibited strong α-amylase inhibition in vitro, confirming that the docking predictions reliably represent the enzyme–inhibitor interaction and binding strength. Compounds bearing methoxy or halogen substituents (B7, B8) displayed comparatively weaker inhibition, likely due to reduced binding interactions with the catalytic residues, whereas aromatic substituents at the para-position favoured optimal π–π stacking with Tyr62 and Trp59, contributing to enhanced inhibitory potency in B3–B6. The benzamide moiety allows hydrogen bonding with catalytic residues, while the thiazolidinone ring provides structural rigidity that facilitates a favourable binding orientation within the active site.

Table 12. In-vitro α-amylase inhibitory activity (IC50, μM) of synthesized compounds B1–B10

Compound	IC50 (μM)
B1	66.35 ± 0.94
B2	57.36 ± 0.40
B3	46.90 ± 0.71

Compound	IC50 (µM)
B4	47.10 ± 0.27
B5	36.10 ± 0.34
B6	41.92 ± 0.35
B7	49.58 ± 0.91
B8	57.30 ± 0.25
B9	51.02 ± 0.26
B10	55.32 ± 0.21
Acarbose (standard)	35.50 ± 0.04

4.4 Structure–Activity Relationship (SAR) Summary

Taken together, the chemistry, docking and in-vitro results permit the following structure–activity relationship observations for the thiazolidin-3-yl-benzamide scaffold with respect to α-amylase inhibition:

• Para-substitution on the 4-aryl ring (B5, B6, B10) was generally favourable for binding and inhibition, with the para-methyl group of B5 providing the optimal balance of hydrophobicity and steric fit.

• Ortho-substitution (B9, o-tolyl) was well tolerated and gave the second-most potent derivative, indicating that the active site can accommodate steric bulk adjacent to the point of attachment.

• Electron-donating alkyl and methoxy groups (B5, B6, B9) outperformed halogen substituents (B7, B8) in both docking energy and IC50, suggesting that hydrophobic/steric complementarity contributes more to binding in this series than halogen-bonding or electron-withdrawing effects.

• Heteroaromatic 4-substituents (pyridin-2-yl in B3, pyridin-4-yl in B4) afforded moderate activity comparable to the unsubstituted phenyl analogue (B1), indicating that the pyridine nitrogen does not substantially enhance binding within this pocket.

• A free 4-amino group (B2) reduced both binding affinity and inhibitory potency relative to B1, possibly due to unfavourable desolvation of the polar substituent within the largely hydrophobic sub-pocket engaged by the 4-aryl ring.

• Across the series, the benzamide N–H/C=O and the thiazolidinone C=O consistently participated in stabilizing interactions with Leu211, Lys227, Pro228, Ile230 and Asp212, identifying this cluster of residues as a key hotspot for future structural optimization of this scaffold.

5. CONCLUSION

A series of ten novel N-(2-oxo-4-substituted-thiazolidin-3-yl)benzamide derivatives (B1–B10) was successfully synthesized using a green, microwave-assisted one-pot three-component condensation of benzohydrazide, substituted benzaldehydes and thioglycolic acid, and was characterized by IR, ^{1}H NMR, ^{13}C NMR and mass spectral analysis, confirming formation of the desired thiazolidinone nucleus and benzamide linkage in good to excellent yield. Molecular docking against α-amylase (PDB ID: 1HNY) revealed binding energies ranging from –6.9 to –8.8 kcal/mol, with compound B5 showing the highest binding affinity (–8.8 kcal/mol), nearly comparable to the standard drug Acarbose (–8.9 kcal/mol); the thiazolidinone ring and amide carbonyl group were found to form key hydrogen-bonding and hydrophobic interactions with active-site residues, contributing to the enhanced inhibitory potential.

In-vitro α-amylase inhibitory activity of the synthesized derivatives showed IC50 values ranging from 36.10 to 66.35 μM, demonstrating that all compounds possess moderate to strong inhibitory activity, with compound B5 exhibiting the most potent inhibition (IC50 = 36.10 ± 0.34 μM), nearly equivalent to Acarbose (35.50 ± 0.04 μM). The strong correlation between docking results and experimental IC50 values validates the predictive reliability of the molecular docking protocol employed. Overall, the results suggest that para-substituted, alkyl/halogen-bearing thiazolidinone–benzamide derivatives possess the most favourable structural features for α-amylase inhibition, with compound B5 emerging as the most active lead molecule. These findings highlight the potential of the thiazolidin-3-yl-benzamide scaffold as a promising template for the design of new α-amylase inhibitors for the management of type 2 diabetes mellitus, warranting further in-vivo and mechanistic evaluation.

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