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Original Article

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Design and Synthesis of Novel Imidazo[2,1-*b*]thiazole-Based 4-Thiazolidinone Derivatives as Potent α-Glucosidase Inhibitors

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Abstract

Background and Aims: Inhibiting the α-glucosidase reduces the rate at which glucose is absorbed, helping to control blood sugar levels. This strategy presents a potential alternative for managing type 2 diabetes, offering a promising approach with fewer adverse effects compared with conventional treatments. Based on this, we synthesised novel imidazo[2,1-*b*]thiazole-based 4-thiazolidinone derivatives (**5a**-**e**) and evaluated them for their α-glucosidase inhibitory activities.

Methods: Structural confirmation of the synthesised compounds was carried out using various spectroscopic techniques, including IR, ^{1}H-NMR and ^{13}C-NMR spectroscopy, elemental analysis and ESI-MS. The newly synthesised compounds were subjected to *in vitro* evaluation to assess their inhibitory effects on α-glucosidase activity.

Results: Spectroscopic analyses confirmed the successful synthesis of the target compounds. Among them, compound **5e** exhibited the most potent α-glucosidase inhibitory effect, with a half-maximal inhibitory concentration (IC_{50}) value of 115.94 ± 0.58 μM, outperforming the standard drug acarbose, which showed an IC_{50} of 179.25 ± 3.41 μM.

Conclusion: In summary, a series of novel imidazo[2,1-*b*]thiazole-based 4-thiazolidinone derivatives (**5a**–**e**) were successfully synthesised, among which compound **5e** emerged as the most potent α-glucosidase inhibitor, surpassing the activity of the reference drug acarbose. These findings position compound **5e** as a promising lead candidate for developing new α-glucosidase inhibitory agents. To fully assess the therapeutic value of this scaffold, further *in vitro* investigations on structurally related analogs, followed by comprehensive *in vivo* assessments, are warranted.

Keywords Synthesis · Imidazothiazole · 4-Thiazolidinone · α-Glucosidase Inhibitory Activity

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INTRODUCTION

Diabetes mellitus is a major metabolic disease that poses a growing public health challenge worldwide, primarily because of its potential to cause severe and chronic complications over time. (Javid et al., 2018). The global incidence of diabetes is rising at an alarming rate, and it is expected to become a leading cause of mortality by the year 2045 (Sun et al., 2022). Type 2 diabetes, which comprises nearly 90% of all diagnosed cases, is generally managed without the need for insulin treatment (Reaven, 1988). This type of diabetes is characterised by elevated post-meal blood glucose levels, which can cause substantial damage to blood vessels, particularly the endothelium (Wright et al., 2003). As a result, individuals with type 2 diabetes face an elevated risk of severe conditions such as heart disease, strokes, and vision problems (Guariguata et al., 2014).

Several classes of oral antidiabetic drugs are currently available, including biguanides, thiazolidinediones, sulfonylureas, meglitinide, and α-glucosidase inhibitors (Kasturi et al., 2017). Although α-glucosidase inhibitors are already used to treat diabetes, there is still a need for the development of novel compounds with better safety profiles and fewer adverse effects. This need continues to drive research in the field of pharmaceutical chemistry to design and develop next-generation inhibitors with greater therapeutic potential.

α-Glucosidase plays a crucial role in the breakdown of carbohydrates and the biosynthesis of glycoproteins, which makes it a key therapeutic target in the treatment of type 2 diabetes (Ghani, 2015). Currently, there are only a limited number of α-glucosidase inhibitors available on the market, including drugs such as acarbose (Glucobay®), voglibose (Volix®, Basen®), and miglitol (Glyset®) (Figure 1). However, these drugs are based on sugar structures and require complex, multi-step synthesis processes. For instance, the synthesis of voglibose consists of 13 sequential steps beginning with (-)-shikimic acid, while the production of miglitol also involves 13 steps, starting from (*R*)-methyl 2-benzamido-3-((tert-butyldimethylsilyl)oxy)propanoate (Dincel et al., 2021; Playford et al., 2013). These challenges highlight the need for alternative non-sugar-based molecules that are simpler to synthesise, offering more efficient and potentially safer therapeutic options.

Besides these difficulties, many existing antidiabetic drugs are associated with gastrointestinal side effects, such as bloating and diarrhea, which may restrict their clinical application. Due to these limitations, current research is increasingly focused on identifying safer, more potent α-glucosidase inhibitors that can be synthesised through more straightforward and efficient methods (Dincel et al., 2021).

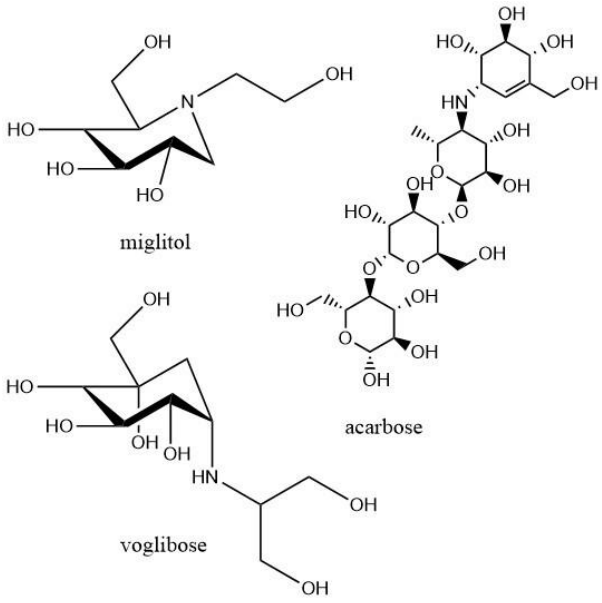

Figure 1. Structures of some commercially available α-glucosidase inhibitors.

In recent years, fused heterocyclic compounds have attracted considerable interest because of their wide-ranging pharmacological properties. Among these, imidazo[2,1-*b*]thiazole derivatives have emerged as particularly promising because of their extensive biological activities. Multiple studies have demonstrated their potential in several therapeutic applications (Andreani et al., 2001; Dincel et al., 2021; Ulusoy Guzeldemirci et al., 2017). Owing to their broad spectrum of pharmacological activities, imidazo[2,1-*b*]thiazole derivatives remain a central topic of interest in medicinal chemistry, presenting valuable prospects for the discovery and design of new drug candidates.

4-Thiazolidinones, which are based on the thiazolidine core structure, are characterised by the presence of a sulfur atom at position one, a nitrogen atom at position three, and a carbonyl group at position four. Their unique structural attributes and wide range of biological properties have made them a prominent subject of investigation in medicinal chemistry, as documented in numerous studies (Havrylyuk et al., 2010; Omar et al., 2010; Trotsko, 2021). Various therapeutic agents containing the 4-thiazolidinone core have been successfully introduced into clinical practice. Examples include ralitoline, which functions as an anticonvulsant; pioglitazone, a hypoglycaemic drug used in the treatment of diabetes; and thiazolidomycin, an antibiotic effective against *Streptomyces* species (Desouza & Shivaswamy, 2010; Fischer et al., 1992; Loscher et al., 1991; Tratrat et al., 2022).

The incorporation of fluorine atoms into antidiabetic compounds has proven to be a powerful strategy in drug design. This is largely due to the unique properties of fluorine, particularly its ability to form highly stable carbon-fluorine bonds. These bonds confer resistance to metabolic degradation, allowing the fluorinated molecules to remain active in the body for longer durations. As a result, the pharmacokinetic profiles of such drugs are significantly improved, which is highly advantageous for chronic conditions such as diabetes (Gillis et al., 2015). Additionally, fluorination increases the lipophilicity of a molecule, which facilitates its transport across biological membranes and improves systemic absorption when taken orally (Jeschke, 2004). Fluorine's influence extends beyond physical properties; it also alters electronic characteristics and molecular geometry. These changes can enhance the binding efficiency of a compound to its biological target, such as the enzymes or receptors involved in glucose metabolism. Fluorinated analogs of sugars, for instance, serve as potent glycosidase inhibitors because of their enhanced structural stability and resistance to enzymatic cleavage. This makes them attractive candidates in the development of antidiabetic therapies aimed at modulating carbohydrate breakdown and glucose uptake (Wei et al., 2023).

This research focuses on the design, characterisation, and evaluation of the α-glucosidase inhibitory properties of novel imidazo[2,1-*b*]thiazole-based 4-thiazolidinones incorporating a 4-fluorophenyl group. The synthesised compounds were comprehensively examined using several analytical methods, including IR, ^{1}H-NMR, ^{13}C-NMR spectroscopy, ESI-MS, and elemental analysis techniques.

MATERIALS AND METHODS

Chemistry

The anhydrous solvents and all chemical reagents were obtained from Merck and Tokyo Chemical Industry. IR spectra were recorded by preparing potassium bromide (KBr) pellets and analysing them with a Shimadzu IR Affinity-1 Fourier Transform Infrared Spectroscopy (FT-IR) spectrometer. ^{1}H-NMR and ^{13}C-NMR spectroscopy were performed using a Bruker Advance III 500 MHz spectrometer. Chemical shifts are reported in parts per million (ppm) on the δ scale, with the deuterated dimethyl sulfoxide (DMSO-d_6) solvent signal serving as an internal reference, set at δ 2.55 ppm for ^{1}H-NMR and δ 39.52 ppm for ^{13}C-NMR. The coupling constants (*J*) are given in Hertz (Hz), and the splitting patterns are denoted as singlet (s), doublet (d), triplet (t), multiplet (m), and broad singlet (brs). Exchangeable protons, such as NH, were confirmed by the addition of deuterium oxide (D_2O).

Analytical thin-layer chromatography (TLC) was performed on silica gel F-254 plates from Merck. The melting points were measured using a STUART SMP40 melting point apparatus. The elemental composition was determined using a Leco CHNS-932 analyser. Finally, the mass spectrometric data were acquired with an Agilent LC/MS system.

The Procedure for the Synthesis of 2-amino-3-[(4-fluorobenzoyl)methyl]–4-(ethoxycarbonylmethyl)thiazolium Bromide (1)

Compound **1** was obtained according to the procedure described by Robert et al (Robert et al., 1975). A solution of 0.005 mol of 4-fluorophenacyl bromide in 10 mL acetone was mixed with 10 mL acetone containing 0.005 mol of ethyl 2-aminothiazole-4-acetate. After being left at room temperature for three days, the resulting 2-amino-3-[(4-fluorobenzoyl)methyl]–4-ethoxycarbonylmethyl)thiazolium bromide (**1**) was filtered, dried, and purified by washing or recrystallization with boiling ethanol.

Procedure for the Synthesis of Ethyl 2-[6-(4-fluorophenyl)imidazo[2,1-b]thiazole-3-yl] Acetate Hydrobromide (2)

Compound **2** was obtained according to the procedure described by Robert et al (Robert et al., 1975). 2-Amino-3-[(4-fluorobenzoyl)methyl]–4-ethoxycarbonylmethyl)thiazolium bromide (**1**) was boiled in absolute ethanol under a reflux condenser for 20 min. The precipitate formed from the reaction was filtered, dried, and purified by washing or recrystallization with boiling ethanol.

Procedure for the Synthesis of 2-[6-(4-fluorophenyl)imidazo[2,1-b]thiazole-3-yl] Acethydrazide (3)

Compound **3** was obtained according to the procedure described by Harraga et al (Harraga et al., 1994). To a suspension of 0.005 mol of ethyl 2-[6-(4-fluorophenyl)imidazo[2,1-*b*]thiazole-3-yl]acetate hydrobromide (**2**) in 60-70 mL of absolute ethanol, 0.025 mol of hydrazine hydrate (98%) was added, and the mixture was heated in a water bath under a reflux condenser for 5 h. After allowing the reaction mixture to cool to room temperature, the resulting precipitate was filtered and purified by washing or recrystallization with boiling ethanol.

General Procedure for the Synthesis of 2-[2-[6-(4-fluorophenyl)imidazo[2,1-b]thiazole-3-yl)acetyl]-N-alkyl/arylhydrazinecarbothioamide (4a-e)

A solution containing 0.005 mol of 2-[6-(4-fluorophenyl)imidazo[2,1-*b*]thiazole-3-yl]acetohydrazide (**3**) was

prepared in 30 mL of absolute ethanol. To this, 0.005 mol of various substituted isothiocyanates were added. The mixture was then heated in a water bath at reflux for 3 h. After cooling, the resulting precipitate was isolated and purified either by washing with hot ethanol or by recrystallizing from ethanol. The spectral data belonging to **4a-e** were reported in our previous study (Dincel et al., 2021, 2022).

General Procedure for the Synthesis of 2-(6-(4-Fluorophenyl)imidazo[2,1-b]thiazol-3-yl)-N'-(3-alkyl/aryl-4-oxothiazolidin-2-ylidene)acetohydrazide (5a-e)

0.005 mol of the appropriate thiosemicarbazide (**4a-e**) and 0.0055 mol of ethyl bromoacetate were refluxed in 20 mL of absolute ethanol in the presence of 0.020 mol of anhydrous CH_3COONa for 6 h. The crystalline product was washed with H_2O and recrystallized from EtOH.

2-(6-(4-Fluorophenyl)imidazo[2,1-b]thiazol-3-yl)-N'-(3-methyl-4-oxothiazolidin-2-ylidene)acetohydrazide (5a)

White powder, mp 181 °C, yield: 82.58%. Anal. Calcd. for: $C_{17}H_{14}FN_5O_2S_2$ C, 50.61; H, 3.50; N, 17.36. Found: C, 50.34; H, 3.72; N, 16.98%. **FT-IR υ_{max} (cm^{-1}):** 3126 (N-H stretching band), 1722 (thiazolidinone C=O stretching band), 1620 (amide C=O stretching band). **^{1}HNMR (600 MHz) (DMSO-d_6/TMS) δ (ppm):** 10.65 (s, 1H, CONH), 8.19, 8.14 (2s, 1H, imidazo[2,1-*b*]thiazole C5-H), 7.85 (dd, *J* = 8.6, 2.9 Hz, 2H, 4-FPh $C_{2,6}$-H), 7.24 (t, *J* = 9.2 Hz, 2H, 4- FPh $C_{3,5}$-H), 7.05 (s, 1H, imidazo[2,1-*b*]thiazole C2-H), 4.09, 4.06 (2s, 2H, CH_2CONH), 4.07, 3.88 (2s, 2H, SCH_2), 3.08 (s, 3H, CH_3). **^{13}C NMR (125 MHz, DMSO-d_6) δ (ppm):** 171.79, 163.65, 162.63, 161.02, 159.00, 149.17, 145.53, 131.28, 127.00, 126.95, 116.09, 115.94, 110.38, 108.66, 33.59, 33.38, 29.64. **LC-MS:** m/z 404.0 (100%), **LC-DAD Purity:** 97.8749%.

2-(6-(4-Fluorophenyl)imidazo[2,1-b]thiazol-3-yl)-N'-(3-ethyl-4-oxothiazolidin-2-ylidene)acetohydrazide (5b)

White powder, mp 232 °C, yield: 80.14%. Anal. Calcd. For: $C_{18}H_{16}FN_5O_2S_2$ calculated: C, 51.79; H, 3.86; N, 16.78%. Found: C, 51.36; H, 4.235; N, 16.49%. **IR υmax (KBr, cm^{-1}):** 3149 (N-H stretching band), 1718 (thiazolidinone C=O stretching band), 1614 (amide C=O stretching band). **^{1}HNMR (600 MHz) (DMSO-d_6/TMS) δ (ppm):** 10.63 (s, 1H, CONH), 8.17, 8.12 (2s, 1H, imidazo[2,1-*b*]thiazole C_5-H), 7.87 – 7.79 (m, 2H, 4-FPh $C_{2,6}$-H), 7.21 (t, *J* = 8.9 Hz, 2H, 4-FPh $C_{3,5}$-H), 7.03, 7.00 (2s, 1H, imidazo[2,1-*b*]thiazole C_2-H), 4.06, 4.04 (2s, 2H, CH_2CONH), 4.05, 3.85, (2s, 2H, SCH_2), 3.65 (q, *J* = 7.3 Hz, 2H, *N*-$C\underline{H}_2$-CH_3), 1.11 – 1.07 (m, 3H, *N*-CH_2-CH_3). **^{13}C NMR (125 MHz, DMSO-d_6) δ (ppm):** 171.57, 163.66, 162.64, 161.02, 158.69, 149.17, 145.54, 131.30, 131.28, 127.00, 126.95, 116.07, 115.93, 110.37, 108.70, 38.00, 33.60, 33.29, 12.53. **LC-MS:** m/z 418.1 (100%), **LC-DAD Purity:** 98.7947%.

2-(6-(4-Fluorophenyl)imidazo[2,1-b]thiazol-3-yl)-N'-(3-propyl-4-oxothiazolidin-2-ylidene)acetohydrazide (5c)

White powder, mp 211 °C, yield: 85.86%. Anal. Calcd. For: $C_{19}H_{18}FN_5O_2S_2.0.75H_2O$ C, 51.28; H, 4.42; N, 15.74%. Found: C, 51.16; H, 4.110; N, 15.64%. **IR υmax (KBr, cm^{-1}):** 3116 (N-H stretching band), 1712 (thiazolidinone C=O stretching band), 1620 (amide C=O stretching band). **^{1}HNMR (600 MHz) (DMSO-*d*6/TMS) δ (ppm):** 10.65 (s, 1H, CONH), 8.21, 8.15 (2s, 1H, imidazo[2,1-*b*]thiazole C_5-H), 7.85 (dd, *J* = 8.4, 2.5 Hz, 2H, 4-FPh $C_{2,6}$-H), 7.24 (t, *J* = 9.0 Hz, 2H, 4-FPh $C_{3,5}$-H), 7.06, 7.03 (2s, 1H, imidazo[2,1-*b*]thiazole C_2-H), 4.10, 4.08 (2s, 2H, CH_2CONH), 4.09, 3.88 (2s, 2H, SCH_2), 3.65-3.59 (m, 2H, $NC\underline{H}_2CH_2CH_3$), 1.64-1.56 (m, 2H, $NCH_2C\underline{H}_2CH_3$), 0.83 (t, *J* = 7.5 Hz, 3H, $NCH_2CH_2C\underline{H}_3$). **^{13}C NMR (125 MHz, DMSO-d_6) δ (ppm):** 171.91, 163.64,162.64, 161.02, 159.28, 149.17, 145.54, 131.31, 131.29,127.00, 126.95, 116.07, 115.92,110.37, 108.71, 44.4, 33.60, 33.18, 20.21, 11.48. **LC-MS:** m/z 432.1 (100%), **LC-DAD Purity:** 97.7384%.

2-(6-(4-Fluorophenyl)imidazo[2,1-b]thiazol-3-yl)-N'-(3-butyl-4-oxothiazolidin-2-ylidene)acetohydrazide (5d)

White powder, mp 170 °C, yield 81.89%. Anal. Calcd. For: $C_{20}H_{20}FN_5O_2S_2.0.5H_2O$ C, 52.85; H, 4.66; N, 15.41%. Found: C, 52.86; H, 4.488; N, 15.40%. **IR υmax (KBr, cm^{-1}):** 3151 (N-H stretching band), 1718 (thiazolidinone C=O stretching band), 1614 (amide C=O stretching band). **^{1}HNMR (600 MHz) (DMSO-*d*6/TMS) δ (ppm):** 10.66 (s, 1H, CONH), 8.20, 8.15 (2s, 1H, imidazo[2,1-*b*]thiazole C_5-H), 7.85 (dd, *J* = 8.3, 2.5 Hz, 2H, 4-FPh $C_{2,6}$-H), 7.24 (t, *J* = 8.8 Hz, 2H, 4-FPh $C_{3,5}$-H), 7.06, 7.02 (2s, 1H, imidazo[2,1-*b*]thiazole C_2-H), 4.09, 4.07 (2s, 2H, H5-thiazolidinone), 3.87 (s, 2H, $C\underline{H}_2CONH$), 3.64 (t, *J* = 7.5 Hz, 2H, N-$C\underline{H}_2CH_2CH_2CH_3$), 1.57 – 1.55 (m, 2H, N-$CH_2C\underline{H}_2CH_2CH_3$), 1.29 – 1.23 (m, 2H, N-$CH_2CH_2C\underline{H}_2CH_3$), 0.87 (t, *J* = 8.0, 7.4 Hz, 3H, *N*-$CH_2CH_2CH_2C\underline{H}_3$). **^{13}C NMR (125 MHz, DMSO-d_6) δ (ppm):** 171.86, 171.37, 169.47, 163.62, 162.63, 161.02, 159.25, 151.09, 149.17, 148.06, 145.53, 131.31, 127.00, 126.95, 125.86, 116.08, 110.39, 108.71, 42.63, 33.59, 33.51, 33.17, 29.04, 28.95, 19.93, 19.85, 14.01. **LC-MS:** m/z 446.1 (100%).

2-(6-(4-Fluorophenyl)imidazo[2,1-b]thiazol-3-yl)-N'-(3-(4-nitrophenyl)-4-oxothiazolidin-2-ylidene)acetohydrazide (5e)

Yellow powder, mp 283 °C, yield 82.36%. Anal. Calcd. For. $C_{22}H_{15}FN_6O_4S_2$ C, 51.76; H, 2.96; N, 16.46%. Found: C, 51.40; H, 2.878; N, 16.31%. **IR υmax (KBr, cm^{-1}):** (N-H stretching band), 1745 (thiazolidinone C=O stretching band), 1697 (amide C=O stretching band). **^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm):** 11.46 (s, 1H, CONH), 8.19 (d, *J* = 9.6 Hz, 2H, $4NO_2PhC_{3,5}$-H), 8.09 (s, 1H, imid.thia C_5-H), 7.66 (dd, *J* = 8.4, 2.8 Hz, 2H, $4FPhC_{2,6}H$), 7.16 (s, 1H, imid.thia. C_2-H), 7.13-7.05, (m, 4H, $4NO_2PhC_{2,6}H$ and $4FPhC_{3,5}$-H), 4.34-4.26 (m, 2H, $C\underline{H}_2CONH$), 4.14 (d, *J* = 16.6 Hz, 1H, H5-thiazolidinone), 4.09 (d, *J* = 16.6 Hz, 1H, H5-thiazolidinone).

^{13}C NMR (125 MHz, DMSO-d_6) δ (ppm): 168.98, 166.30, 162.56, 160.94, 154.63, 154.11, 149.23, 145.6 8, 144.46, 131.09, 126.89, 126.83, 125.95, 125.74, 122.47, 122.20, 116.79, 115.81, 115.67, 111.41, 108.39, 32.83, 30.97. **LC-MS:** m/z 511.0 (100%), **LC-DAD Purity:** 92.5585%.

α-Glucosidase Inhibitory Activity

The *in vitro* α-glucosidase inhibitory potential of the test compounds was assessed following a previously reported method (Bothon et al., 2013). In this procedure, 10 µL of each sample was combined with 90 µL of 0.1 M sodium phosphate buffer (pH 6.8) and 50 µL of an α-glucosidase enzyme solution (0.4 U/mL). The reaction mixture was preincubated at 37 °C for 10 min. Subsequently, 50 µL of a 1 mM solution of *p*-nitrophenyl-α-D-glucopyranoside was introduced to start the enzymatic reaction. Absorbance readings were then taken at 405 nm over a 10-min interval at 37 °C. Acarbose served as the reference inhibitor, and the corresponding solvent was used as the control. The inhibitory effect was calculated according to the following equation using the final sample concentrations in the wells. The potency of each compound was expressed as the half-maximal inhibitory concentration (IC_{50}) values obtained using the dose-response curves.

Inhibition (%) = [1 – (Reaction rate of the sample at 405 nm/Reaction rate of the control at 405 nm)] × 100

RESULTS AND DISCUSSION

Chemistry

The target compounds (**5a–e**), shown in Figure 2, were successfully synthesised from 2-(6-(4-fluorophenyl)imidazo[2,1-*b*]thiazole-3-yl)acetohydrazide (**3**) through a five-step synthetic route, as illustrated in Figure 3.

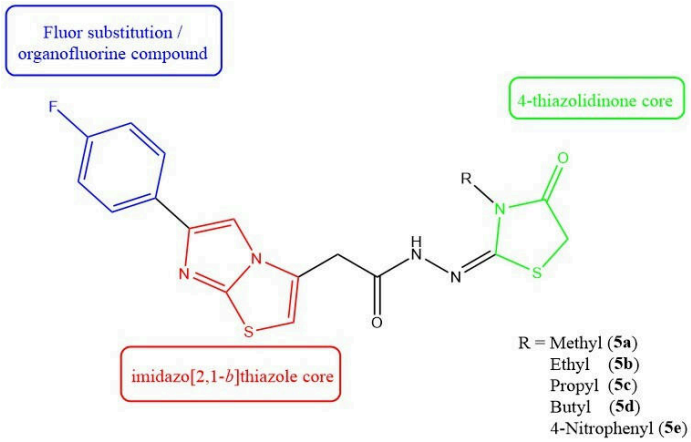

Figure 2. The design of the title compound (**5a-e**).

The initial reaction involved dissolving 4-fluorophenacyl bromide and ethyl 2-aminothiazole-4-acetate in acetone, followed by stirring at ambient temperature for 3 days. This procedure yielded 2-amino-3-[(4-fluorobenzoyl)methyl]–4-(ethoxycarbonylmethyl)thiazolium bromide (**1**). Notably, the reaction predominantly occurred at the thiazole ring nitrogen rather than the primary amine group, a preference well-documented in the literature (Kickhöfen & Kröhnke, 1955).

The 2-position of the thiazole ring is substituted with a primary amine, an electron-donating group, which plays a key role in this selectivity. According to the principle of vinylogy, the π-electrons from the amine group can delocalise across the thiazole ring structure, facilitated by the ring's nitrogen atom. This delocalisation leads to the formation of various resonance structures for the 2-substituted thiazoles. These resonance forms increase the electrophilic reactivity of the thiazole ring nitrogen while reducing the nucleophilicity of the primary amine. Consequently, electrophiles such as protons, alkylating agents, and metal ions preferentially interact with the thiazole ring nitrogen instead of the primary amine.

Compound **1** was subjected to reflux in absolute ethanol, leading to the ring closure and formation of ethyl 2-[6-(4-fluorophenyl)imidazo[2,1-*b*]thiazole-3-yl]acetate hydrobromide (**2**). Subsequently, compound **2** was heated with hydrazine hydrate in ethanol, resulting in the synthesis of 2-[6-(4-fluorophenyl)imidazo[2,1-*b*]thiazole-3-yl]acetohydrazide (**3**). Compound **3** was refluxed with diverse substituted isothiocyanates in ethanol to yield 2-[2-[6-(4-fluorophenyl)imidazo[2,1-*b*]thiazole-3-yl)acetyl]-*N*-alkyl/arylhydrazinecarbothioamide (**4a-e**). Finally, the obtained thiosemicarbazide derivatives (**4a-e**) and ethyl bromoacetate were refluxed in ethanol in the presence of anhydrous CH_3COONa to yield 2-(6-(4-Fluorophenyl)imidazo[2,1-*b*]thiazol-3-yl)-*N*'-(3-alkyl/aryl-4-oxothiazolidin-2-ylidene)acetohydrazide (**5a-e**). The reaction yields of **5a-e** were determined between 80.14 % (**5b**) and 85.86 % (**5c**). The thiosemicarbazide group in compounds **4a-e** contains three NH protons, whereas compounds **5a-e** have only one NH proton. The NH stretching bands for **5a-e** were observed in the IR spectra within the range of 3151 cm^{-1} to 3107 cm^{-1}. While the **4a-e** compounds contain one carbonyl group in their structure, the **5a-e** compounds feature two carbonyl groups. In the IR spectra of **5a-e**, the amide C=O bands were observed between 1614 cm^{-1} and 1697 cm^{-1}, and the thiazolidinone C=O bands appeared between 1745 cm^{-1} and 1712 cm^{-1} (All relevant spectra of the title compounds are presented in the supporting information).

LC-MS data confirmed the structures, with the molecular ion peaks observed as base peaks. For **5a-e**, the presence of thiazolidinone C5-H protons was verified by signals in the range of 4.14–3.85 ppm with a total integral value corresponding to 2H. The structure was further validated using IR, ^{1}H-NMR, ^{13}C-NMR, elemental analysis, and mass spectrometric data, all of which are consistent with the literature (Cihan-Ustundag

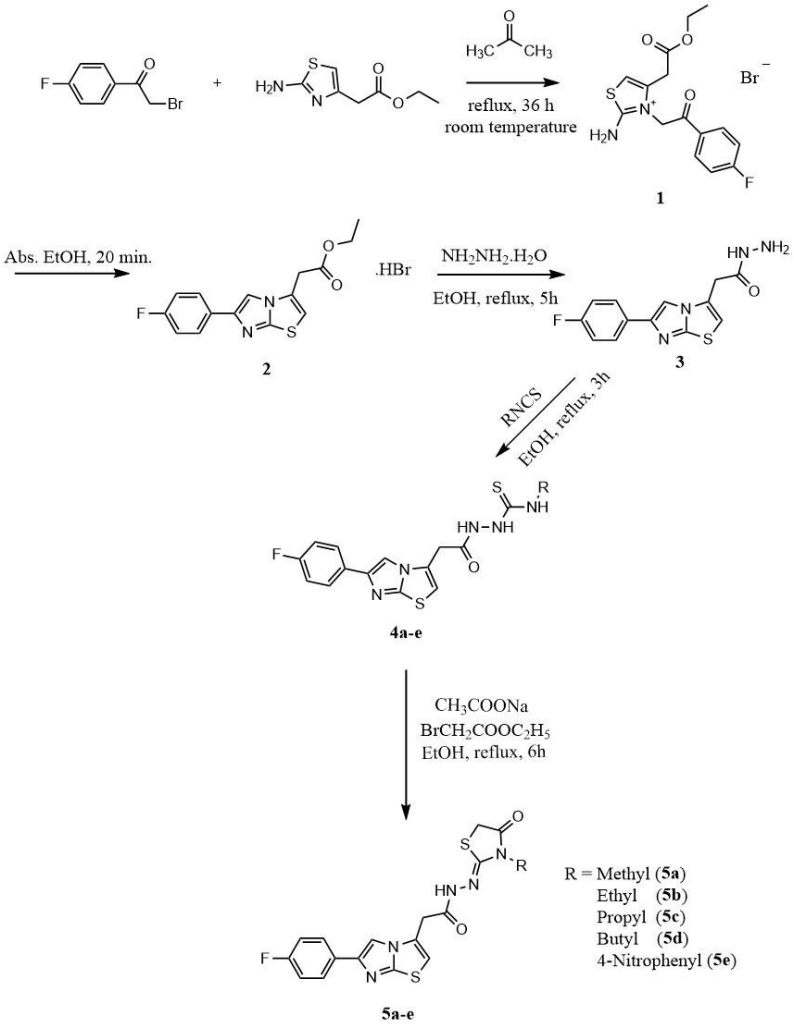

Figure 3. Synthesis pathway of the title compounds (**5a-e**).

et al., 2016; Deep et al., 2011; Dincel et al., 2021, 2022). The NMR spectra of compounds **5a-d** revealed both Entgegen (*E*) and Zusammen (*Z*) isomers, which exist together as a racemic mixture. In contrast, the aromatic-substituted derivative **5e** was formed exclusively as a single isomer, presumed to be the Entgegen (*E*) form. This observation aligns with the thermodynamic preferences of the products, where factors such as steric hindrance, electronic effects, and resonance stabilisation play significant roles in favouring the formation of the Entgegen isomer.

α-Glucosidase Inhibitory Activity

The imidazo[2,1-*b*]thiazole framework has been extensively investigated by our research group over many years, through which in-depth knowledge of its structure and therapeutic potential has been obtained. Building on this foundation, a novel class of α-glucosidase inhibitors based on imidazo[2,1-*b*]thiazole derivatives was introduced in our previous research, marking their first appearance in the literature (Dincel et al., 2021). In that study, six newly synthesised imidazo[2,1-*b*]thiazole derivatives exhibited superior α-glucosidase inhibitory activity compared with the reference compound acarbose.

In the current study, 5 novel imidazo[2,1-*b*]thiazole-based 4-thiazolidinone derivatives, incorporating aliphatic and aromatic substituents, were designed and synthesised to assess their α-glucosidase inhibitory activity. Acarbose was used as a reference because of its established clinical efficacy. Among the synthesised compounds, the 4-nitrophenyl-substituted derivative (**5e**) demonstrated remarkable inhibitory activity (IC_{50}: 115.94 ± 0.58 μM) which was more effective than that of acarbose (IC_{50}: 179.25 ± 3.41 μM) (Table 1). This indicates that aromatic substituents may improve the biological activity significantly according to the aliphatic substituents for these derivatives. In our previous study on 1,2,4-triazole derivatives containing the imidazo[2,1-*b*]thiazole moiety, the compound bearing a 4-nitrophenyl substituent was reported to exhibit superior α-glucosidase inhibitory activity compared to acarbose (Dincel et al., 2021). Interestingly, a similar trend was observed in the present study, where the incorporation of the 4-nitrophenyl group within the newly synthesised 4-thia-

zolidinone scaffold also played a significant role in enhancing the inhibitory activity. This consistent observation highlights the potential importance of the 4-nitrophenyl moiety in improving α-glucosidase inhibition. Future synthetic efforts should focus on optimising aromatic substituents to further refine the structure–activity relationship and improve the potency.

Table 1. α-Glucosidase inhibitory activity of the title compounds (**5a-e**)

Compound	IC_{50} values (μM)
5a	not determined
5b	not determined
5c	not determined
5d	not determined
5e	115.94 ± 0.58
Acarbose	179.25 ± 3.41

Values are the means of three replicates ± SD.

CONCLUSION

In conclusion, the design and synthesis of novel imidazo[2,1-*b*]thiazole-based 4-thiazolidinone derivatives have led to the identification of a promising α-glucosidase inhibitor with superior potency compared with the established standard, acarbose. Compound **5e** demonstrated impressive *in vitro* inhibitory activity, with IC_{50} values significantly lower than that of acarbose, indicating their potential as more effective alternatives for managing type 2 diabetes. Structure–activity relationship analysis highlighted the importance of aromatic substituents for biological activity. Overall, the findings from this study indicate that the imidazo[2,1-*b*]thiazole-based 4-thiazolidinones represent a promising new class of α-glucosidase inhibitors with the potential for development as therapeutic agents for type 2 diabetes. Further *in vivo* evaluation and optimisation of these compounds could lead to the development of novel, more effective treatments for glycemic control in diabetes management.

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