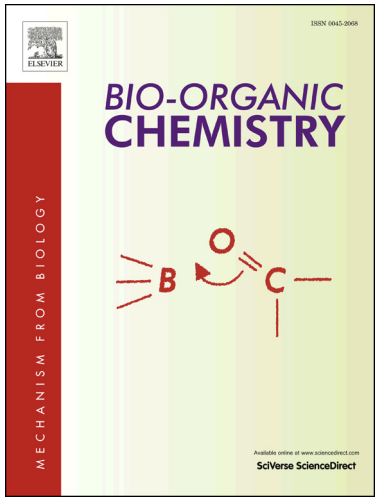

Design, synthesis and biological evaluation of novel coumarin thiazole derivatives as α-glucosidase inhibitors

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Design, synthesis and biological evaluation of novel coumarin thiazole derivatives as α-glucosidase inhibitors

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Abstract.

A new series of coumarin thiazole derivatives **7a-7t** were synthesized, characterized by ^{1}H NMR, ^{13}C NMR and element analysis, evaluated for their α-glucosidase inhibitory activity. The majority of the screened compounds displayed potent inhibitory activities with IC_{50} values in the range of 6.24±0.07 to 81.69±0.39 μM, when compared to the standard acarbose (IC_{50} = 43.26±0.19 μM). Structure–activity relationship (SAR) studies suggest that the pattern of substitution in the phenyl ring is closely related to the biological activity of this class of compounds. Among all the tested molecules, compound **7e** (IC_{50} = 6.24±0.07 μM) was found to be the most active compound in the library of coumarin thiazole derivatives. Enzyme kinetic studies showed that compound **7e** is a non-competitive inhibitor with a K_i of 6.86 μM. Furthermore, the binding interactions of compound **7e** with the active site of α-glucosidase were confirmed through molecular docking. This study has identified a new class of potent α-glucosidase inhibitors for further investigation.

Keywords: Coumarin; Thiazole; α-Glucosidase inhibitor; Enzyme kinetic study; Molecular docking

1. Introduction.

Diabetes mellitus is the most common metabolic disorder worldwide, characterized by hyperglycemia, which is due to insulin deficiency or insulin resistance [1]. The chronic hyperglycemia of diabetes causes serious damage to many of the body's organs, especially the eyes, kidneys, nerves, heart, and blood vessels [2, 3]. Therefore, one therapeutic approach for diabetes is to reduce the abnormally high blood sugar level and control subsequent complications.

α-Glucosidase is a membrane-bound enzyme located in the brush-border surface membrane of intestinal cells, which catalyzes the cleavage of glucose from disaccharides [4]. Inhibition of α-glucosidase can significantly delay the glucose absorption and decrease postprandial blood glucose level and therefor can be an important strategy for the treatment type-2 diabetic patients [5, 6]. In addition, α-glucosidase inhibition is a potential strategy for development of novel anti-HIV [7, 8] and anti-cancer agents [9]. For this reason, α-glucosidase is an attractive target for pharmaceutical studies, and the development of new α-glucosidase inhibitors is still in progress.

Coumarin derivatives are an important class of naturally organic compounds, which are predominantly found in higher plants. Coumarin derivatives are of great interest due to their diverse structural features and versatile biological properties, such as anticancer [10], antimalarial [11], antiinflammatory [12], antioxidant [13], antitubercular [14] and antimicrobial [15]. Over the last few years, numerous efforts

have been focusing on the research and development of coumarin derivatives as potential drugs and some of them have been approved for clinic use [16, 17]. Furthermore, recent studies have shown that numbers of compounds containing the coumarin skeleton act as α-glycosidase inhibitors (**Figure 1**) [18-21].

On the other hand, thiazoles and their derivatives have attracted continuing interest over the years because of their varied biological activities such as anti-inflammatory [22], antiproliferative [23], anticonvulsant [24], antifungal [25] and antibacterial [26]. Recently, several substituted thiazole derivatives has been reported in the literature to possess potent α-glucosidase inhibitory activities (**Figure 1**) [27, 28].

Over the years, molecular hybrid-based approaches had gained more attention by researchers to discover some more potent α-glucosidase inhibitors [29-31], which containing two or more bioactive pharmacophores. Based on these things mentioned above, and in an attempt to find new potent α-glucosidase inhibitors; we designed and synthesized a series of novel coumarin thiazole derivatives **7a-7t**. The synthesized derivatives were screened for their α-glucosidase inhibitory activity in *in vitro* modes. We also describe the structure-activity relationships and mechanism of action on α-glucosidase of this series of compounds.

Please insert **Figure 1** here.

2. Chemistry.

The synthetic pathway to achieve title compounds **7a-7t** is shown in **Scheme 1**. Salicylaldehyde **1** is reflux with ethyl acetoacetate in the presence of piperidine which

gave 3-acetyl coumarin **2**. Treatment of **2** with NBS in the presence of p-toluenesulfonic acid (TsOH) in acetonitrile to give 3-(2-bromoacetyl)-2H-chromen-2-one **3** in high yield [32]. Cyclization of **3** with ethyl thiooxamate in refluxing EtOH efficiently provides ethyl 4-(2-oxo-2H-chromen- 3-yl)thiazole-2-carboxylate **4**, which reacted with hydrazine hydrate to provide the key intermediate **5**. Finally, the new desired compounds **7a-7t** were obtained, in good yields (55 %-88 %), by condensing hydrazide **5** with the corresponding appropriate aldehydes in the presence of glacial acetic acid. The structures of newly synthesized compounds were confirmed by their ^{1}H NMR, ^{13}C NMR and elemental analysis. In their ^{1}H NMR spectra, the single peak of CH proton of coumarin was observed at 8.69-8.74 ppm, and the single peak of CH proton of thiazole was observed at 9.00-9.06 ppm. The resonances of aromatic protons were observed in the range 6.78-7.86 ppm. The single peak of CH proton of hydrazone moiety was observed at 8.56-8.95 ppm, and the signal of NH was showed at 10.95-12.15 ppm. The ^{1}H NMR spectra of all newly synthesized compounds (**7a-7t**) showed the expected proton resonances and integration values. Moreover, in their ^{13}C NMR spectra, the number of signals equals the number of different carbons in the molecule.

Please insert **Scheme 1** here.

3. Results and discussion.

3.1. α-Glucosidase inhibition assay

The α-glucosidase inhibitory activities of coumarin thiazole derivatives **7a-7t** were

evaluated according to the literature procedure with minor modification [27]. Acarbose (commercially available carbohydrate-based α-glucosidase inhibitor) was used as positive controls in the assays. The results were summarized in **Table 1**. The majority of the screened compounds displayed potent α-glucosidase inhibitory activity, with IC_{50} values in the range of 6.24±0.07 to 81.69±0.39 μM, when compared to acarbose (43.26±0.19 μM, The value of IC_{50} is similar to previous literature report [27, 33-35]). Among them, compound **7e** and **7h** represented the most potent α-glucosidase inhibitory activity with IC_{50} values of 6.24±0.07 and 8.23±0.13 μM, respectively.

Please insert **Table 1** here.

3.2. Structure-activity relationships summary

Based on our results, the following structure-activity relationships (SARs) of the coumarin thiazole derivatives can be summarized. Introduction of electron withdrawing groups such as trifluoromethyl (**7o**), fluorine (**7g**, **7p** and **7q**), chlorine (**7e**, **7h**, **7m** and **7n**), and bromine (**7r**) into the phenyl ring, results in a significant increase the inhibitory activity. Among them, it is interesting to point out that **7e** and **7h** (3,5-Cl_2, 2-OH in **7e** and 5-Cl, 2-OH in **7h**) containing the hydroxyl group at ortho-position of the phenyl ring and chlorine at the phenyl ring displayed the most potent α-glucosidase inhibitory activity, especially with the IC_{50} value of 6.24±0.07 μM in **7e** (**Table 1**). The activity of **7h** (5-Cl, 2-OH) was lower than **7e** (3,5-Cl_2, 2-OH), which indicates that the number and position of chlorine group is very

important for the activity. Additionally, the introduction of methoxyl group at the phenyl ring (**7a**, **7f**, **7l**, **7s** and **7t**) resulted in a remarkable decrease the biological activity, except the phenyl ring have ortho-hydroxyl group (**7i**). These results indicated the pattern of substitution in the phenyl ring is closely related to the biological activity of this class of compounds. In summary, the information of structure-activity relationships provided us a guideline to improve α-glucosidase inhibitory activity in the future structural modification.

3.3. Enzyme kinetic study

To study the mechanism of action on α-glucosidase of this series of compounds, the kinetic studies of the most active compound **7e** was performed using Lineweaver-Burk plot analysis. In the enzyme kinetic studies, the rate of the enzyme activity was measured at four different concentrations of compound **7e** using four different concentrations of the substrate p-nitrophenyl α-D-glucopyranoside (0.25, 0.5, 1.0, 2.0 mM). Graphical analysis of the reciprocal Lineweaver-Burk plots showed that V_{max} of enzyme decreased without affecting the K_m of enzyme (**Figure 2A**). This pattern indicates a non-competitive inhibition. In order to determine *Ki* constants of compound **7e** in the media, the secondary re-plots of Lineweaver-Burk plots were plotted (**Figure 2B**). The *Ki* value was 6.86 μM and the point of intersection of lines represents the value of *Ki*, which was drawn by using slope (obtained from Lineweaver-Burk plot) versus inhibitor concentrations values. The results proved that compound **7e** was a non-competitive inhibitor against α-glucosidase with a K_i of 6.86

μM.

Please insert **Figure 1** here.

3.4. Homology model

The crystallographic structure of *Saccharomyces cerevisiae* α-glucosidase enzyme has not been published yet, a number of homology models of α-glucosidase have been reported in the literature [27, 36]. In order to expose the binding mode between the compounds and *Saccharomyces cerevisiae* α-glucosidase at the molecular level, the 3D structure of α-glucosidase was built by means of modeller 9.15 homology modeling software (http://salilab.org/modeller/). The sequence in FASTA format of α-glucosidase was retrieved from UniProt (access code P53341). The crystallographic structure of *Saccharomyces cerevisiae* isomaltase (PDB ID: 3AJ7) with 72.4% was selected as the template for modeling.

3.5. Molecular docking simulation

The theoretical binding mode of **7e** and *Saccharomyces cerevisiae* α-glucosidase was shown in **Figure 3**. Compound **7e** adopted a compact conformation binding at the porket of the α-glucosidase. The 3,5-dichloro-2-hydroxyphenyl group of **7e** bind at the bottom of the α-glucosidase pocket and made a high density of vander Waals contacts, whereas the other side of **7e** was positioned near the entrance of the pocket and made only a few contacts. Detailed analysis showed that 3,5-dichloro-2-hydroxyphenyl group of **7e** formed arene-cation interactions with residues Arg-439 and Arg-312, respectively. Moreover, a Cl-π interaction was observed between the

residue Phe-300 and the 5 position of the chlorine atom atom at the phenyl ring of **7e**. In addition, the coumarin group of **7e** located at the hydrophobic pocket, surrounded by residues Phe-157, Phe-177 and Pro-240. It was shown that both Glu-276 (bond length: 2.6 Å) and His-279 (bond length: 3.0 Å) formed hydrogen bonds with **7e**, which was the main interactions between **7e** and α-glucosidase. In summary, the above molecular simulations give us rational explanation of the interactions between **7e** and α-glucosidase, which provided valuable information for further development of α-glucosidase inhibitors.

Please insert **Figure 3** here.

4. Conclusions.

In conclusion, we designed, synthesized and biological evaluation of a series of novel coumarin thiazole derivatives **7a**-**7t**. The majority of the screened compounds displayed potent α-glucosidase inhibitory activity. Among them, compound **7e** (IC_{50} = 6.24±0.07 μM) was found to be the most active compound. Enzyme kinetic studies showed that compound **7e** is a non-competitive inhibitor with a K_i of 6.86 μM. Moreover, some structure-activity relationships of coumarin thiazole derivatives were determined and will be useful in the future to guide the design and modification of this type of compound derivatives as α-glucosidase inhibitors. Furthermore the docking study has predicted that compound **7e** bind to the active site of the *Saccharomyces cerevisiae* α-glucosidase through both hydrophobic and hydrogen interactions. This study presented here provide a new class structure type for the

development of novel α-glucosidase inhibitors. In the future research we will be exploring for a clear structure-activity relationship of this type of compound and discovering more potent α-glucosidase inhibitors.

5. Experimental section.

5.1. Chemistry.

All starting materials and reagents were purchased from commercial suppliers. Melting points were determined on an X-4 microscope melting point apparatus (Shanghai instrument physical optics instrument Co., LTD) and were uncorrected. TLC was performed on 0.20 mm Silica Gel 60 F_{254} plates (Qingdao Ocean Chemical Factory, Shandong, China). Nuclear magnetic resonance spectra (NMR) were recorded at 400 MHz on a Bruker Advance II spectrometer and reported in parts per million.) The elemental analysis was measured by an Elementary Vario EL III analyzer.

5.1.1. 3-Acetyl-2H-chromen-2-one (2).

A mixture of salicylaldehyde **1** (1.22 g, 10 mmol) and ethyl acetoacetate (2 g, 15 mmol) in ethanol were taken in round bottom flask. To this mixture, few drops of piperidine were added and refluxed for 3 h. After completion of reaction, the content was poured on crushed ice and the precipitate was collected by filtration to obtain **2** (1.5 g, 79 %). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 2.73 (s, 3H, $COCH_3$), 7.33-7.35 (m, 2H, ArH), 7.64-7.69 (m, 2H, ArH), 8.51 (s, 1H, CH).

5.1.2. 3-(2-Bromoacetyl)-2H-chromen-2-one (3).

To a solution of **2** (188 mg, 1 mmol) in CH_3CN (10 mL) was added NBS (182 mg, 1.02 mmol) and p-toluenesulfonic acid (190 mg, 1 mmol). The mixture was stirred at 50 °C for 5 h and monitored by TLC. After completion of reaction, the solvent was removed under reduced pressure and the residue was poured into 10 % $NaHCO_3$ solution (50 mL). The aqueous layer was extracted with ethyl acetate, washed with brine, dried (Na_2SO_4), and then concentrated in vacuo. The residue was purified by silica gel column chromatography to provide **3** as a white solid in 75 % yield. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 4.76 (s, 2H, $COCH_2Br$), 7.37-7.42 (m, 2H, ArH), 7.69-7.73 (m, 2H, ArH), 8.65 (s, 1H, CH).

5.1.3. Ethyl 4-(2-oxo-2H-chromen-3-yl)thiazole-2-carboxylate (4).

A solution of **3** (267 mg, 1 mmol) and ethyl thiooxamate (133 mg, 1 mmol) in absolute EtOH (20 mL) was stirred at 80 °C for 5 h. After the completion of the reaction, the solvent was evaporated under reduced pressure and water was added to the reaction mixture and extracted 3 times for ethyl acetate. The combined organic layers were dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography to give 190 mg (63 %) of product. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.49 (t, 3H, *J* = 7.2 Hz, CH_3), 4.51 (q, 2H, *J* = 7.2 Hz, OCH_2), 7.32 (t, 1H, *J* = 8.0 Hz, ArH), 7.38 (d, 1H, *J* = 8.0 Hz, ArH), 7.58 (t, 1H, *J* = 8.0 Hz, ArH), 7.66 (d, 1H, *J* = 8.0 Hz, ArH), 8.74 (s, 1H, CH), 8.92 (s, 1H, SCH).

5.1.4. 4-(2-Oxo-2H-chromen-3-yl)thiazole-2-carbohydrazide (5).

To a solution of **4** (301 mg, 1 mmol) in ethanol (10 mL) was added hydrazine (100 mg,

2 mmol) and the mixture was heated to reflux for 4 hours. After cooling, the precipitate was collected by filtration and washed with ethanol to give **5** (208 mg, 72 %) as a white solid. ^{1}H NMR (d^{6}-DMSO, 400 MHz) δ: 4.76 (s, 2H, NH_2), 7.46 (t, 1H, *J* = 8.0 Hz, ArH), 7.50 (d, 1H, *J* = 8.0 Hz, ArH), 7.69 (t, 1H, *J* = 8.0 Hz, ArH), 7.76 (d, 1H, *J* = 8.0 Hz, ArH), 8.59 (s, 1H, CH), 9.07 (s, 1H, SCH), 10.23 (s, 1H, CONH).

5.1.5.(E)-N'-(4-Methoxybenzylidene)-4-(2-oxo-2H-chromen-3-yl)thiazole-2-carbo hydrazide (7a).

A mixture of **5** (287 mg, 1 mmol), Anisic aldehyde **6a** (136 mg, 1 mmol) were refluxed in ethanol for 4 h in the presence of few drops of glacial acetic acid. After the mixture is cooled at room temperature, the product precipitated is filtered off and then washed with petroleum ether to give **7a** as a white solid (319 mg, 79 %); m.p. 244-246 ^{o}C; ^{1}H NMR (d^{6}-DMSO, 400 MHz) δ: 3.83 (s, 3H, OCH_3), 7.05 (d, 2H, *J* = 8.8 Hz, ArH), 7.47 (t, 1H, *J* = 8.0 Hz, ArH), 7.51 (d, 1H, *J* = 8.0 Hz, ArH), 7.69 (t, 1H, *J* = 8.0 Hz, ArH), 7.72 (d, 2H, *J* = 8.8 Hz, ArH), 7.84 (d, 1H, *J* = 8.0 Hz, ArH), 8.65 (s, 1H, NCH), 8.69 (s, 1H, CH), 9.04 (s, 1H, SCH), 12.10 (s, 1H, NH); ^{13}C NMR (d^{6}-DMSO, 100 MHz) δ: 55.3 (OCH_3), 114.4, 116.2, 119.0, 120.0, 124.9, 125.1, 126.5, 128.5, 129.0, 132.4, 140.5, 148.4, 150.1, 152.8, 155.2, 158.8, 161.2, 162.4; Anal. Calcd for $C_{21}H_{15}N_3O_4S$: C, 62.21; H, 3.73; N, 10.36; O, 15.79; S, 7.91; Found: C, 62.19; H, 3.75; N, 10.33.

5.1.6.(E)-N'-(2-Hydroxybenzylidene)-4-(2-oxo-2H-chromen-3-yl)thiazole-2-carbo

hydrazide (7b).

The compound **7b** was prepared in a similar manner to the procedure described for the preparation of **7a** to yield a solid (78 %); m.p. 251-252 ^{o}C; ^{1}H NMR (d^{6}-DMSO, 400 MHz) δ: 6.93-6.98 (m, 2H, ArH), 7.34 (t, 1H, *J* = 7.2 Hz, ArH), 7.46 (t, 1H, *J* = 8.0 Hz, ArH), 7.51 (d, 1H, *J* = 8.0 Hz, ArH), 7.63 (d, 1H, *J* = 8.0 Hz, ArH), 7.70 (t, 1H, *J* = 8.0 Hz, ArH), 7.86 (d, 1H, *J* = 8.0 Hz, ArH), 8.71 (s, 1H, CH), 8.95 (s, 1H, NCH), 9.05 (s, 1H, SCH), 10.95 (s, 1H, NH); ^{13}C NMR d^{6}-DMSO, 100 MHz) δ: 116.2, 116.4, 118.9, 119.5, 120.0, 125.1, 128.8, 128.9, 131.9, 132.4, 140.5, 148.5, 149.7, 152.8, 155.3, 157.5, 158.8, 161.8; Anal. Calcd for $C_{20}H_{13}N_3O_4S$: C, 61.37; H, 3.35; N, 10.74; O, 16.35; S, 8.19; Found: C, 61.34; H, 3.38; N, 10.71.

5.1.7.(E)-N'-(4-Hydroxybenzylidene)-4-(2-oxo-2H-chromen-3-yl)thiazole-2-carbo hydrazide (7c).

The compound **7c** was prepared in a similar manner to the procedure described for the preparation of **7a** to yield a solid (86 %); m.p. 273-275 ^{o}C; ^{1}H NMR (d^{6}-DMSO, 400 MHz) δ: 6.87 (d, 2H, *J* = 8.8 Hz, ArH), 7.46 (t, 1H, *J* = 8.0 Hz, ArH), 7.51 (d, 1H, *J* = 8.0 Hz, ArH), 7.61 (d, 2H, *J* = 8.8 Hz, ArH), 7.70 (t, 1H, *J* = 8.0 Hz, ArH), 7.84 (d, 1H, *J* = 8.0 Hz, ArH), 8.61 (s, 1H, NCH), 8.69 (s, 1H, CH), 9.05 (s, 1H, SCH), 10.22 (s, 1H, NH); ^{13}C NMR (d^{6}-DMSO, 100 MHz) δ: 115.8, 116.2, 119.0, 120.0, 124.8, 124.9, 125.1, 128.8, 129.2, 132.3, 140.5, 148.4, 150.5, 152.8, 155.1, 158.8, 159.8, 162.5; Anal. Calcd for $C_{20}H_{13}N_3O_4S$: C, 61.37; H, 3.35; N, 10.74; O, 16.35; S, 8.19; Found: C, 61.35; H, 3.37; N, 10.72.

5.1.8.(E)-N'-(3,5-Di-tert-butyl-2-hydroxybenzylidene)-4-(2-oxo-2H-chromen-3-yl) thiazole-2-carbohydrazide (7d).

The compound **7d** was prepared in a similar manner to the procedure described for the preparation of **7a** to yield a solid (67 %); m.p. 235-237 ^{o}C; ^{1}H NMR (d^{6}-DMSO, 400 MHz) δ: 1.31 (s, 9H, CH_3), 1.43 (s, 9H, CH_3), 7.24 (d, 1H, *J* = 2.0 Hz, ArH), 7.36 (d, 1H, *J* = 2.0 Hz, ArH), 7.47 (t, 1H, *J* = 8.0 Hz, ArH), 7.52 (d, 1H, *J* = 8.0 Hz, ArH), 7.71 (t, 1H, *J* = 8.0 Hz, ArH), 7.84 (d, 1H, *J* = 8.0 Hz, ArH), 8.74 (s, 1H, CH), 8.86 (s, 1H, NCH), 9.02 (s, 1H, SCH), 12.03 (s, 1H, NH), 12.61 (s, 1H, OH); ^{13}C NMR (d^{6}-DMSO, 100 MHz) δ: 29.3 (CH_3), 31.2 (CH_3), 33.9 (-C-CH_3), 34.7 (-C-CH_3), 116.2, 116.8, 118.9, 120.0, 125.1, 125.4, 126.0, 126.2, 128.7, 132.5, 135.9, 140.5, 140.6, 148.6, 152.8, 153.7, 154.9, 155.2, 158.8, 161.5; Anal. Calcd for $C_{28}H_{29}N_3O_4S$: C, 66.78; H, 5.80; N, 8.34; O, 12.71; S, 6.37; Found: C, 66.75; H, 5.83; N, 8.35.

5.1.9.(E)-N'-(3,5-Dichloro-2-hydroxybenzylidene)-4-(2-oxo-2H-chromen-3-yl)thia zole-2-carbohydrazide (7e).

The compound **7e** was prepared in a similar manner to the procedure described for the preparation of **7a** to yield a solid (76 %); m.p. 285-288 ^{o}C; ^{1}H NMR (d^{6}-DMSO, 400 MHz) δ: 7.44 (t, 1H, *J* = 8.0 Hz, ArH), 7.50 (d, 1H, *J* = 8.0 Hz, ArH), 7.59 (s, 2H, ArH), 7.69 (t, 1H, *J* = 8.0 Hz, ArH), 7.88 (d, 1H, *J* = 8.0 Hz, ArH), 8.69 (s, 1H, CH), 8.84 (s, 1H, NCH), 9.00 (s, 1H, SCH), 12.05 (s, 1H, NH); ^{13}C NMR (d^{6}-DMSO, 100 MHz) δ: 116.2, 118.9, 119.9, 121.0, 122.0, 125.1, 128.0, 128.9, 130.6, 132.4, 140.5, 148.6, 148.7, 152.8, 156.1, 158.8, 160.9; MS (ESI, m/z): 458.02 [M-H]$^{-}$; Anal. Calcd

for $C_{20}H_{11}Cl_2N_3O_4S$: C, 52.19; H, 2.41; Cl, 15.40; N, 9.13; O, 13.90; S, 6.97; Found: C, 52.15; H, 2.44; N, 9.10.

5.1.10.(E)-N'-(3-Hydroxy-4-methoxybenzylidene)-4-(2-oxo-2H-chromen-3-yl)thiazole-2-carbohydrazide (7f).

The compound **7f** was prepared in a similar manner to the procedure described for the preparation of **7a** to yield a solid (55 %); m.p. 218-219 ^{o}C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 3.83 (s, 3H, OCH_3), 7.01 (d, 1H, *J* = 8.0 Hz, ArH), 7.11 (dd, 1H, *J* = 8.0 Hz, 2.0 Hz, ArH), 7.32 (d, 1H, *J* = 2.0 Hz, ArH), 7.47 (t, 1H, *J* = 8.0 Hz, ArH), 7.51 (d, 1H, *J* = 8.0 Hz, ArH), 7.69 (t, 1H, *J* = 8.0 Hz, ArH), 7.85 (d, 1H, *J* = 8.0 Hz, ArH), 8.56 (s, 1H, NCH), 8.69 (s, 1H, CH), 9.05 (s, 1H, SCH), 9.37 (s, 1H, OH), 12.06 (s, 1H, NH); ^{13}C NMR (d^6-DMSO, 100 MHz) δ: 55.6 (OCH_3), 111.9, 112.4, 116.2, 119.0, 120.0, 120.7, 124.9, 125.1, 126.7, 128.8, 132.4, 140.5, 147.0, 148.4, 150.2, 150.4, 152.8, 155.2, 158.8, 162.4; Anal. Calcd for $C_{21}H_{15}N_3O_5S$: C, 59.85; H, 3.59; N, 9.97; O, 18.98; S, 7.61; Found: C, 59.82; H, 3.63; N, 9.93.

5.1.11.(E)-N'-(3-Fluoro-4-hydroxybenzylidene)-4-(2-oxo-2H-chromen-3-yl)thiazole-2-carbohydrazide (7g).

The compound **7g** was prepared in a similar manner to the procedure described for the preparation of **7a** to yield a solid (83 %); m.p. 225-226 ^{o}C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.06 (t, 1H, *J* = 8.0 Hz, ArH), 7.41 (d, 1H, *J* = 8.0 Hz, ArH), 7.46 (t, 1H, *J* = 8.0 Hz, ArH), 7.51-7.55 (m, 2H, ArH), 7.70 (t, 1H, *J* = 8.0 Hz, ArH), 7.85 (d, 1H, *J* = 8.0 Hz, ArH), 8.60 (s, 1H, NCH), 8.69 (s, 1H, CH), 9.04 (s, 1H, SCH), 10.49 (s, 1H,

OH), 12. 15 (s, 1H, NH); ^{13}C NMR (d^6-DMSO, 100 MHz) δ: 114.1, 114.3, 116.2, 118.0, 119.0, 120.0, 124.8, 125.0, 125.1, 125.7, 128.8, 132.4, 140.5, 147.4, 148.5, 149.4, 152.8, 155.3, 158.8, 162.3; Anal. Calcd for $C_{20}H_{12}FN_3O_4S$: C, 58.68; H, 2.95; F, 4.64; N, 10.26; O, 15.63; S, 7.83; Found: C, 58.69; H, 2.97; N, 10.23.

5.1.12.(E)-N'-(5-Chloro-2-hydroxybenzylidene)-4-(2-oxo-2H-chromen-3-yl)thiazole-2-carbohydrazide (7h).

The compound **7h** was prepared in a similar manner to the procedure described for the preparation of **7a** to yield a solid (79 %); m.p. 285-286 ^{o}C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 6.96 (d, 1H, *J* = 8.8 Hz, ArH), 7.33 (dd, 1H, *J* = 8.8 Hz, 2.0 Hz, ArH), 7.46 (t, 1H, *J* = 8.0 Hz, ArH), 7.51 (d, 1H, *J* = 8.0 Hz, ArH), 7.68-7.72 (m, 2H, ArH), 7.86 (d, 1H, *J* = 8.0 Hz, ArH), 8.71 (s, 1H, CH), 8.91 (s, 1H, NCH), 9.04 (s, 1H, SCH), 10.92 (s, 1H, NH); ^{13}C NMR (d^6-DMSO, 100 MHz) δ: 116.2, 118.3, 118.9, 120.0, 120.9, 123.1, 125.1, 125.2, 126.8, 128.8, 131.2, 132.4, 140.5, 147.1, 148.6, 152.8, 155.5, 156.0, 158.8, 161.7; MS (ESI, m/z): 424.03 $[M-H]^-$; Anal. Calcd for $C_{20}H_{12}ClN_3O_4S$: C, 56.41; H, 2.84; Cl, 8.33; N, 9.87; O, 15.03; S, 7.53; Found: C, 56.40; H, 2.82; N, 9.85.

5.1.13.(E)-N'-(2-Hydroxy-4-methoxybenzylidene)-4-(2-oxo-2H-chromen-3-yl)thiazole-2-carbohydrazide (7i).

The compound **7i** was prepared in a similar manner to the procedure described for the preparation of **7a** to yield a solid (66 %); m.p. 222-224 ^{o}C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 3.79 (s, 3H, OCH_3), 6.51 (d, 1H, *J* = 2.0 Hz, ArH), 6.54 (dd, 1H, *J* = 8.0 Hz,

2.0 Hz, ArH), 7.46 (t, 1H, *J* = 8.0 Hz, ArH), 7.49-7.53 (m, 2H, ArH), 7.70 (t, 1H, *J* = 8.0 Hz, ArH), 7.85 (d, 1H, *J* = 8.0 Hz, ArH), 8.69 (s, 1H, CH), 8.83 (s, 1H, NCH), 9.03 (s, 1H, SCH), 11.10 (s, 1H, NH); ^{13}C NMR (d^6-DMSO, 100 MHz) δ: 55.3 (OCH_3), 101.1, 106.6, 111.9, 116.2, 118.9, 120.0, 125.0, 125.1, 128.8, 130.7, 132.4, 140.5, 148.5, 150.3, 152.8, 155.2, 158.8, 159.5, 162.1, 162.4; Anal. Calcd for $C_{21}H_{15}N_3O_5S$: C, 59.85; H, 3.59; N, 9.97; O, 18.98; S, 7.61; Found: C, 59.82; H, 3.53; N, 9.94.

5.1.14.(E)-N'-(2,4-Dihydroxybenzylidene)-4-(2-oxo-2H-chromen-3-yl)thiazole-2-carbohydrazide (7j).

The compound **7j** was prepared in a similar manner to the procedure described for the preparation of **7a** to yield a solid (81 %); m.p. 276-278 ^{o}C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 6.78 (s, 2H, ArH), 7.08 (s, 1H, ArH), 7.46 (t, 1H, *J* = 8.0 Hz, ArH), 7.51 (d, 1H, *J* = 8.0 Hz, ArH), 7.70 (t, 1H, *J* = 8.0 Hz, ArH), 7.86 (d, 1H, *J* = 8.0 Hz, ArH), 8.70 (s, 1H, CH), 8.87 (s, 1H, NCH), 9.06 (s, 1H, SCH), 10.25 (s, 1H, OH), 10.81 (s, 1H, NH); ^{13}C NMR (d^6-DMSO, 100 MHz) δ: 113.0, 116.2, 117.2, 119.0, 119.2, 119.4, 120.0, 125.0, 125.1, 128.8, 132.4, 140.5, 148.5, 149.0, 149.9, 150.3, 152.8, 155.4, 158.8, 162.1; Anal. Calcd for $C_{20}H_{13}N_3O_5S$: C, 58.96; H, 3.22; N, 10.31; O, 19.64; S, 7.87; Found: C, 58.93; H, 3.26; N, 10.28.

5.1.15.(E)-N'-(3,4-Dihydroxybenzylidene)-4-(2-oxo-2H-chromen-3-yl)thiazole-2-carbohydrazide (7k).

The compound **7k** was prepared in a similar manner to the procedure described for the

preparation of **7a** to yield a solid (77 %); m.p. 205-208 ^{o}C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 6.82 (d, 1H, *J* = 8.8 Hz, ArH), 6.99 (d, 1H, *J* = 8.8 Hz, ArH), 7.30 (s, 1H, ArH), 7.46 (t, 1H, *J* = 8.0 Hz, ArH), 7.51 (d, 1H, *J* = 8.0 Hz, ArH), 7.70 (t, 1H, *J* = 8.0 Hz, ArH), 7.85 (d, 1H, *J* = 8.0 Hz, ArH), 8.52 (s, 1H, NCH), 8.69 (s, 1H, CH), 9.05 (s, 1H, SCH), 9.81 (s, 1H, NH); ^{13}C NMR (d^6-DMSO, 100 MHz) δ: 112.8, 115.6, 116.2, 119.0, 120.0, 121.0, 124.8, 125.1, 125.3, 128.8, 132.4, 140.5, 145.8, 148.4, 148.5, 150.7, 152.8, 155.1, 158.8, 162.5; Anal. Calcd for $C_{20}H_{13}N_3O_5S$: C, 58.96; H, 3.22; N, 10.31; O, 19.64; S, 7.87; Found: C, 58.94; H,3.24 ; N, 10.28.

5.1.16.(E)-N'-(4-Hydroxy-3,5-dimethoxybenzylidene)-4-(2-oxo-2H-chromen-3-yl) thiazole-2-carbohydrazide (7l).

The compound **7l** was prepared in a similar manner to the procedure described for the preparation of **7a** to yield a solid (59 %); m.p. 261-262 ^{o}C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 3.85 (s, 6H, OCH_3), 7.03 (s, 2H, ArH), 7.47 (t, 1H, *J* = 8.0 Hz, ArH), 7.51 (d, 1H, *J* = 8.0 Hz, ArH), 7.70 (t, 1H, *J* = 8.0 Hz, ArH), 7.83 (d, 1H, *J* = 8.0 Hz, ArH), 8.59 (s, 1H, NCH), 8.69 (s, 1H, CH), 9.05 (s, 1H, SCH), 10.08 (s, 1H, NH); ^{13}C NMR (d^6-DMSO, 100 MHz) δ: 56.0 (OCH_3), 104.9, 116.2, 119.0, 120.0, 124.1, 124.9, 125.1, 128.7, 132.4, 138.4, 140.5, 148.2, 148.4, 150.9, 152.8, 155.2, 158.8, 162.4; Anal. Calcd for $C_{22}H_{17}N_3O_6S$: C, 58.53; H, 3.80; N, 9.31; O, 21.26; S, 7.10; Found: C, 58.51; H, 3.75; N, 9.30.

5.1.17.(E)-N'-(4-Chlorobenzylidene)-4-(2-oxo-2H-chromen-3-yl)thiazole-2-carbohydrazide (7m).

The compound **7m** was prepared in a similar manner to the procedure described for the preparation of **7a** to yield a solid (88 %); m.p. 282-284 ^{o}C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.46 (t, 1H, *J* = 8.0 Hz, ArH), 7.51 (d, 1H, *J* = 8.0 Hz, ArH), 7.55 (d, 2H, *J* = 8.8 Hz, ArH), 7.70 (t, 1H, *J* = 8.0 Hz, ArH), 7.79 (d, 2H, *J* = 8.8 Hz, ArH), 7.85 (d, 1H, *J* = 8.0 Hz, ArH), 8.71 (s, 2H, CH, NCH), 9.04 (s, 1H, SCH), 11.05 (s, 1H, NH); ^{13}C NMR (d^6-DMSO, 100 MHz) δ: 116.2, 118.9, 120.0, 125.1, 125.2, 128.8, 128.9, 129.0, 132.4, 132.9, 135.0, 140.5, 148.5, 148.9, 152.8, 155.5, 158.8, 162.1; MS (ESI, m/z): 408.03 $[M-H]^-$; Anal. Calcd for $C_{20}H_{12}ClN_3O_3S$: C, 58.61; H, 2.95; Cl, 8.65; N, 10.25; O, 11.71; S, 7.82; Found: C, 58.63; H, 2.99; N, 10.21.

5.1.18.(E)-N'-(3-Chlorobenzylidene)-4-(2-oxo-2H-chromen-3-yl)thiazole-2-carbohydrazide (7n).

The compound **7n** was prepared in a similar manner to the procedure described for the preparation of **7a** to yield a solid (70 %); m.p. 235-238 ^{o}C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.45 (t, 1H, *J* = 8.0 Hz, ArH), 7.50-7.55 (m, 3H, ArH), 7.68-7.73 (m, 2H, ArH), 7.80 (s, 1H, ArH), 7.86 (d, 1H, *J* = 8.0 Hz, ArH), 8.71 (s, 2H, CH, NCH), 9.05 (s, 1H, SCH), 11.12 (s, 1H, NH); ^{13}C NMR (d^6-DMSO, 100 MHz) δ: 116.2, 118.9, 119.9, 125.1, 125.2, 126.1, 126.4, 128.8, 130.1, 130.8, 132.4, 133.7, 136.2, 140.5, 148.5, 152.8, 155.7, 158.8, 162.0; Anal. Calcd for $C_{20}H_{12}ClN_3O_3S$: C, 58.61; H, 2.95; Cl, 8.65; N, 10.25; O, 11.71; S, 7.82; Found: C, 58.56; H, 3.01; N, 10.21.

5.1.19.(E)-4-(2-Oxo-2H-chromen-3-yl)-N'-(4-(trifluoromethyl)benzylidene)thiazole-2-carbohydrazide (7o).

The compound **7o** was prepared in a similar manner to the procedure described for the preparation of **7a** to yield a solid (64 %); m.p. 243-245 ^{o}C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.46 (t, 1H, *J* = 8.0 Hz, ArH), 7.51 (d, 1H, *J* = 8.0 Hz, ArH), 7.70 (t, 1H, *J* = 8.0 Hz, ArH), 7.84-7.86 (m, 3H, ArH), 7.78 (d, 2H, *J* = 8.8 Hz, ArH), 8.72 (s, 1H, CH), 8.80 (s, 1H, NCH), 9.04 (s, 1H, SCH), 11.47 (s, 1H, NH); ^{13}C NMR (d^6-DMSO, 100 MHz) δ: 116.2, 118.9, 120.0, 122.7, 125.1, 125.3, 125.8, 127.9, 127.9, 128.8, 132.4, 137.9, 140.5, 141.0, 148.4, 148.5, 152.1, 152.8, 155.7, 158.8, 162.0; Anal. Calcd for $C_{21}H_{12}F_3N_3O_3S$: C, 56.88; H, 2.73; F, 12.85; N, 9.48; O, 10.83; S, 7.23; Found: C, 56.83; H, 2.77; N, 9.45.

5.1.20.(E)-N'-(2-Fluorobenzylidene)-4-(2-oxo-2H-chromen-3-yl)thiazole-2-carbohydrazide (7p).

The compound **7p** was prepared in a similar manner to the procedure described for the preparation of **7a** to yield a solid (72 %); m.p. 293-296 ^{o}C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.46-7.54 (m, 4H, ArH), 7.57 (d, 1H, *J* = 8.0 Hz, ArH), 7.71 (t, 1H, *J* = 8.0 Hz, ArH), 7.88 (d, 1H, *J* = 8.0 Hz, ArH), 8.06 (d, 1H, *J* = 8.0 Hz, ArH), 8.73 (s, 1H, CH), 9.05 (s, 1H, SCH), 9.13 (s, 1H, NCH), 12.54 (s, 1H, NH); ^{13}C NMR (d^6-DMSO, 100 MHz) δ: 116.2, 118.9, 120.0, 125.1, 125.3, 127.1, 127.7, 128.9, 130.0, 131.4, 131.9, 132.4, 133.5, 140.5, 146.0, 148.6, 152.8, 155.7, 158.8, 162.0; Anal. Calcd for $C_{20}H_{12}FN_3O_3S$: C, 61.06; H, 3.07; F, 4.83; N, 10.68; O, 12.20; S, 8.15; Found: C, 61.02; H, 3.10; N, 10.65.

5.1.21.(E)-N'-(3-Fluorobenzylidene)-4-(2-oxo-2H-chromen-3-yl)thiazole-2-carboh

ydrazide (7q).

The compound **7q** was prepared in a similar manner to the procedure described for the preparation of **7a** to yield a solid (85 %); m.p. 254-255 ^{o}C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.33 (t, 1H, *J* = 8.0 Hz, ArH), 7.46 (t, 1H, *J* = 8.0 Hz, ArH), 7.50-7.58 (m, 3H, ArH), 7.61 (d, 1H, *J* = 8.0 Hz, ArH), 7.70 (t, 1H, *J* = 8.0 Hz, ArH), 7.85 (d, 1H, *J* = 8.0 Hz, ArH), 8.71 (s, 1H, CH), 8.72 (s, 1H, NCH), 9.04 (s, 1H, SCH), 12.00 (s, 1H, NH); ^{13}C NMR (d^6-DMSO, 100 MHz) δ: 113.3, 116.2, 118.9, 119.9, 123.7, 125.1, 125.2, 128.8, 131.0, 132.4, 136.5, 140.5, 148.5, 148.8, 152.8, 155.6, 158.8, 161.2, 162.0, 163.6; Anal. Calcd for $C_{20}H_{12}FN_3O_3S$: C, 61.06; H, 3.07; F, 4.83; N, 10.68; O, 12.20; S, 8.15; Found: C, 61.08; H, 3.10; N, 10.63.

5.1.22.(E)-N'-(3-bromobenzylidene)-4-(2-oxo-2H-chromen-3-yl)thiazole-2-carboh

ydrazide (7r).

The compound **7r** was prepared in a similar manner to the procedure described for the preparation of **7a** to yield a solid (80 %); m.p. 233-234 ^{o}C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.44-7.48 (m, 2H, ArH), 7.50 (d, 1H, *J* = 8.0 Hz, ArH), 7.66-7.70 (m, 2H, ArH), 7.76 (d, 1H, *J* = 8.0 Hz, ArH), 7.84 (d, 1H, *J* = 8.0 Hz, ArH), 7.95 (s, 1H, ArH), 8.68 (s, 1H, CH), 8.71 (s, 1H, NCH), 9.03 (s, 1H, SCH), 11.23 (s, 1H, NH); ^{13}C NMR (d^6-DMSO, 100 MHz) δ: 116.2, 118.9, 119.9, 122.2, 125.1, 125.2, 126.5, 128.8, 129.3, 131.1, 132.4, 133.0, 136.4, 140.5, 148.4, 148.5, 152.8, 155.6, 158.8, 162.0; Anal. Calcd for $C_{20}H_{12}BrN_3O_3S$: C, 52.88; H, 2.66; Br, 17.59; N, 9.25; O, 10.57; S, 7.06; Found: C, 52.85; H, 2.64; N, 9.23.

5.1.23.(E)-N'-(2-Methoxybenzylidene)-4-(2-oxo-2H-chromen-3-yl)thiazole-2-carbohydrazide (7s).

The compound **7s** was prepared in a similar manner to the procedure described for the preparation of **7a** to yield a solid (75 %); m.p. 234-235 ^{o}C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 3.92 (s, 3H, OCH_3), 7.06 (t, 1H, *J* = 8.0 Hz, ArH), 7.14 (d, 1H, *J* = 8.0 Hz, ArH), 7.45-7.49 (m, 2H, ArH), 7.51 (d, 1H, *J* = 8.0 Hz, ArH), 7.71 (t, 1H, *J* = 8.0 Hz, ArH), 7.87 (d, 1H, *J* = 8.0 Hz, ArH), 7.91 (d, 1H, *J* = 8.0 Hz, ArH), 8.70 (s, 1H, CH), 9.06 (s, 1H, SCH), 9.08 (s, 1H, NCH), 11.35 (s, 1H, NH); ^{13}C NMR (d^{6}-DMSO, 100 MHz) δ: 55.5 (OCH_3), 116.2, 116.4, 118.9, 119.0, 119.5, 120.0, 125.1, 125.2, 128.8, 128.9, 131.9, 132.4, 140.6, 148.5, 149.7, 152.8, 155.3, 157.5, 158.8, 161.8; Anal. Calcd for $C_{21}H_{15}N_3O_4S$: C, 62.21; H, 3.73; N, 10.36; O, 15.79; S, 7.91; Found: C, 62.19; H, 3.77; N, 10.33.

5.1.24.(E)-4-(2-Oxo-2H-chromen-3-yl)-N'-(3,4,5-trimethoxybenzylidene)thiazole-2-carbohydrazide (7t).

The compound **7t** was prepared in a similar manner to the procedure described for the preparation of **7a** to yield a solid (69 %); m.p. 235-237 ^{o}C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 3.73 (s, 3H, OCH_3), 3.86 (s, 6H, OCH_3), 7.05 (s, 2H, ArH), 7.46 (t, 1H, *J* = 8.0 Hz, ArH), 7.51 (d, 1H, *J* = 8.0 Hz, ArH), 7.70 (t, 1H, *J* = 8.0 Hz, ArH), 7.83 (d, 1H, *J* = 8.0 Hz, ArH), 8.64 (s, 1H, NCH), 8.69 (s, 1H, CH), 9.05 (s, 1H, SCH), 10.46 (s, 1H, NH); ^{13}C NMR (d^{6}-DMSO, 100 MHz) δ: 55.3 (OCH_3), 55.6 (OCH_3), 115.8, 116.2, 119.0, 120.0, 124.8, 124.9, 125.1, 128.8, 129.2, 132.4, 140.5, 148.4, 150.5,

152.8, 155.1, 158.8, 159.8, 162.5; Anal. Calcd for $C_{23}H_{19}N_3O_6S$: C, 59.35; H, 4.11; N, 9.03; O, 20.62; S, 6.89; Found: C, 59.33; H, 4.15; N, 9.01.

5.2. Biological evaluation

α-Glucosidase from *Saccharomyces cerevisiae* and p-nitrophenyl α-D-glucopyranoside (pNPG) were purchased from Sigma Aldrich Chemical Company.

5.2.1. *In vitro* assay of α-glucosidase inhibitory activity

The test compounds were dissolved in DMSO to prepare the required distributing concentration. α-Glucosidase inhibitory activity was assayed by using 50 mM phosphate buffer (pH 6.8) at 37 ^{o}C. The enzymatic reaction mixture composed of 20 µL α-glucosidase (0.2 U), 10 µL of various concentrations of test compounds and 140 µL of phosphate buffer was incubated at 37 °C for 10 min. Then 0.5 mM p-nitrophenyl α-D-glucopyranoside (30 µL) was added to the mixture as a substrate. After further incubation at 37 ^{o}C for 30 min. The absorbance was measured spectrophotometrically at 405 nm. The sample solution was replaced by DMSO as a control. Acarbose was used as a positive control. All experiments were carried out in triplicates.

The % inhibition has been obtained using the formula:

$$\text{Inhibition (\%)} = (1-\Delta A_{sample}/\Delta A_{control}) * 100\ \%$$

IC_{50} value is defined as a concentration of samples inhibiting 50 % of α-glucosidase activity under the stated assay conditions.

5.3. Molecular docking

Molecular docking studies were performed to investigate the binding mode of the compound **7e** to α-glucosidase using Autodock vina 1.1.2 (http://vina.scripps.edu). The 3D structure of **7e** was obtained by ChemBioDraw Ultra 14.0 and ChemBio3D Ultra 14.0 softwares. The AutoDockTools 1.5.6 package (http://mgltools.scripps.edu) was employed to generate the docking input files. The search grid of α-glucosidase was identified as center_x: -19.676, center_y: -7.243, and center_z: -21.469 with dimensions size_x: 15, size_y: 15, and size_z: 15. The value of exhaustiveness was set to 20. For Vina docking, the default parameters were used if it was not mentioned. The best-scoring pose as judged by the Vina docking score was chosen and visually analyzed using PyMOL 1.7.6 software (http://www.pymol.org/).

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Scheme Captions

Scheme 1. Reagents and conditions: (a) piperidine, ethanol, reflux, 3 h; (b) NBS, p-toluenesulfonic acid, CH_3CN, 50 °C, 5 h; (c) ethanol, 80 °C, 5 h; (d) hydrazine, ethanol, reflux, 4 h; (e) AcOH, ethanol, reflux, 4 h.

Figure Captions

Figure 1. Chemical structures of some α-glucosidase inhibitors containing coumarin or thiazole moieties.

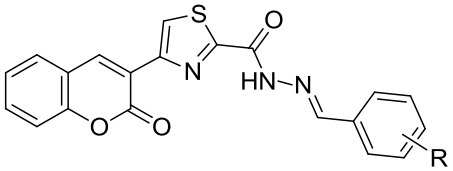
Figure 2. (A) Lineweaver-Burke plot of the inhibition kinetics of α-glucosidase by **7e**. (B) Secondary re-plot of Lineweaver-Burk plot between the slopes of each line on Lineweaver-Burk plot *vs* various concentrations of **7e**.

Figure 3. Compound **7e** was docked to the binding pocket of the *Saccharomyces cerevisiae* α-glucosidase.

Table Captions

Table 1. α-Glucosidase inhibitory activities of coumarin thiazole derivatives.

Table 1. α-Glucosidase inhibitory activities of coumarin thiazole derivatives



7a-7t

Compd	R	IC_{50} (μM)[a]	Compd	R	IC_{50} (μM) [a]
7a	4-OMe	81.69±0.39	**7k**	3,4-OH_2	18.25±0.19
7b	2-OH	37.18±0.61	**7l**	4-OH,3,5-OMe_2	NA
7c	4-OH	25.22±0.32	**7m**	4-Cl	10.59±0.13
7d	3,5-tBu_2, 2-OH	10.19±0.11	**7n**	3-Cl	11.95±0.14
7e	3,5-Cl_2, 2-OH	6.24±0.07	**7o**	4-CF_3	15.99±0.19
7f	3-OH, 4-OMe	NA	**7p**	2-F	23.55±0.32
7g	3-F, 4-OH	16.61±0.23	**7q**	3-F	22.62±0.27
7h	5-Cl, 2-OH	8.23±0.13	**7r**	3-Br	14.03±0.18
7i	2-OH, 4-OMe	29.90±0.46	**7s**	2-OMe	64.27±0.22
7j	2,5-OH_2	38.62±0.35	**7t**	3,4,5-OMe_3	NA
Acarbose		43.26±0.19			

[a] NA not active; acarbose is standard for α-glucosidase inhibition activity.

Scheme 1

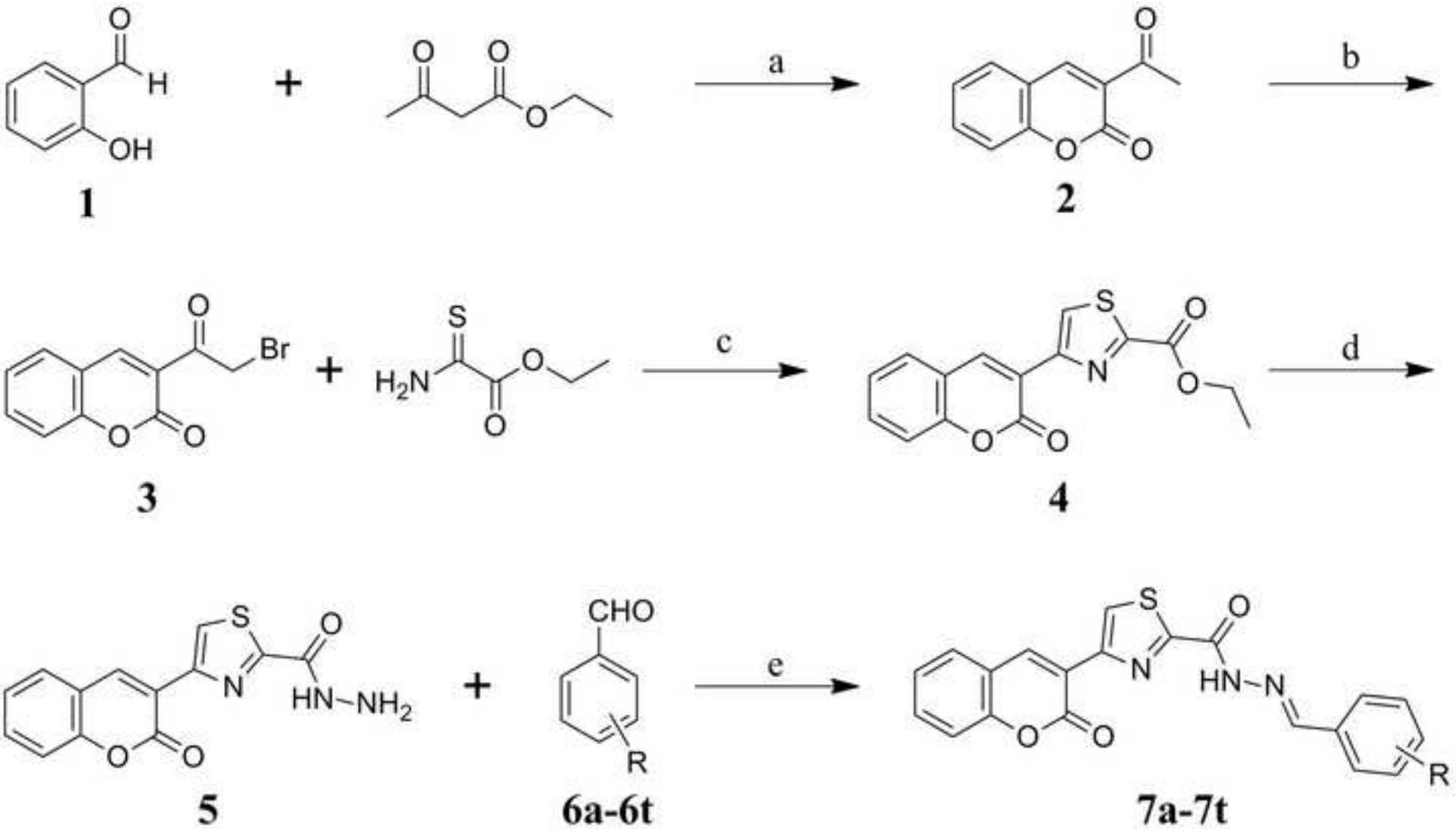


Figure 1

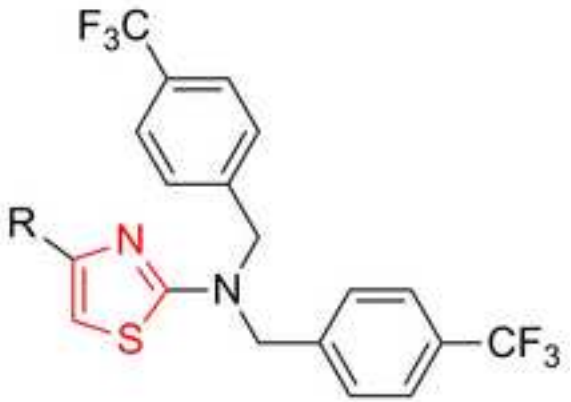
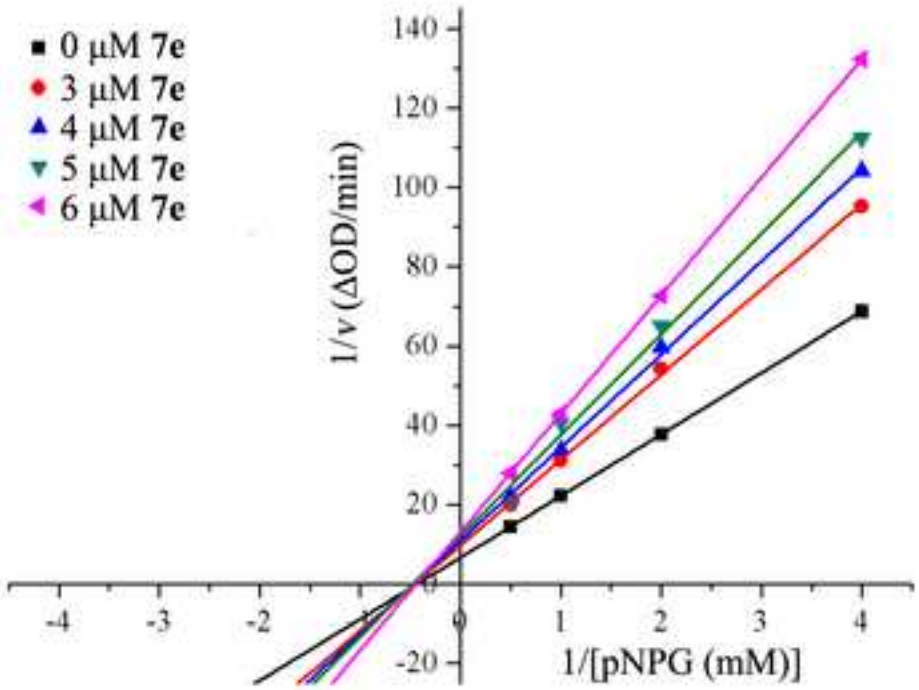


Figure 2



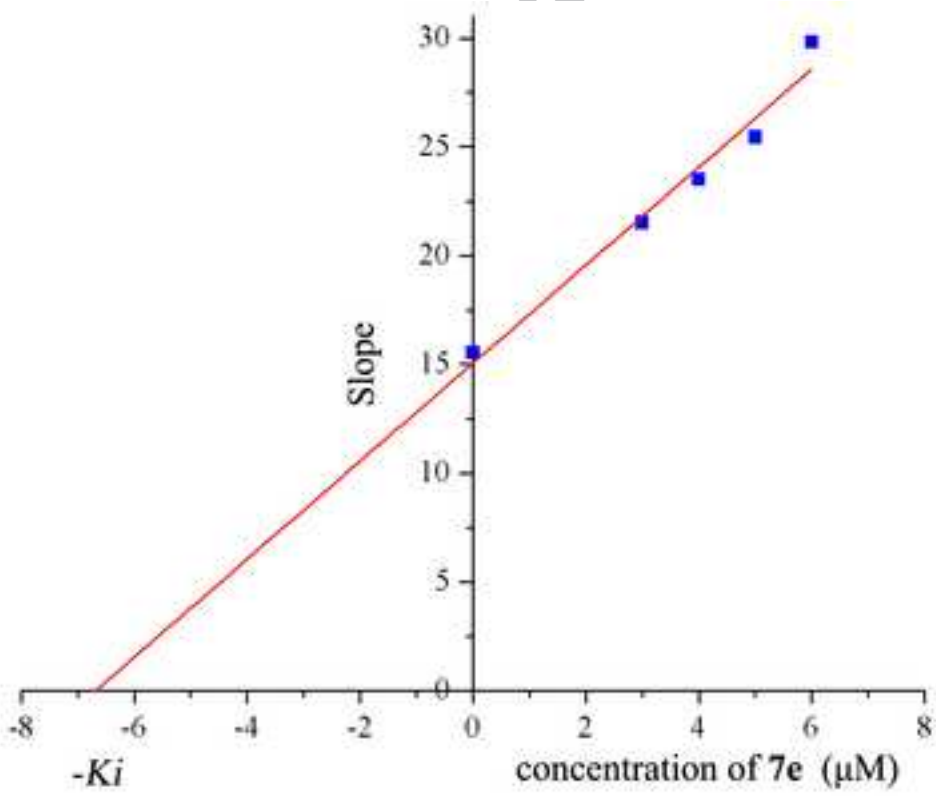
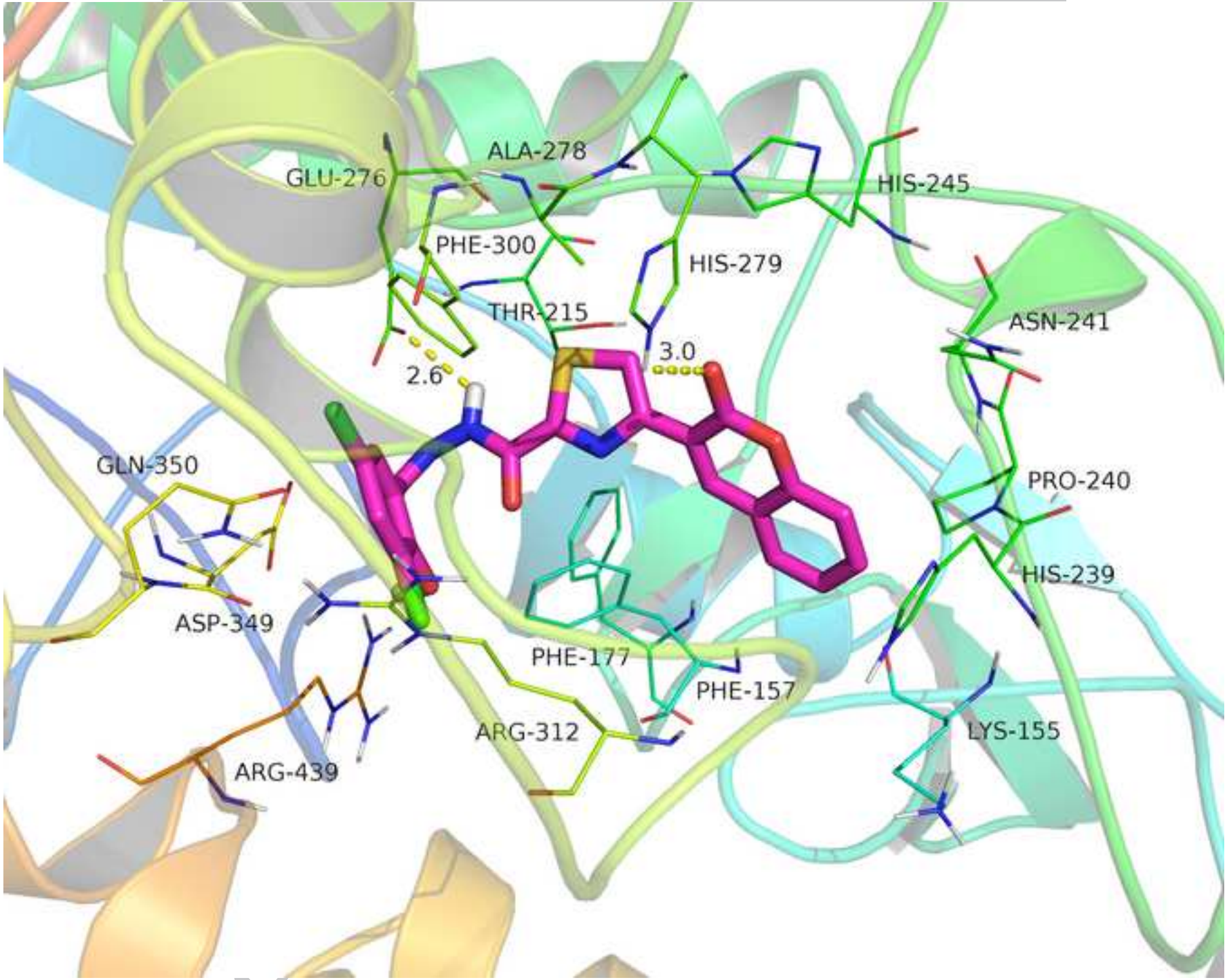


Figure 3



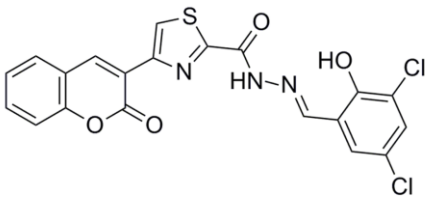
Highlights

►We designed and synthesized a series of coumarin thiazole derivatives.

►The majority of the screened compounds displayed potent α-glucosidase inhibitory activity.

► Compound **7e** was found to be the most active compound.

►The structure–activity relationship has been discussed.



7e

α-Glucosidase inhibitory activity: 6.24±0.07 μM