

Article

Synthesis, Biological Evaluation, and Molecular Docking Studies of Novel Isatin-Thiazole Derivatives as α -Glucosidase Inhibitors

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Abstract: A series of novel isatin-thiazole derivatives were synthesized and screened for their in vitro α -glucosidase inhibitory activity. These compounds displayed a varying degree of α -glucosidase inhibitory activity with IC_{50} ranging from 5.36 ± 0.13 to 35.76 ± 0.31 μm as compared to the standard drug acarbose ($IC_{50} = 817.38 \pm 6.27$ μm). Among the series, compound **6p** bearing a hydroxyl group at the 4-position of the right phenyl and 2-fluorobenzyl substituent at the *N*1-positions of the 5-methylisatin displayed the highest inhibitory activity with an IC_{50} value of 5.36 ± 0.13 μm . Molecular docking studies revealed the existence of hydrophobic interaction, CH- π interaction, arene-anion interaction, arene-cation interaction, and hydrogen bond between these compounds and α -glucosidase enzyme.

Keywords: α -glucosidase inhibitor; molecular docking; isatin; thiazole; diabetic

1. Introduction

Diabetes mellitus is a group of metabolic disorders of carbohydrate metabolism characterized by high blood glucose levels (hyperglycemia), resulting from defects in insulin secretion, insulin action, or both [1]. Currently, there are an estimated 422 million people have diabetes mellitus in the world, according to the latest 2016 data from the World Health Organization (WHO) [2]. In diabetic patients, untreated and chronic hyperglycemia can cause serious complications, such as heart disease, stroke, blindness, high blood pressure, kidney disease, and nervous system disease [3]. α -Glucosidase is a membrane-bound enzyme at the epithelium of the small intestine and hydrolyzes terminal non-reducing 1–4 linked α -glucose residues to release monomeric glucose molecules which is mainly responsible to cause hyperglycemia [4]. Inhibition of α -glucosidase activity can delay carbohydrate absorption and have been used as one of the therapeutic approaches for the treatment of diabetes [4,5]. Some α -glucosidase inhibitors (acarbose, miglitol, and voglibose) have been approved for clinical use and also used as anticancer [6], anti-HIV [7], and anti-hepatitis agents [8]. Therefore, design and synthesis of small molecules as α -glucosidase inhibitors is an important research area in medicinal chemistry.

Isatin (1*H*-indole-2,3-dione, **I**) is the reference compound of an important class of nitrogen-containing aromatic heterocyclic compounds, which have been found in many plants and human blood and tissue [9]. Isatin has emerged as a promising nucleus and attracted increasing

attention in medicinal chemistry and drug discovery over the past decade [10]. Previous literature reports indicated that isatin and its derivatives have diverse types of biological activity, including anticancer [11], antibacterial [12], antiviral [13], anticonvulsant [14], anti-inflammatory [15], and antifungal activity [16]. Notably, some isatin derivatives have been approved for clinic use such as sunitinib, toceranib, and nintedanib. Furthermore, Rahim et al. reported the synthesis of isatin based Schiff bases **II** (Figure 1) which showed excellent inhibitory potential many fold better than the standard acarbose [17]. Sun et al. reported the synthesis of tetracyclic oxindole derivatives **III** (Figure 1) and the most active compound ($IC_{50} = 0.7 \mu\text{m}$) was about 170 times as active as acarbose [18]. Recently, we have also synthesized a series of coumarin-isatin derivatives **IV** (Figure 1), and some of the obtained compound exhibited excellent α -glucosidase inhibition activity [19].

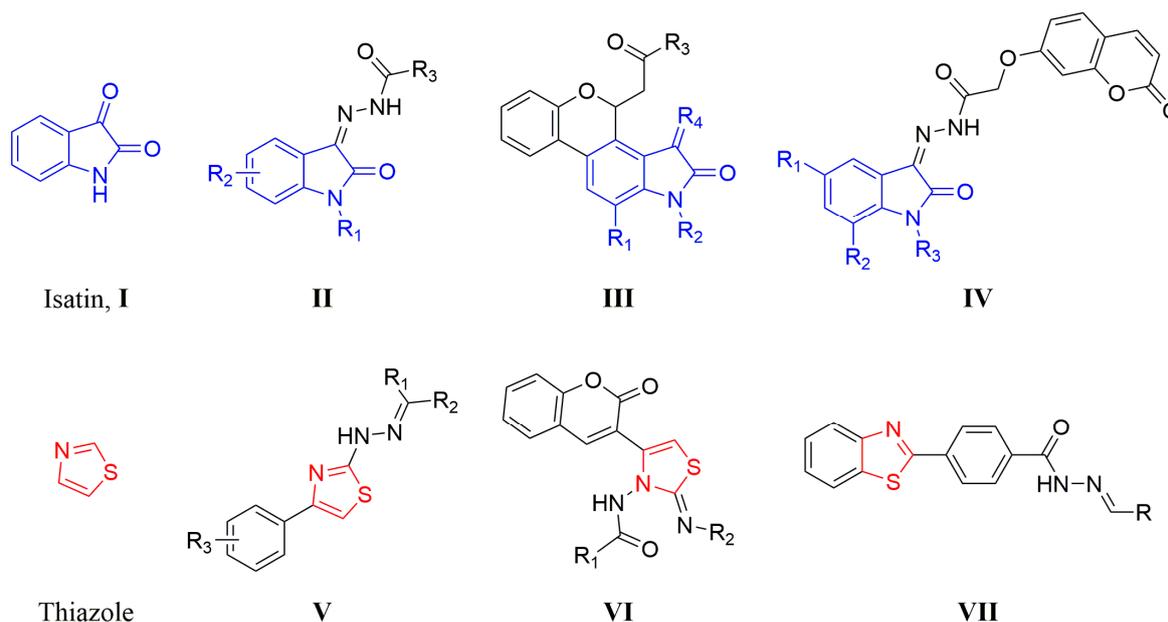


Figure 1. The chemical structures of the reported α -glucosidase inhibitors containing isatin or thiazole moiety.

On the other hand, thiazole derivatives are considered as another important class of heterocyclic compounds, which displayed a wide range of pharmacological activities such as anti-inflammatory [20], anticancer [21], anticonvulsant [22], and antibacterial [23]. It is interesting that numerous studies pointed out thiazole could be used as a useful moiety in the design of potent α -glucosidase inhibitors [24–28]. For example, compound series **V** [25], **VI** [28], and **VII** [26] displayed potent α -glucosidase inhibitory activity (Figure 1).

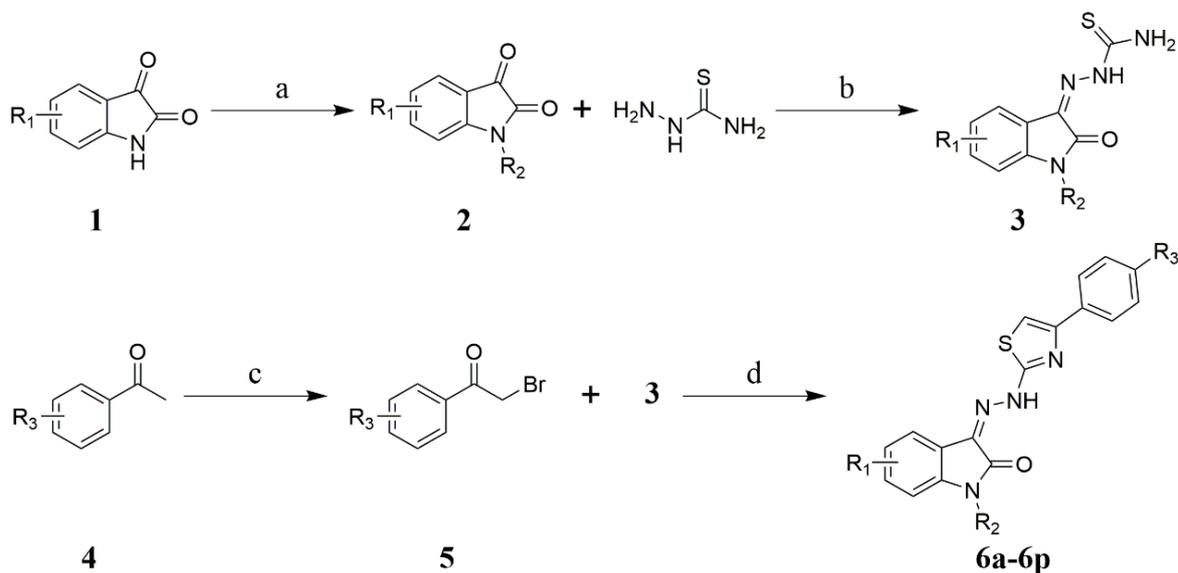
Over the years, molecular hybrid-based approaches had been exploited by researchers to discover some promising chemical architectures which containing two or more bioactive pharmacophores [29,30]. Using this approach, and as part of our ongoing effort to develop potent α -glucosidase inhibitors [31–35], herein we report the design and synthesis of a series of novel isatin-thiazole derivatives containing isatin and thiazole moieties. The synthesized compounds were evaluated for their inhibitory activity against α -glucosidase. Furthermore, molecular docking was also performed to investigate the interaction of inhibitors with enzymes.

2. Results and Discussion

2.1. Chemistry

The synthesis of isatin-thiazole derivatives **6a–6p** was shown in Scheme 1. Reaction of commercially available isatins **1** with various alkyl halides in the presence of K_2CO_3 in DMF provided N-alkyl isatins **2**. Isatins (**1** and **2**) were stirred with thiosemicarbazide in ethanol at 45°C for 3 h

to provide the isatin thiosemicarbazones **3**. Various substitutions of acetophenone **4** were treated with NBS in the presence of *p*-toluenesulfonic acid in acetonitrile to give α -bromoacetophenone **5**. α -bromoacetophenone **5**, with appropriate isatin thiosemicarbazones **3**, was condensed in refluxing ethanol for 2 h to afford the corresponding isatin-thiazole derivatives **6a–6p** in moderate to high yield (52.4–78.4%). All of the title compounds **6a–6p** have not yet been reported in the literature.



Scheme 1. Reagents and conditions: (a) R_2X , K_2CO_3 , DMF, room temperature, 2 h; (b) EtOH, 45 °C, 3 h; (c) *p*-MeC₆H₄SO₃H, NBS, CH₃CN, reflux, 2 h; (d) EtOH, reflux, 2 h.

The structures of all of the title compounds **6a–6p** were characterized by ¹H-NMR spectra. The ¹H-NMR spectrum of **6a** exhibited two singlet signals at 11.36 and 13.33 ppm, attributed to the protons of NH-indolin-2-one and =NNH group, respectively. Two doublet signals at 6.97 ppm ($J = 8.4$ Hz) and 7.52 ppm ($J = 2.0$ Hz) were attributed to C7-H and C4-H of isatin ring, respectively. The double-double peak of C6-H of the isatin ring was observed at 7.36 ppm with a coupling constant of 8.4 Hz and 2.0 Hz. Two double peaks at 7.61 and 7.85 ppm with coupling constant of 8.4 Hz were attributed to the aromatic protons of C3,5-H and C2,6-H, respectively. The hydrogen atom of thiazole ring appeared as a singlet signal at 7.74 ppm. The ¹H-NMR spectrum of all new compounds consistent with their structures. Moreover, in their ¹³C-NMR spectra, the number of signals equals the number of different carbons in the molecule (Supplementary Materials).

2.2. α -Glucosidase Inhibition Assay

All the synthetic compounds **6a–6p** were screened for their *in vitro* α -glucosidase inhibitory activity (Table 1). The results were shown that all the tested compounds displayed potent to moderate α -glucosidase inhibitory activity with IC₅₀ ranging from 5.36 ± 0.13 to 35.76 ± 0.31 μ m more potent than the standard drug acarbose (IC₅₀ = 817.38 ± 6.27 μ m [17,36]). Among the series, compounds **6a**, **6g**, **6h**, **6i**, **6j**, **6l**, **6m**, **6n**, and **6p** displayed potent inhibitory activity with IC₅₀ values of 6.87 ± 0.14, 5.98 ± 0.12, 6.12 ± 0.15, 7.51 ± 0.17, 6.51 ± 0.13, 8.33 ± 0.18, 7.17 ± 0.15, 6.36 ± 0.12, and 5.36 ± 0.13 μ m. In particular, compound **6p** (IC₅₀ = 5.36 ± 0.13 μ m) with a hydroxyl group at the 4-position of the right phenyl ring and methyl and 2-fluorobenzyl groups at 5- and N1-positions of the isatin ring, was found to be the most active compound. In comparison to compound **6p**, a decrease in activity was observed for **6i** (IC₅₀ = 7.51 ± 0.17) in which 2-fluorobenzyl groups is replaced with hydrogen at N1-positions of the isatin ring. Compounds **6c**, **6k**, and **6o** also displayed good inhibition with IC₅₀ value 10.34 ± 0.17, 15.68 ± 0.24, and 11.78 ± 0.21 μ m, respectively. Other compounds displayed

low α -glucosidase inhibitory activity. The binding interactions of the most active compounds with α -glucosidase were confirmed through molecular docking studies.

Table 1. α -Glucosidase inhibitory activity of novel isatin-thiazole derivatives (6a–6p).

Compound	R ₁	R ₂	R ₃	IC ₅₀ (μ m) ^a
6a	5-Cl	H	Br	6.87 \pm 0.14
6b	5-Me	2-F-benzyl	Me	35.76 \pm 0.31
6c	5-Me	2-F-benzyl	MeO	10.34 \pm 0.17
6d	H	Me	Me	32.17 \pm 0.29
6e	H	Me	F	33.20 \pm 0.24
6f	H	Me	MeO	24.17 \pm 0.28
6g	H	H	Cl	5.98 \pm 0.12
6h	5.7-Me ₂	H	Br	6.12 \pm 0.15
6i	5-Me	H	OH	7.51 \pm 0.17
6j	5.7-Me ₂	H	F	6.51 \pm 0.13
6k	5.7-Me ₂	H	Me	15.68 \pm 0.24
6l	5-F	H	Me	8.33 \pm 0.18
6m	5-F	H	F	7.17 \pm 0.15
6n	H	H	F	6.36 \pm 0.12
6o	H	H	Me	11.78 \pm 0.21
6p	5-Me	2-F-benzyl	OH	5.36 \pm 0.13
Acarbose				817.38 \pm 6.27

^a Acarbose is standard for α -glucosidase inhibition activity.

2.3. Homology Model

The crystallographic structure of *Saccharomyces cerevisiae* α -glucosidase enzyme has not been reported. To understand the ligand-enzyme interactions, 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, Resolution 1.30 Å) with 72.4% of sequence identity with the target was selected as the template for homology modeling [37]. The quality of homology model was verified by PROCHECK (<http://services.mbi.ucla.edu/PROCHECK/>). The result was shown that the model could be used to study the interactions between this class of compounds and the active site of α -glucosidase [35].

2.4. Molecular Docking

The theoretical binding mode between 6i and *Saccharomyces cerevisiae* α -glucosidase was shown in Figure 2. Compound 6i adopted a “V-shaped” conformation in the pocket of the α -glucosidase. The indolin-2-one scaffold of 6i located at the hydrophobic pocket, surrounded by the residues Phe-157, Leu-176, Pro-240, Phe-300, and Leu-218, forming a stable hydrophobic binding. Detailed analysis showed that the indolin-2-one scaffold of 6i formed CH- π interaction with the residue Phe-157. In addition, the 4-hydroxyphenyl group of 6i formed CH- π interactions with the residues Phe-158 and Tyr-71, and arene-anion interactions with the residues Asp-68 and Asp-349. Also, the arene-cation interactions were observed between the 4-hydroxyphenyl group of 6i and the residues Arg-439 and Arg-443. It was shown that the residues Thr-215 (bond length: 3.3 Å) and Asp-68 (length: 2.1 Å) formed two hydrogen bonds with 6i, which was the main interaction between 6i and α -glucosidase. On the other hand, molecular docking study of the standard drug acarbose with α -glucosidase was also performed (Figure 2B). The results were shown that compound 6i (binding energy was about -9.2 kcal mol⁻¹) has a similar binding affinity as compared to standard drug acarbose (binding energy was about -6.8 kcal mol⁻¹).

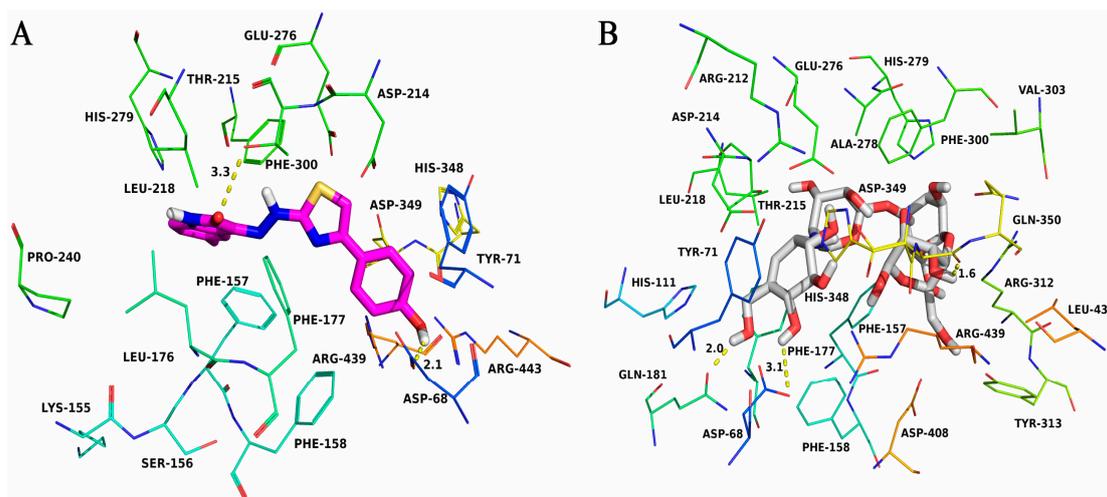


Figure 2. Compound **6i** (A) and acarbose (B) was docked to the binding pocket of the *Saccharomyces cerevisiae* α -glucosidase.

To explain the activity order of **6i** and **6p** against α -glucosidase in the molecular level, **6p** was further docked into the binding pocket of α -glucosidase, and the theoretical binding mode between **6p** and α -glucosidase was shown in Figure 3A. The interaction between **6p** and α -glucosidase was nearly the same as the compound **6i** (Figure 3B). The main difference was that the 2-fluorophenyl group of **6p** formed extra hydrophobic interactions with the residues Phe-157, Leu-176, Pro-240, and Leu-218, and formed two extra hydrogen bonds with the residue Glu-276 (length: 2.4 Å) and Asp-68 (length: 2.4 Å), which made **6p** was more active than **6i** against α -glucosidase (Figure 3B). In addition, the estimated binding energies were -9.2 kcal mol $^{-1}$ for **6i** and -10.1 kcal mol $^{-1}$ for **6p**, respectively, which was consistent with the results of the in vitro α -glucosidase inhibitory activity.

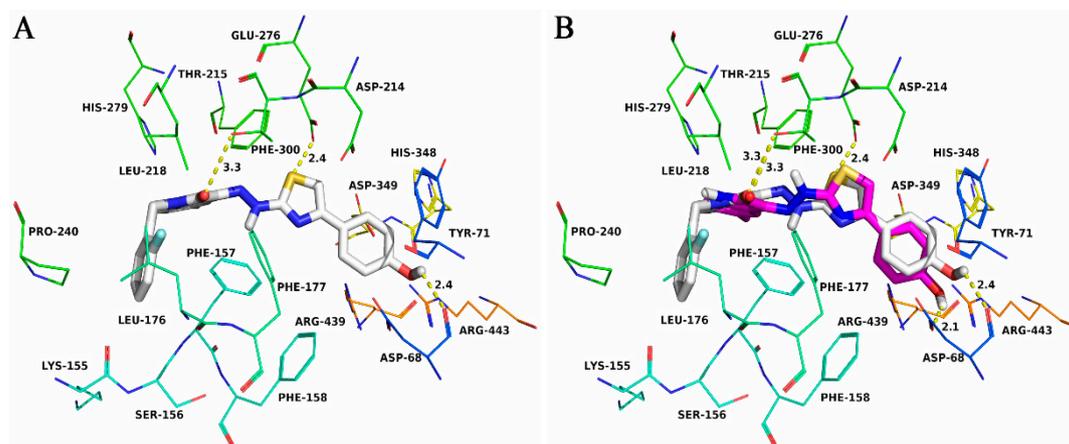


Figure 3. (A) Compound **6p** was docked to the binding pocket of the *Saccharomyces cerevisiae* α -glucosidase; (B) Compounds **6i** and **6p** were docked to the binding pocket of the *Saccharomyces cerevisiae* α -glucosidase (overlapped).

To explain the activity order of **6b** and **6p** against α -glucosidase in the molecular level, **6b** was further docked into the binding pocket of α -glucosidase, and the theoretical binding mode between **6b** and α -glucosidase was shown in Figure 4A. Compound **6b** adopted a 'V-shaped' conformation in the pocket of the α -glucosidase. The 2-fluorophenylindolin-2-one group of **6b** stretched into the hydrophobic pocket that consisted of Phe-157, Leu-176, Pro-240, Phe-300, and Leu-218, forming a stable hydrophobic binding. Detailed analysis showed that the indolin-2-one scaffold of **6b** formed

CH- π interaction with the residue Phe-157. In addition, the 4-methylphenyl group of **6b** formed CH- π interactions with the residues Phe-158 and Tyr-71, and arene-anion interactions with the residues Asp-68 and Asp-349, respectively. Also, the arene-cation interactions were observed between the 4-methylphenyl group of **6b** and the residues Arg-439 and Arg-443. It was shown that the residues Thr-215 (bond length: 3.2 Å) and Glu-276 (length: 2.4 Å) formed two hydrogen bonds with **6b**, which was the main interaction between **6b** and α -glucosidase. The interaction between **6p** and α -glucosidase was nearly the same as the compound **6b** (Figure 4B). The main difference was that the 4-methoxyphenyl group of **6p** formed an extra hydrogen bond with the residue Asp-68 (length: 2.4 Å), which made **6p** was more active than **6b** against α -glucosidase (Figure 4B). In addition, the estimated binding energies were $-9.5 \text{ kcal mol}^{-1}$ for **6b** and $-10.1 \text{ kcal mol}^{-1}$ for **6p**, respectively, which was consistent with the results of the in vitro α -glucosidase inhibitory activity.

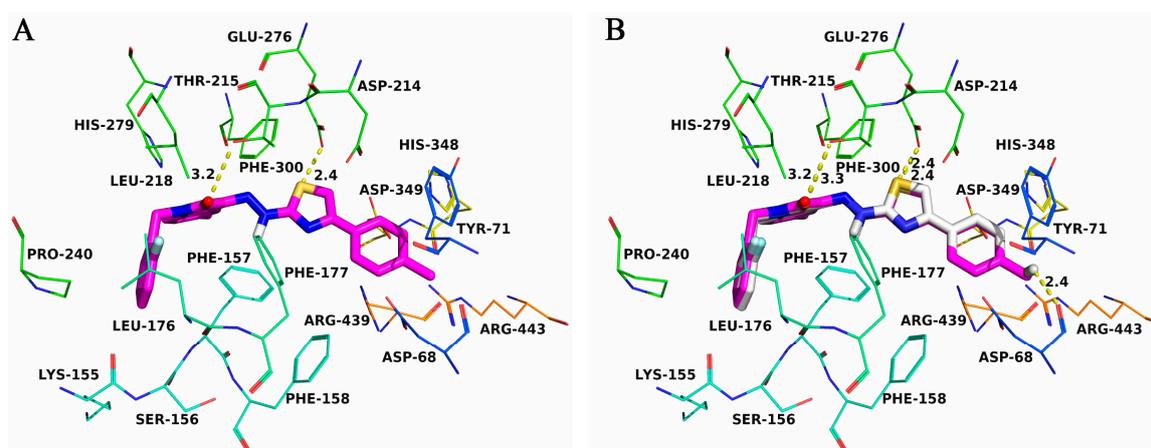


Figure 4. (A) Compound **6b** was docked to the binding pocket of the *Saccharomyces cerevisiae* α -glucosidase; (B) Compounds **6b** and **6p** were docked to the binding pocket of the *Saccharomyces cerevisiae* α -glucosidase (overlapped).

3. Experimental Section

3.1. General

All starting materials and reagents were purchased from commercial suppliers. TLC was performed on 0.20 mm Silica Gel 60 F₂₅₄ plates (Qingdao Ocean Chemical Factory, Shandong, China). ¹H- and ¹³C-NMR spectra were recorded on a Bruker spectrometer (400 MHz) with TMS as an external reference and reported in parts per million.

3.2. General Procedures for the Synthesis of **6a–6p**

A mixture of **3** (1.0 mmol) and **5** (1.2 mmol) in EtOH (10 mL) was stirred at reflux for 2 h. After the completion of the reaction, the precipitates that formed were collected by filtration and washed with ethanol (3 × 10 mL) to give the desired products **6a–6p**. The spectroscopic and analytical data of compounds are as follows:

(Z)-3-(2-(4-(4-Bromophenyl)thiazol-2-yl)hydrazono)-5-chloroindolin-2-one (**6a**). Orange solid, yield 77.5%, ¹H-NMR (*d*₆-DMSO, 400 MHz) δ : 6.97 (d, 1H, *J* = 8.4 Hz, ArH), 7.36 (dd, 1H, *J* = 8.4 Hz, 2.0 Hz, ArH), 7.52 (d, 1H, *J* = 2.0 Hz, ArH), 7.61 (d, 2H, *J* = 8.4 Hz, ArH), 7.74 (s, 1H, CH-thiazole), 7.85 (d, 2H, *J* = 8.4 Hz, ArH), 11.36 (s, 1H, NH), 13.33 (s, 1H, NH); ¹³C-NMR (*d*₆-DMSO, 100 MHz) δ : 108.6, 113.0, 119.8, 121.5, 121.9, 127.1, 128.1, 128.2, 130.3, 131.6, 132.1, 132.2, 133.6, 140.4, 150.4, 163.4, 166.5.

(Z)-1-(2-Fluorobenzyl)-5-methyl-3-(2-(4-(*p*-tolyl)thiazol-2-yl)hydrazono) indolin-2-one (**6b**). Red solid, yield 52.5%, ¹H-NMR (*d*₆-DMSO, 400 MHz) δ : 2.33 (s, 6H, CH₃), 5.06 (s, 2H, CH₂), 6.93 (d, 1H, *J* = 8.4 Hz,

ArH), 7.14–7.19 (m, 2H, ArH), 7.23–7.26 (m, 3H, ArH), 7.32–7.37 (m, 2H, ArH), 7.44 (s, 1H, ArH), 7.58 (s, 1H, ArH), 7.79 (d, 2H, $J = 8.0$ Hz, ArH), 13.22 (s, 1H, NH); $^{13}\text{C-NMR}$ (d_6 -DMSO, 100 MHz) δ : 21.0, 21.3, 37.4, 106.6, 110.3, 115.9 (d, 1C, $J = 20.9$ Hz), 119.7, 120.6, 122.9, 123.0, 125.2 (d, 1C, $J = 3.4$ Hz), 126.0, 126.1, 129.7, 129.9, 130.0, 130.1, 130.3 (d, 1C, $J = 8.1$ Hz), 131.2, 131.4, 131.8, 132.9, 137.8, 139.7, 151.7, 159.4 (d, 1C, $J = 243.9$ Hz), 161.8, 166.3; MS (ESI, m/z): 457.11 $[\text{M} + \text{H}]^+$.

(*Z*)-1-(2-Fluorobenzyl)-3-(2-(4-(4-methoxyphenyl)thiazol-2-yl)hydrazono)-5-methylindolin-2-one (**6c**). Red solid, yield 77.2%, $^1\text{H-NMR}$ (d_6 -DMSO, 400 MHz) δ : 2.32 (s, 3H, CH_3), 3.79 (s, 3H, OCH_3), 5.06 (s, 2H, CH_2), 6.92 (d, 1H, $J = 8.0$ Hz, ArH), 6.98 (d, 2H, $J = 8.0$ Hz, ArH), 7.13–7.18 (m, 2H, ArH), 7.22–7.26 (m, 1H, ArH), 7.32–7.37 (m, 2H, ArH), 7.43 (s, 1H, ArH), 7.48 (s, 1H, CH-thiazole), 7.83 (d, 2H, $J = 8.0$ Hz, ArH), 13.21 (s, 1H, NH); $^{13}\text{C-NMR}$ (d_6 -DMSO, 100 MHz) δ : 21.0, 37.4, 55.6, 105.3, 110.3, 114.5, 114.7, 115.9 (d, 1C, $J = 20.9$ Hz), 119.7, 120.5, 122.9, 123.0, 125.2 (d, 1C, $J = 3.5$ Hz), 127.3, 127.6, 130.0, 130.1, 130.3 (d, 1C, $J = 8.1$ Hz), 131.2, 131.3, 132.8, 139.7, 151.5, 159.4 (d, 1C, $J = 243.9$ Hz), 159.6, 161.7; MS (ESI, m/z): 473.09 $[\text{M} + \text{H}]^+$.

(*Z*)-1-Methyl-3-(2-(4-(*p*-tolyl)thiazol-2-yl)hydrazono)indolin-2-one (**6d**). Red solid, yield 75.4%, $^1\text{H-NMR}$ (d_6 -DMSO, 400 MHz) δ : 2.33 (s, 3H, ArCH_3), 3.27 (s, 3H, NCH_3), 7.15–7.19 (m, 2H, ArH), 7.23 (d, 2H, $J = 8.0$ Hz, ArH), 7.44 (t, 1H, $J = 8.0$ Hz, ArH), 7.57 (s, 1H, CH-thiazole), 7.57 (d, 1H, $J = 8.0$ Hz, ArH), 7.79 (d, 2H, $J = 8.0$ Hz, ArH), 13.26 (s, 1H, NH); $^{13}\text{C-NMR}$ (d_6 -DMSO, 100 MHz) δ : 21.3, 26.2, 106.4, 110.2, 119.5, 119.9, 123.3, 126.1, 129.7, 130.8, 131.6, 131.8, 137.8, 143.0, 151.6, 161.8, 166.3.

(*Z*)-3-(2-(4-(4-Fluorophenyl)thiazol-2-yl)hydrazono)-1-methylindolin-2-one (**6e**). Orange solid, yield 70.3%, $^1\text{H-NMR}$ (d_6 -DMSO, 400 MHz) δ : 3.27 (s, 3H, NCH_3), 7.15–7.18 (m, 2H, ArH), 7.26 (t, 2H, $J = 8.8$ Hz, ArH), 7.44 (t, 1H, $J = 8.0$ Hz, ArH), 7.57 (d, 1H, $J = 8.0$ Hz, ArH), 7.62 (s, 1H, CH-thiazole), 7.93 (dd, 2H, $J = 8.8$ Hz, 5.6 Hz, ArH), 13.25 (s, 1H, NH); $^{13}\text{C-NMR}$ (d_6 -DMSO, 100 MHz) δ : 26.2, 107.1, 110.3, 115.9 (d, 1C, $J = 21.5$ Hz), 119.5, 120.0, 123.4, 128.2 (d, 1C, $J = 8.1$ Hz), 130.9, 131.0 (d, 1C, $J = 2.9$ Hz), 131.1, 131.9, 143.1, 150.5, 161.1 (d, 1C, $J = 243.7$ Hz), 161.8, 166.6.

(*Z*)-3-(2-(4-(4-Methoxyphenyl)thiazol-2-yl)hydrazono)-1-methylindolin-2-one (**6f**). Red solid, yield 69.9%, $^1\text{H-NMR}$ (d_6 -DMSO, 400 MHz) δ : 3.27 (s, 3H, NCH_3), 3.80 (s, 3H, OCH_3), 6.98 (d, 2H, $J = 8.8$ Hz, ArH), 7.15–7.19 (m, 2H, ArH), 7.44 (t, 1H, $J = 8.0$ Hz, ArH), 7.48 (s, 1H, CH-thiazole), 7.58 (d, 1H, $J = 7.2$ Hz, ArH), 7.83 (d, 2H, $J = 8.8$ Hz, ArH), 13.26 (s, 1H, NH); $^{13}\text{C-NMR}$ (d_6 -DMSO, 100 MHz) δ : 26.2, 55.6, 105.2, 110.3, 114.5, 114.7, 119.5, 119.9, 123.4, 127.3, 127.5, 127.6, 130.8, 131.6, 143.0, 151.5, 159.6, 161.8, 166.3.

(*Z*)-3-(2-(4-(4-Chlorophenyl)thiazol-2-yl)hydrazono)indolin-2-one (**6g**). Orange solid, yield 66.9%, $^1\text{H-NMR}$ (d_6 -DMSO, 400 MHz) δ : 6.96 (d, 1H, $J = 8.8$ Hz, ArH), 7.10 (t, 1H, $J = 8.8$ Hz, ArH), 7.35 (t, 1H, $J = 8.8$ Hz, ArH), 7.47 (d, 2H, $J = 8.8$ Hz, ArH), 7.54 (d, 1H, $J = 8.8$ Hz, ArH), 7.70 (s, 1H, CH-thiazole), 7.92 (d, 2H, $J = 8.8$ Hz, ArH), 11.26 (s, 1H, NH-indolin-2-one), 13.35 (s, 1H, NH); $^{13}\text{C-NMR}$ (d_6 -DMSO, 100 MHz) δ : 108.0, 111.5, 120.2, 120.3, 122.9, 127.9, 129.1, 131.0, 132.7, 132.9, 133.3, 141.8, 150.3, 163.6, 166.7.

(*Z*)-3-(2-(4-(4-Bromophenyl)thiazol-2-yl)hydrazono)-5,7-dimethylindolin-2-one (**6h**). Orange solid, yield 64.4%, $^1\text{H-NMR}$ (d_6 -DMSO, 400 MHz) δ : 2.21 (s, 3H, ArCH_3), 2.29 (s, 3H, ArCH_3), 6.99 (s, 1H, ArH), 7.19 (s, 1H, ArH), 7.61 (d, 2H, $J = 8.8$ Hz, ArH), 7.71 (s, 1H, CH-thiazole), 7.85 (d, 2H, $J = 8.8$ Hz, ArH), 11.22 (s, 1H, NH-indolin-2-one), 13.40 (s, 1H, NH); $^{13}\text{C-NMR}$ (d_6 -DMSO, 100 MHz) δ : 16.3, 20.9, 107.9, 118.1, 119.9, 120.6, 121.4, 128.2, 131.9, 132.0, 132.9, 133.2, 133.7, 138.2, 150.3, 164.2, 166.7.

(*Z*)-3-(2-(4-(4-Hydroxyphenyl)thiazol-2-yl)hydrazono)-5-methylindolin-2-one (**6i**). Orange solid, yield 52.4%, $^1\text{H-NMR}$ (d_6 -DMSO, 400 MHz) δ : 2.33 (s, 3H, ArCH_3), 6.80 (d, 2H, $J = 8.8$ Hz, ArH), 6.85 (d, 1H, $J = 8.0$ Hz, ArH), 7.15 (d, 1H, $J = 8.0$ Hz, ArH), 7.36 (s, 2H, CH-thiazole and ArH), 7.71 (d, 2H, $J = 8.8$ Hz, ArH), 11.16 (s, 1H, NH-indolin-2-one), 13.35 (s, 1H, NH); $^{13}\text{C-NMR}$ (d_6 -DMSO, 100 MHz) δ : 21.0, 104.2, 111.3, 115.6, 115.9, 120.2, 120.6, 125.6, 127.6, 129.9, 131.4, 131.9, 132.7, 139.5, 151.5, 157.9, 163.7, 166.3.

(*Z*)-3-(2-(4-(4-Fluorophenyl)thiazol-2-yl)hydrazono)-5,7-dimethylindolin-2-one (**6j**). Orange solid, yield 59.6%, $^1\text{H-NMR}$ (d_6 -DMSO, 400 MHz) δ : 2.21 (s, 3H, ArCH_3), 2.29 (s, 3H, ArCH_3), 6.99 (s, 1H, ArH),

7.19 (s, 1H, ArH), 7.26 (t, 2H, $J = 8.8$ Hz), 7.61 (s, 1H, CH-thiazole), 7.93 (d, 2H, $J = 8.8$ Hz, 5.6 Hz, ArH), 11.22 (s, 1H, NH-indolin-2-one), 13.39 (s, 1H, NH); $^{13}\text{C-NMR}$ (d_6 -DMSO, 100 MHz) δ : 16.3, 20.9, 106.8, 115.8 (d, 1C, $J = 21.5$ Hz), 118.1, 119.9, 120.6, 128.2 (d, 1C, $J = 8.1$ Hz), 131.1 (d, 1C, $J = 2.7$ Hz), 131.8, 132.8, 133.1, 138.2, 150.5, 161.1 (d, 1C, $J = 243.7$ Hz), 164.2, 166.6.

(*Z*)-5,7-Dimethyl-3-(2-(4-(*p*-tolyl)thiazol-2-yl)hydrazono)indolin-2-one (**6k**). Orange solid, yield 62.1%, $^1\text{H-NMR}$ (d_6 -DMSO, 400 MHz) δ : 2.21 (s, 3H, ArCH₃), 2.29 (s, 3H, ArCH₃), 2.34 (s, 3H, ArCH₃), 6.99 (s, 1H, ArH), 7.20 (s, 1H, ArH), 7.23 (d, 2H, $J = 8.0$ Hz, ArH), 7.55 (s, 1H, CH-thiazole), 7.79 (d, 2H, $J = 8.0$ Hz, ArH), 11.22 (s, 1H, NH-indolin-2-one), 13.39 (s, 1H, NH); $^{13}\text{C-NMR}$ (d_6 -DMSO, 100 MHz) δ : 16.3, 20.9, 21.3, 106.2, 118.1, 119.9, 120.6, 126.1, 129.7, 131.9, 132.8, 133.0, 137.7, 138.2, 151.6, 164.2, 166.4.

(*Z*)-5-Fluoro-3-(2-(4-(*p*-tolyl)thiazol-2-yl)hydrazono)indolin-2-one (**6l**). Orange solid, yield 60.8%, $^1\text{H-NMR}$ (d_6 -DMSO, 400 MHz) δ : 2.24 (s, 3H, ArCH₃), 6.96 (dd, 1H, $J = 8.4$ Hz, 4.4 Hz, ArH), 7.19 (dt, 1H, $J = 8.4$ Hz, 2.4 Hz, ArH), 7.23 (d, 2H, $J = 8.0$ Hz, ArH), 7.35 (dd, 1H, $J = 8.4$ Hz, 2.4 Hz, ArH), 7.59 (s, 1H, CH-thiazole), 7.79 (d, 2H, $J = 8.0$ Hz, ArH), 11.28 (s, 1H, NH-indolin-2-one), 13.39 (s, 1H, NH); $^{13}\text{C-NMR}$ (d_6 -DMSO, 100 MHz) δ : 21.3, 106.7, 107.1, 107.4, 112.5, 112.6, 117.0 (d, 1C, $J = 24.5$ Hz), 121.4 (d, 1C, $J = 8.9$ Hz), 125.9, 126.1, 129.7, 129.9, 131.7, 131.9 (d, 1C, $J = 3.1$ Hz), 137.8, 137.9, 151.7, 157.6 (d, 1C, $J = 236.4$ Hz), 163.8, 166.1.

(*Z*)-5-Fluoro-3-(2-(4-(4-fluorophenyl)thiazol-2-yl)hydrazono)indolin-2-one (**6m**). Orange solid, yield 57.7%, $^1\text{H-NMR}$ (d_6 -DMSO, 400 MHz) δ : 6.95 (dd, 1H, $J = 8.4$ Hz, 4.4 Hz, ArH), 7.19 (dt, 1H, $J = 8.4$ Hz, 2.4 Hz, ArH), 7.25 (d, 2H, $J = 8.8$ Hz, ArH), 7.35 (dd, 1H, $J = 8.4$ Hz, 2.4 Hz, ArH), 7.66 (s, 1H, CH-thiazole), 7.94 (dd, 2H, $J = 8.8$ Hz, 5.6 Hz, ArH), 11.28 (s, 1H, NH-indolin-2-one), 13.39 (s, 1H, NH); $^{13}\text{C-NMR}$ (d_6 -DMSO, 100 MHz) δ : 107.2, 107.4, 107.4, 112.5, 112.6, 115.9 (d, 1C, $J = 21.4$ Hz), 116.2 (d, 1C, $J = 21.5$ Hz), 117.1, 117.3, 121.4, 121.5, 128.2, 128.3, 128.4, 131.0 (d, 1C, $J = 2.9$ Hz), 132.0 (d, 1C, $J = 3.6$ Hz), 138.0, 150.5, 157.6 (d, 1C, $J = 236.3$ Hz), 161.1 (d, 1C, $J = 243.6$ Hz), 163.8, 166.3.

(*Z*)-3-(2-(4-(4-Fluorophenyl)thiazol-2-yl)hydrazono)indolin-2-one (**6n**). Orange solid, yield 78.4%, $^1\text{H-NMR}$ (d_6 -DMSO, 400 MHz) δ : 6.97 (d, 1H, $J = 8.0$ Hz, ArH), 7.10 (t, 1H, $J = 8.0$ Hz, ArH), 7.26 (d, 2H, $J = 8.8$ Hz, ArH), 7.36 (t, 1H, $J = 8.0$ Hz, ArH), 7.54 (d, 1H, $J = 8.0$ Hz, ArH), 7.62 (s, 1H, CH-thiazole), 7.94 (dd, 2H, $J = 8.8$ Hz, 5.6 Hz, ArH), 11.27 (s, 1H, NH-indolin-2-one), 13.35 (s, 1H, NH); $^{13}\text{C-NMR}$ (d_6 -DMSO, 100 MHz) δ : 117.0, 111.5, 115.9 (d, 1C, $J = 21.4$ Hz), 120.2, 120.3, 122.9, 128.2 (d, 1C, $J = 8.1$ Hz), 130.9, 131.1 (d, 1C, $J = 2.9$ Hz), 132.6, 141.8, 150.5, 161.1 (d, 1C, $J = 243.6$ Hz), 163.6, 166.6.

(*Z*)-3-(2-(4-(*p*-Tolyl)thiazol-2-yl)hydrazono)indolin-2-one (**6o**). Red solid, yield 73.3%, $^1\text{H-NMR}$ (d_6 -DMSO, 400 MHz) δ : 2.34 (s, 3H, ArCH₃), 6.97 (d, 1H, $J = 8.0$ Hz, ArH), 7.10 (t, 1H, $J = 8.0$ Hz, ArH), 7.23 (d, 2H, $J = 8.0$ Hz, ArH), 7.35 (t, 1H, $J = 8.0$ Hz, ArH), 7.54–7.56 (m, 2H, CH-thiazole and ArH), 7.79 (d, 2H, $J = 8.4$ Hz, ArH), 11.27 (s, 1H, NH-indolin-2-one), 13.35 (s, 1H, NH); $^{13}\text{C-NMR}$ (d_6 -DMSO, 100 MHz) δ : 21.3, 106.3, 111.5, 120.2, 120.3, 122.9, 126.1, 129.7, 129.8, 130.9, 131.8, 132.5, 137.8, 141.7, 151.6, 163.7, 166.4.

(*Z*)-1-(2-Fluorobenzyl)-3-(2-(4-(4-hydroxyphenyl)thiazol-2-yl)hydrazono)-5-methylindolin-2-one (**6p**). Red solid, yield 53.1%, $^1\text{H-NMR}$ (d_6 -DMSO, 400 MHz) δ : 2.33 (s, 3H, ArCH₃), 5.07 (s, 2H, ArCH₂), 6.81 (d, 2H, $J = 7.2$ Hz, ArH), 6.93 (d, 1H, $J = 7.2$ Hz, ArH), 7.12–7.25 (m, 3H, ArH), 7.36–7.44 (m, 3H), 7.72 (d, 2H, $J = 7.2$ Hz, ArH), 9.62 (s, 1H, OH), 13.21 (s, 1H, NH); $^{13}\text{C-NMR}$ (d_6 -DMSO, 100 MHz) δ : 21.0, 37.4, 104.4, 110.3, 115.9, 115.9 (d, 1C, $J = 23.0$ Hz), 119.8, 120.5, 122.9, 123.0, 125.2, 125.8, 127.6, 130.0, 130.2 (d, 1C, $J = 8.1$ Hz), 131.1, 132.8, 139.6, 151.9, 157.9, 159.4 (d, 1C, $J = 237.9$ Hz), 166.0; MS (ESI, m/z): 459.06 [M + H]⁺.

3.3. In Vitro Assay of α -Glucosidase Inhibitory Activity

According to the literature procedure [36], α -Glucosidase inhibitory activity was assayed by using 0.1 M phosphate buffer (pH 6.8) at 37 °C. The enzyme (0.1 U/mL) in phosphate buffer saline was incubated with various concentrations of test compounds at 37 °C for 15 min. Then 1.25 mM

p-nitrophenyl α -D-glucopyranoside was added to the mixture as a substrate, after further incubation at 37 °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: inhibition (%) = $(1 - \Delta A_{\text{sample}} / \Delta A_{\text{control}}) \times 100\%$. IC₅₀ value is defined as a concentration of samples inhibiting 50% of α -glucosidase activity under the stated assay conditions.

3.4. Molecular Docking

Molecular docking studies were performed to investigate the binding mode between the compounds **6b**, **6i**, **6p**, and α -glucosidase using Autodock vina 1.1.2 [38]. The 3D structures of **6i** and **6p** were obtained by ChemBioDraw Ultra 14.0 and ChemBio3D Ultra 14.0 softwares. The AutoDockTools 1.5.6 package was employed to generate the docking input files [39,40]. 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 poses as judged by the Vina docking score were chosen and visually analyzed using PyMOL 1.7.6 software (Schrödinger[®], New York, NY, USA) (<http://www.pymol.org/>).

4. Conclusions

In conclusion, we designed and synthesized a novel series of α -glucosidase inhibitor based on the molecular hybrid-based approaches. All the target compounds displayed potent to moderate α -glucosidase inhibitory activity with IC₅₀ ranging from 5.36 ± 0.13 to $35.76 \pm 0.31 \mu\text{m}$ as compared to the standard drug acarbose (IC₅₀ = $817.38 \pm 6.27 \mu\text{m}$). Among the series, compound **6p** bearing a hydroxyl group at the 4-position of the right phenyl and 2-fluorobenzyl substituent at the N1-positions of the 5-methylisatin displayed the highest inhibitory activity with an IC₅₀ value of $5.36 \pm 0.13 \mu\text{m}$. Furthermore, molecular docking studies revealed the existence of hydrophobic interaction, CH- π interaction, arene-anion interaction, arene-cation interaction, and hydrogen bond between these compounds and α -glucosidase enzyme.

Supplementary Materials: Supplementary materials are available online.

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Conflicts of Interest: The authors confirm that this article content has no conflict of interest.

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Sample Availability: Samples of the compounds **6a–6p** are available from the authors.



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