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

Zhenzhen Xie, Guangcheng Wang *, Jing Wang, Ming Chen, Yaping Peng, Luyao Li, Bing Deng, Shan Chen and Wenbiao Li

College of Chemistry and Chemical Engineering, Hunan Engineering Laboratory for Analyse and Drugs Development of Ethnomedicine in Wuling Mountains, Jishou University, Jishou 416000, China; xiezz1993@126.com (Z.X.); wangjingjsu@sina.com (J.W.); mingchen940517@163.com (M.C.); yapingpeng17@163.com (Y.P.); liluyao15@yeah.net (L.L.); dengbingfish@163.com (B.D.); chenshan20142014@163.com (S.C.); liwenbiao0926@yeah.net (W.L.)

* Correspondence: wanggch123@163.com; Tel.: +86-743-8563-911

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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 ± 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 μm) 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].

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).

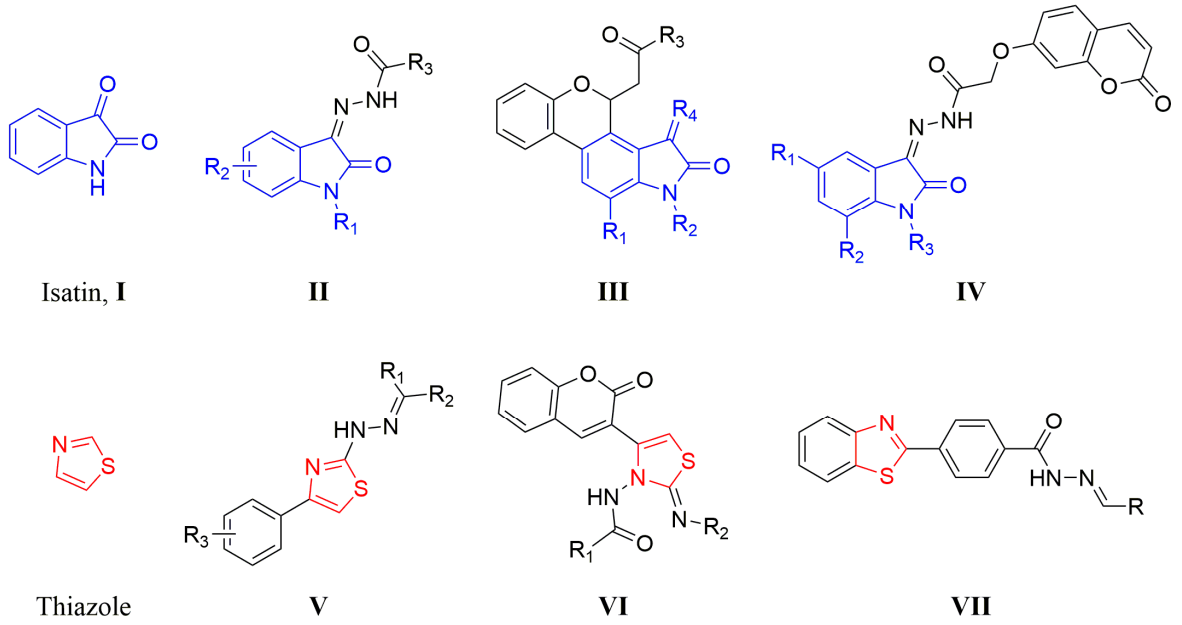


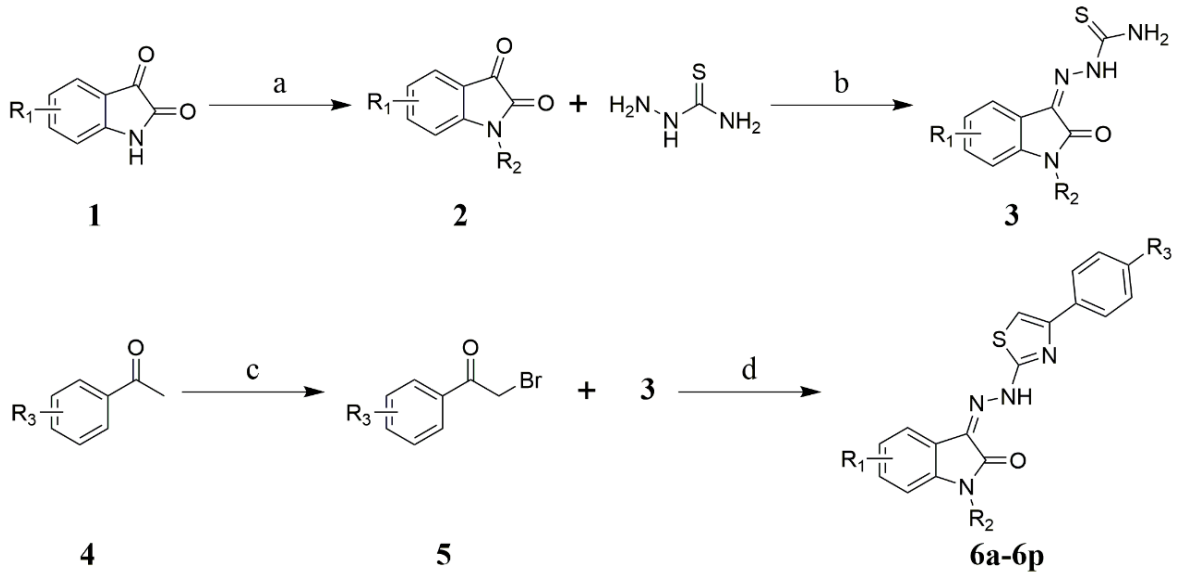
Figure 1. The chemical structures of the reported α-glucosidase inhibitors containing isatin or thiazole moiety.

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*-$MeC_6H_4SO_3H$, NBS, CH_3CN, reflux, 2 h; (**d**) EtOH, reflux, 2 h.

The structures of all of the title compounds **6a–6p** were characterized by ^{1}H-NMR spectra. The ^{1}H-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 ^{1}H-NMR spectrum of all new compounds consistent with their structures. Moreover, in their ^{13}C-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 IC_{50} ranging from 5.36 ± 0.13 to 35.76 ± 0.31 μm more potent than the standard drug acarbose (IC_{50} = 817.38 ± 6.27 μm [17,36]). Among the series, compounds **6a**, **6g**, **6h**, **6i**, **6j**, **6l**, **6m**, **6n**, and **6p** displayed potent inhibitory activity with IC_{50} 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 μm. In particular, compound **6p** (IC_{50} = 5.36 ± 0.13 μm) 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** (IC_{50} = 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 IC_{50} value 10.34 ± 0.17, 15.68 ± 0.24, and 11.78 ± 0.21 μm, 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} (μm) [a]
6a	5-Cl	H	Br	6.87 ± 0.14
6b	5-Me	2-F-benzyl	Me	35.76 ± 0.31
6c	5-Me	2-F-benzyl	MeO	10.34 ± 0.17
6d	H	Me	Me	32.17 ± 0.29
6e	H	Me	F	33.20 ± 0.24
6f	H	Me	MeO	24.17 ± 0.28
6g	H	H	Cl	5.98 ± 0.12
6h	5.7-Me_2	H	Br	6.12 ± 0.15
6i	5-Me	H	OH	7.51 ± 0.17
6j	5.7-Me_2	H	F	6.51 ± 0.13
6k	5.7-Me_2	H	Me	15.68 ± 0.24
6l	5-F	H	Me	8.33 ± 0.18
6m	5-F	H	F	7.17 ± 0.15
6n	H	H	F	6.36 ± 0.12
6o	H	H	Me	11.78 ± 0.21
6p	5-Me	2-F-benzyl	OH	5.36 ± 0.13
Acarbose				817.38 ± 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-hydroxylphenyl 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-hydroxylphenyl 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}).

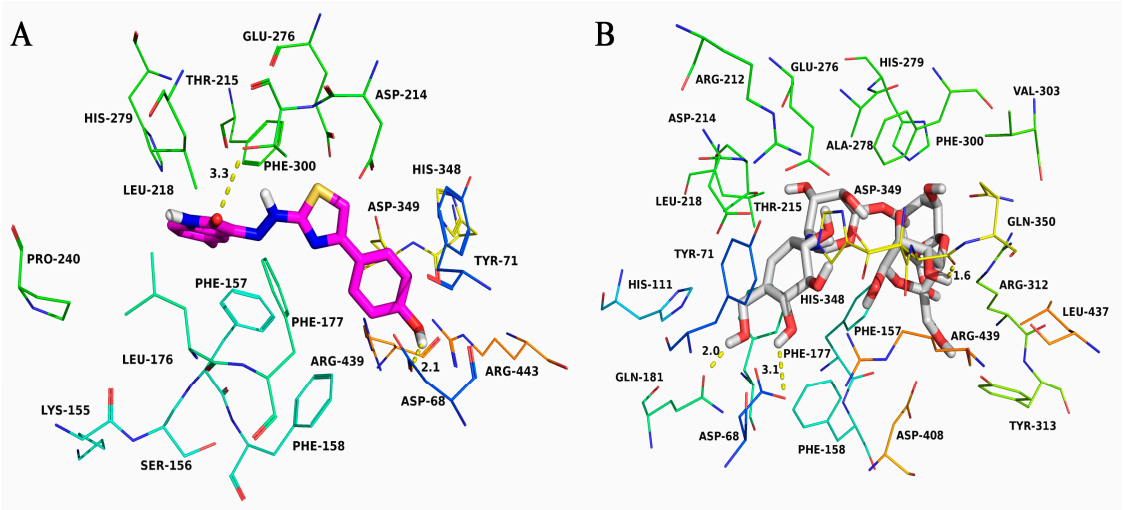


Figure 2. Compound **6i** (**A**) and acarbose (**B**) was docked to the binding pocket of the *Saccharomyces cerevisiae* α-glucosidase.

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.

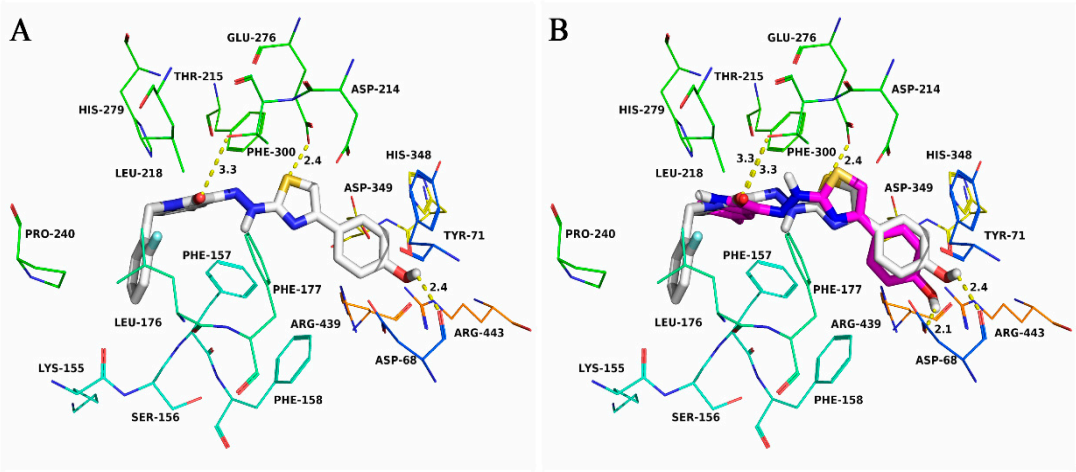


Figure 3. (**A**) Compound **6p** was docked to the binding pocket of the *Saccharomyces cerevisiae* α-glucosidase. (**B**) Compounds **6i** and **6p** were docked to the binding pocket of the *Saccharomyces cerevisiae* α-glucosidase (overlapped).

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 kcal mol^{-1} for **6b** and −10.1 kcal mol^{-1} for **6p**, respectively, which was consistent with the results of the in vitro α-glucosidase inhibitory activity.

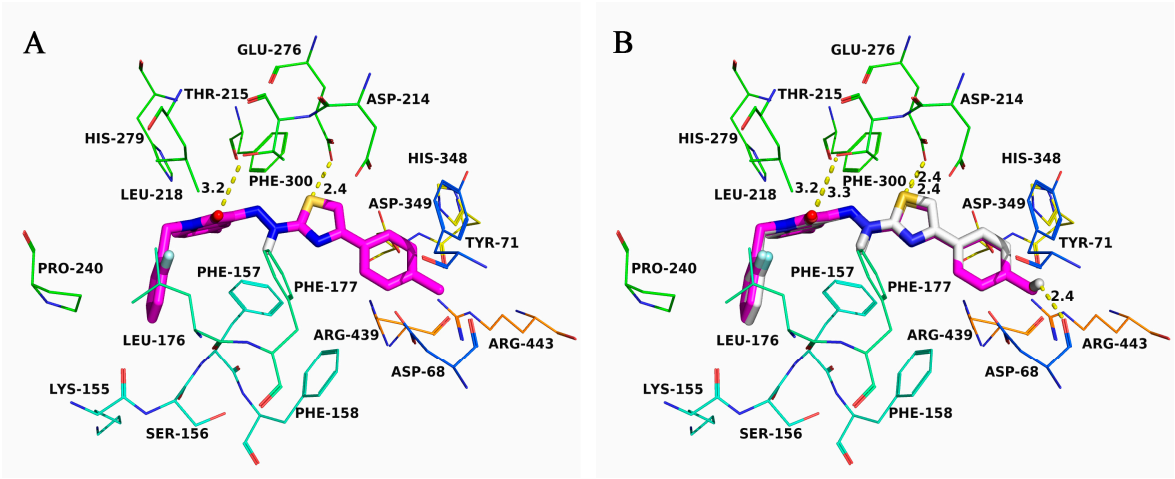


Figure 4. (**A**) Compound **6b** was docked to the binding pocket of the *Saccharomyces cerevisiae* α-glucosidase. (**B**) Compounds **6b** and **6p** were docked to the binding pocket of the *Saccharomyces cerevisiae* α-glucosidase (overlapped).

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 F_{254} plates (Qingdao Ocean Chemical Factory, Shandong, China). ^{1}H- and ^{13}C-NMR spectra were recorded 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%, ^{1}H-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); ^{13}C-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%, ^{1}H-NMR (d_6-DMSO, 400 MHz) δ: 2.33 (s, 6H, CH_3), 5.06 (s, 2H, CH_2), 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}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 $[M + H]^+$.

(Z)-1-(2-Fluorobenzyl)-3-(2-(4-(4-methoxyphenyl)thiazol-2-yl)hydrazono)-5-methylindolin-2-one (**6c**). Red solid, yield 77.2%, ^{1}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}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 $[M + H]^+$.

(Z)-1-Methyl-3-(2-(4-(p-tolyl)thiazol-2-yl)hydrazono)indolin-2-one (**6d**). Red solid, yield 75.4%, ^{1}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}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}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}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}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}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}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}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}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}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}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}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}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}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}H-NMR (d_6-DMSO, 400 MHz) δ: 2.21 (s, 3H, ArCH$_3$), 2.29 (s, 3H, ArCH$_3$), 2.34 (s, 3H, ArCH$_3$), 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}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}H-NMR (d_6-DMSO, 400 MHz) δ: 2.24 (s, 3H, ArCH$_3$), 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}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}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}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}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}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}H-NMR (d_6-DMSO, 400 MHz) δ: 2.34 (s, 3H, ArCH$_3$), 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}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}H-NMR (d_6-DMSO, 400 MHz) δ: 2.33 (s, 3H, ArCH$_3$), 5.07 (s, 2H, ArCH$_2$), 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}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 − ΔAsample/ΔAcontrol) × 100%. IC_{50} 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 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 ± 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 N1-positions of the 5-methylisatin displayed the highest inhibitory activity with an IC_{50} value of 5.36 ± 0.13 μm. 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.