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Synthesis, *in vitro* α-glucosidase inhibitory activity and docking studies of novel chromone-isatin derivatives

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ABSTRACT

A novel series of chromone-isatin derivatives **6a–6p** were designed, synthesized and characterized by ^{1}H NMR, ^{13}C NMR and HRMS. These novel synthetic compounds were evaluated for inhibitory activity against yeast α-glucosidase enzyme. The results of biological test have shown that all tested compounds exhibited excellent to potent inhibitory activity in the range of IC_{50} = 3.18 ± 0.12–16.59 ± 0.17 μM as compared to the standard drug acarbose (IC_{50} = 817.38 ± 6.27 μM). Compound **6j** (IC_{50} = 3.18 ± 0.12 μM) with a hydroxyl group at the 7-position of chromone and a 4-bromobenzyl group at the N1-positions of isatin, was found to be the most active compound among the series. Furthermore, molecular docking study was performed to help understand binding interactions of the most active analogs with α-glucosidase enzyme. These results indicated that this class of compounds had potential for the development of anti-diabetic agents.

Diabetes mellitus is a chronic disease characterized by hyperglycemia with a lot of serious complications. Type 2 diabetes is much more common and accounts for around 90% of all diabetes cases worldwide.[1] α-Glucosidase is a carbohydrate hydrolyzing enzyme secreted from the intestinal chorionic epithelium.[2] It hydrolyzes glycosidic bond in polysaccharide chains to monosaccharide as glucose which is mainly responsible to cause hyperglycemia.[3] Thus, α-glucosidase is a therapeutic target for type 2 diabetes by delay the absorption of glucose after meals, and some of α-glucosidase inhibitors (acarbose, miglitol, and voglibose) have been used in clinical for the treatment of type 2 diabetes (Fig. 1).[4] Therefore, design and development of new α-glucosidase inhibitors to treat diabetes mellitus is essential.

Chromone is a group of naturally occurring oxygen containing heterocyclic compounds having a benzene ring fused with pyran ring, which can be used as a privileged scaffold to design new molecules in drug discovery.[5] A wide spectrum of pharmacological activities was associated with chromone such as anti-inflammatory[6], antimicrobial[7], anti-HIV[8], anticancer[9], antioxidant[10], and antibacterial activities.[11] Furthermore, chromone derivatives also reported as α-glucosidase inhibitors (Fig. 1**I** and **II**).[12,13] More recently, our research group have also synthesized a series of chromone hydrazone derivatives, and some of synthesized compounds displayed potent α-glucosidase inhibitory activity with IC_{50} values in the range of 20.1 ± 0.19 μM to 45.7 ± 0.23 μM, as compared to the standard drug acarbose (IC_{50} = 817.38 ± 6.27 μM).[14]

On the other hand, isatin is an important heterocyclic system, which is a core constituent of many alkaloids and drugs as well as dyes, pesticides and analytical reagents.[15,16] In the past few decades, a large number of isatin derivatives have been reported to exhibit various biological activities including anticancer,[17] antibacterial,[18] antiviral,[19] anticonvulsant,[20] anti-inflammatory,[21] antifungal activity.[22] It is import to point out that isatin core is a privileged scaffold for the design and development of new α-glucosidase inhibitors and number of isatin derivatives have been reported to exhibit α-glucosidase inhibitory activity (Fig. 1**III–V**).[23–25]

In our previous study, we have reported that some chromone derivatives exhibited potent α-glucosidase inhibitory activity[14] as well as also reported isatin derivatives as a potential α-glucosidase inhibitors (Fig. 2).[25–27] As part of our continuing research program,[28–31] we report herein the design and synthesis of a hybrid scaffold by incorporating chromone and isatin in a single molecule

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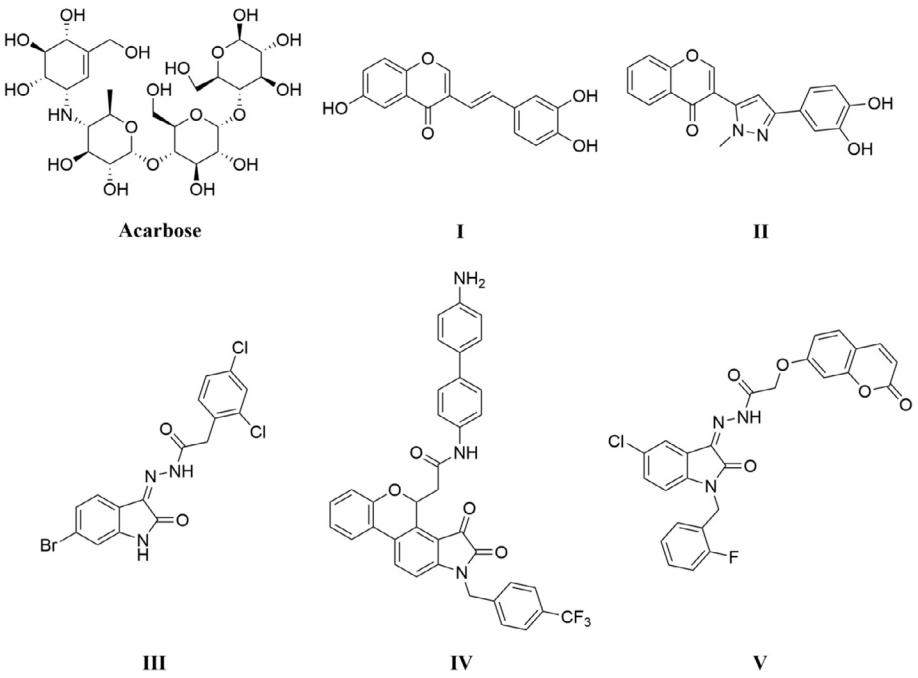


Fig. 1. Chemical structures of acarbose and some α-glucosidase inhibitors.

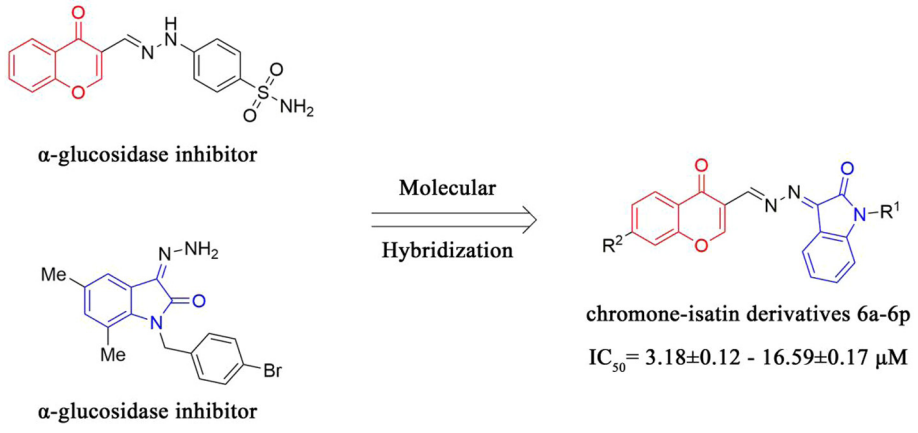
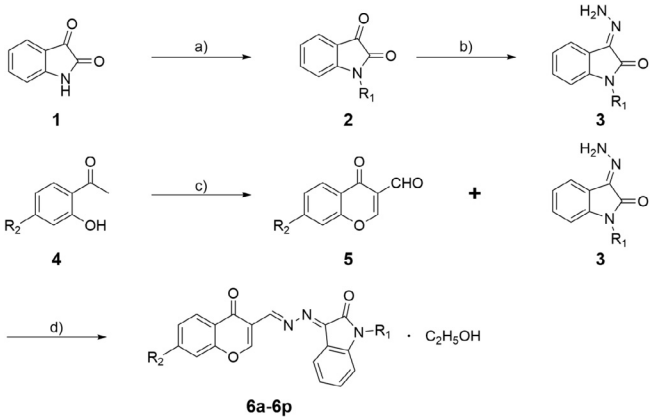


Fig. 2. Rationale design of the title compounds of this study.

(Fig. 2). The synthesized compounds were evaluated for their α-glucosidase inhibitory activity.

The chromone-isatin derivatives **6a–6p** were synthesized as shown in Scheme 1. The starting material isatin **1** was treated with various substituted alkyl halide to form *N*-alkyl isatin **2**. Then reaction compound **2** with hydrazine hydrate to give the corresponding hydrazine derivatives **3**. On the other hand, substituted 3-formylchromones **5** were prepared according to Vilsmeier-Haack reaction by reaction of the corresponding o-hydroxyacetophenones with the Vilsmeier-Haack reagent ($DMF/POCl_3$). Finally, condensation of substituted 3-formylchromones **5** with appropriate 3-hydrazino-isatins **3** in refluxing ethanol and in the presence of acetic acid as catalyst to afford the ethanolate of the corresponding title compounds **6a–6p** in moderate to high yields. The structure of synthesized compounds was elucidated and has been proven using spectral methods such as ^1H NMR and ^{13}C NMR. All the newly synthesized compounds were in good agreement with the proposed structures (Supplemental Material). To the best of our knowledge,



Scheme 1. (a) R_1Cl, R_1Br or R_1I, K_2CO_3, DMF, room temperature, 4 h; (b) NH_2NH_2·H_2O, MeOH, reflux, 3 h; (c) $POCl_3$, DMF, 50 °C, 4 h; (d) EtOH, AcOH (c.), reflux, 6 h.

Table 1
α-Glucosidase inhibitory activities of chromone-isatin derivatives **6a–6p**.

Compound	R_1	R_2	IC_{50} (μM)
6a	4-bromobenzyl	H	8.17 ± 0.18
6b	methyl	H	11.81 ± 0.20
6c	4-chlorobenzyl	H	16.59 ± 0.17
6d	H	H	16.18 ± 0.24
6e	3-fluorobenzyl	H	15.96 ± 0.25
6f	2-fluorobenzyl	H	14.02 ± 0.19
6g	4-fluorobenzyl	H	9.80 ± 0.21
6h	2-chlorobenzyl	H	13.54 ± 0.24
6i	2,4-dichlorobenzyl	OH	4.25 ± 0.14
6j	4-bromobenzyl	OH	3.18 ± 0.12
6K	4-chlorobenzyl	OH	3.90 ± 0.14
6l	3-fluorobenzyl	OH	4.17 ± 0.16
6m	2-fluorobenzyl	OH	4.57 ± 0.13
6n	4-fluorobenzyl	OH	3.82 ± 0.11
6o	2-bromobenzyl	OH	4.73 ± 0.18
6p	2-chlorobenzyl	OH	5.51 ± 0.21
Acarbose			817.38 ± 6.27

all synthetic hybrid molecules **6a–6p** have not yet been reported in the literature.

All the synthesized chromone-isatin derivatives **6a–6p** were screened to evaluate their *in vitro* α-glucosidase inhibitory activity (Table 1). All tested compounds exhibited excellent to potent inhibitory activity in the range of IC_{50} = 3.18 ± 0.12–16.59 ± 0.17 μM as compared to the standard drug acarbose (IC_{50} = 817.38 ± 6.27 μM). Among the series, compound **6j** (IC_{50} = 3.18 ± 0.12 μM) with a hydroxyl group at the 7-position of chromone and a 4-bromobenzyl group at the N1-positions of isatin, was found to be the most active compound. As shown in Table 1, compounds **6a–6h** shown excellent inhibitory activity against α-glucosidase with IC_{50} values ranging from 8.17 ± 0.18 to 16.59 ± 0.17 μM. Compounds **6i–6p** displayed potent inhibitory activity with IC_{50} values of 4.25 ± 0.14, 3.18 ± 0.12, 3.90 ± 0.14, 4.17 ± 0.16, 4.57 ± 0.13, 3.82 ± 0.11, 4.73 ± 0.18 and 5.51 ± 0.21 μM, respectively. Compared the inhibitory activity of **6a–6h** with **6i–6p** and found that the introduction of hydroxyl group into the chromone ring results in dramatically increased inhibitory activity. The results were suggested that the substitution on the chromone ring is very important for the α-glucosidase inhibitory activity in this series. Furthermore, introduction of various alkyl group at N1 position of isatin ring resulted in a slight increase or decrease of the biological activity, which indicated that the N1 alkyl group is not important for activity.

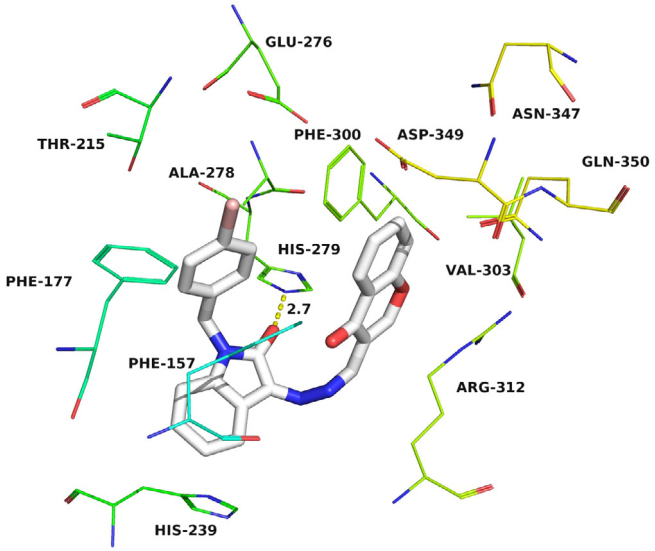


Fig. 3. The binding mode between compound **6a** and the binding site of the *Saccharomyces cerevisiae* α-glucosidase.

To investigate the binding mode of these compounds with α-glucosidase, molecular docking study was carried out by using Autodock VINA 1.1.2. The 3D structure of α-glucosidase of *Saccharomyces cerevisiae* have been predicted using homology modeling in our previous report.[30] The theoretical binding mode between **6a** and *Saccharomyces cerevisiae* α-glucosidase was shown in Fig. 3. Compound **6a** adopted a "U-shaped" conformation in the pocket of the α-glucosidase. The 4-bromophenyl group of **6a** was located at the hydrophobic pocket, surrounded by the residues Phe-157, Phe-177, Ala-278 and Phe-300, forming a stable hydrophobic binding. Detailed analysis showed that the 4-bromophenyl group of **6a** formed π-π stacking and CH-π interactions with the residues Phe-157 and Phe-177, respectively, while the benzopyrone group of **6a** formed π-π stacking interaction with the residue Phe-300. In addition, the benzopyrone group of **6a** formed the cation-π interaction and anion-π interaction with the residues Arg-312 and Asp-349, respectively. It was shown that the residue His-279 (bond length: 2.7 Å) formed a hydrogen bond with **6a**, which was the main interaction between **6a** and α-glucosidase. All these interactions helped **6a** to anchor in the binding site of the α-glucosidase.

To explain the activity order of **6a** and **6j** against α-glucosidase, **6j** was then docked into the binding site of α-glucosidase, and the theoretical binding mode between **6j** and α-glucosidase was shown in Fig. 4A. The interaction between **6j** and α-glucosidase was almost the same as the precursor **6a**. The only difference

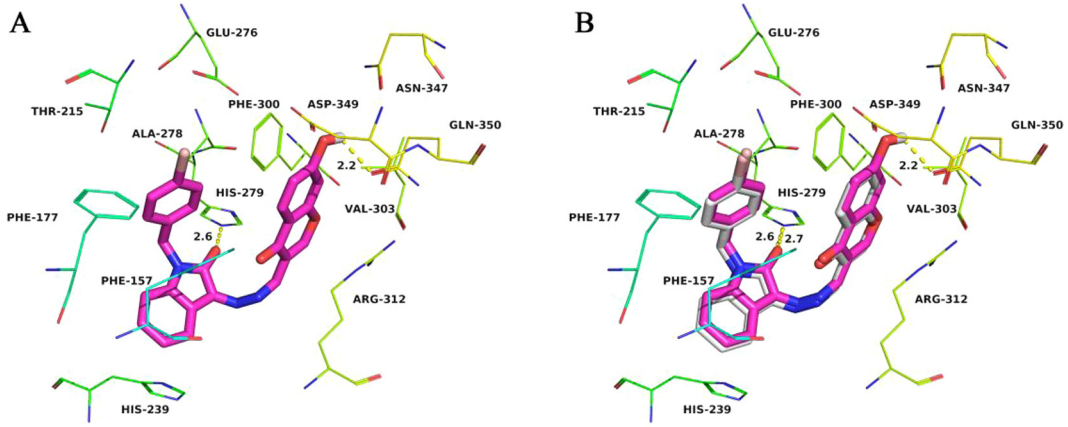


Fig. 4. (A) The binding mode between compound **6j** and the binding site of the *Saccharomyces cerevisiae* α-glucosidase. (B) The binding mode between compounds **6a** and **6j** and the binding site of the *Saccharomyces cerevisiae* α-glucosidase. (overlapped).

was that the hydroxyl group of **6j** formed an extra hydrogen bond with the residue Gln-350 of α-glucosidase when compared with **6a**, which made **6j** was more active than **6a** against α-glucosidase (Fig. 4B). In addition, the estimated binding energies were −8.1 kcal·mol^{-1} for **6a** and −8.8 kcal·mol^{-1} for **6j**, respectively, which was consistent with the results of the *in vitro* α-glucosidase inhibitory assay. In summary, the above molecular simulations give us rational explanation of the interactions between **6a**, **6j** and α-glucosidase, which provided valuable information for further development of α-glucosidase inhibitors.

A novel series of chromone-isatin derivatives **6a**–**6p** were synthesized and their *in vitro* α-glucosidase inhibitory activity were evaluated. All the synthesized compounds shown excellent to potent inhibitory activity in the range of IC_{50} = 3.18 ± 0.12–16.59 ± 0.17 μM as compared to the standard drug acarbose (IC_{50} = 817.38 ± 6.27 μM). Molecular docking study was performed to investigate the possible binding mode of compounds with the active site of enzyme. The results of this study suggest that these compounds may serve as lead molecules for further α-glucosidase inhibitors development.

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A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.bmcl.2017.11.047.

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