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Synthesis, biological evaluation and molecular docking studies of chromone hydrazone derivatives as α-glucosidase inhibitors

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ABSTRACT

A series of chromone hydrazone derivatives **4a**–**4p** have been synthesized, characterized by ^{1}H NMR and ^{13}C NMR and evaluated for their *in vitro* α-glucosidase inhibitory activity. Out of these tested compounds, six (**4a**, **4b**, **4d**, **4j**, **4o** and **4p**) 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). Among this series, compound **4d** (IC_{50} = 20.1 ± 0.19 μM) with 4-sulfonamide substitution at phenyl part of hydrazide was found to be the most active compound. Lineweaver-Burk plot analysis indicated that compound **4d** is a non-competitive inhibitor of α-glucosidase. The binding interactions of the most active analogs were confirmed through molecular docking studies. Docking studies showed **4d** are interacting with the residues Glu-276, Asp-214, Asp-349 and Arg-439 through hydrogen bonds, arene-anion and arene-cation interactions. In summary, our studies shown that these chromone hydrazone derivatives are a new class of α-glucosidase inhibitors.

α-Glucosidase is a membrane-bound enzyme located in the epithelium of the human small intestine, and is a key enzyme in carbohydrate digestion.[1] It hydrolyzes the terminal, non-reducing 1,4-linked α-D-glucose residues with release of α-D-glucose and helps digestion and absorption of sugars. α-Glucosidase inhibitors can be used as a first-line drug for the treatment type-2 diabetes because they can lower the rate of carbohydrate absorption and suppression of postprandial hyperglycemia.[1,2] Three α-glucosidase inhibitors, acarbose, miglitol and voglibose, have been in clinical use for many years. Furthermore, α-glucosidase may also be used as therapeutic target for other carbohydrate mediated diseases including cancer,[3] HIV[4] and hepatitis.[5] Therefore, discovery and development of novel α-glucosidase inhibitors are urgently needed.

Chromone (4*H*-chromen-4-one) is an important class of oxygen containing heterocyclic compounds, which are present in numerous naturally occurring and synthetic compounds.[6] Previous studies revealed that chromone derivatives exhibit a wide range of pharmacological activities including anti-inflammatory,[7] antimicrobial,[8] anti-HIV,[9] anticancer,[10] antioxidant,[11] and antibacterial activities.[12] Several chromone-containing drugs such as cromolyn (anti-inflammatory), nedocromil (anti-inflammatory), flavoxate (anticholinergic) and diosmin (phlebotropic) have been used in clinical for many years (Fig. 1).[6] On the other hand, the biological activity of hydrazones has been known for long time. Hydrazone-containing compounds have been reported to exhibit a variety of biological activities such as anti-inflammatory,[13] antitumor,[14] antibacterial,[15] antimicrobial,[16] and antitubercular properties.[17] In particularly, recent studies have reported that some chromone or hydrazone derivatives have been identified to exhibit α-glucosidase inhibitory activity.[18–22]

Furthermore, molecular hybridization is a useful technique in drug design and development, which combine two or more pharmacophoric moieties to create a new hybrid molecule with improved affinity and efficacy.[23] In view of broad spectrum of biological activities associated with chromone and hydrazine pharmacophoric groups and in continuation of our interest in the synthesis of biologically active heterocyclic compounds,[24–28] it was envisaged to construct a system which combines chromone and hydrazine pharmacophores in a single molecular framework to explore their biological activities. Herein we report the design and synthesis of a series of chromone hydrazone derivatives containing chromone and hydrazone nucleus. All the synthesized compounds were evaluated for their *in vitro* α-glucosidase inhibitory activity. To

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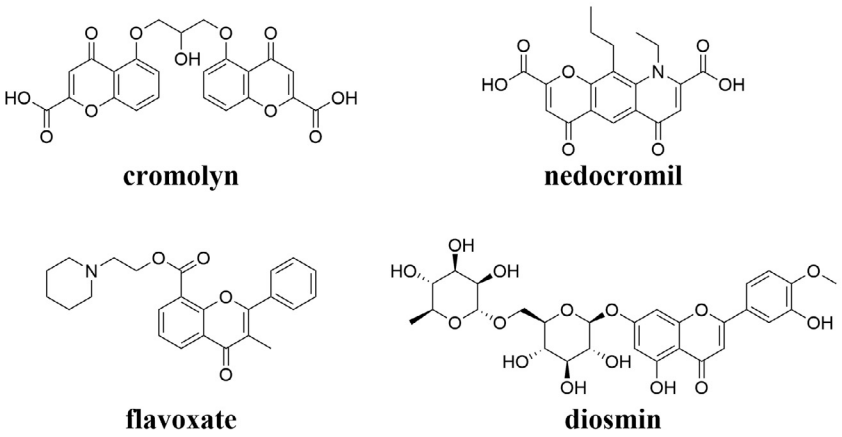
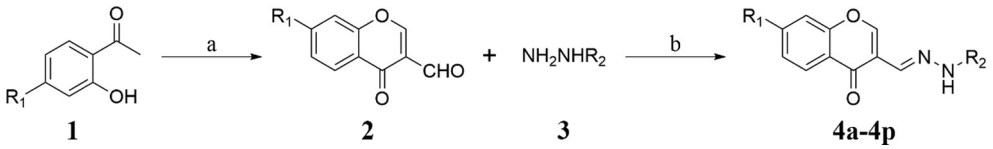


Fig. 1. Chemical structures of some chromone-containing drugs.



Scheme 1. Reagents and conditions: (a) $POCl_3$, DMF, 50 °C, 4 h; (b) EtOH, AcOH, reflux, 6 h.

investigate the interaction of these compounds with α-glucosidase, molecular docking study was also performed.

A general synthesis of chromone hydrazone derivatives **4a**–**4p** is exhibited in Scheme 1. Substituted 3-formylchromones **2** were synthesized by the Vilsmeier-Haack reaction. $POCl_3$ was added dropwise to the dry DMF with vigorous stirring and the mixture was stirred at 50 °C for 2 h, then the solution of substituted 2-hydroxy acetophenone **1** in DMF was added dropwise to the reaction mixture. The mixture was stirred at 50 °C for 2 h. After cooling to room temperature, the content was poured into ice-water and stirred for 6 h. The precipitate was collected by filtration and purified by chromatography to give substituted 3-formylchromones **2**. A series of hydrazones of substituted 3-formylchromone were prepared by a condensation reaction of substituted 3-formylchromones **2** with a variety of aromatic or aliphatic hydrazine **3** in ethanol in the presence of glacial acetic acid. After the completion of the reaction, the precipitates were collected by filtration and washed with ethanol to afford the corresponding chromone hydrazone derivatives **4a**–**4p**.

The structures of all the title compounds **4a**–**4p** were characterized by ^{1}H NMR spectra. The ^{1}H NMR spectrum of **4d** exhibited two doublet signals at 7.71 ppm (J = 8.0 Hz) and 8.12 ppm (J = 8.0 Hz) were attributed to C8-H and C5-H of chromone ring, respectively. The triplet peak of C6-H and C7-H of chromone ring were observed at 7.54 and 7.84 ppm with coupling constant of 8.0 Hz, respectively. The proton of C2-H of chromone ring appeared as singlet at 8.07 ppm. Two doublet peaks at 7.14 and 7.65 ppm with coupling constant of 8.8 Hz were attributed to the aromatic protons of C3′,5′-H and C2′,6′-H, respectively. The protons of $-SO_2NH_2$ appeared at 7.14 ppm as a singlet signal. The singlet peak of CH proton of hydrazone moiety is observed at 8.89 ppm, and the signal of -NNH is showed as a single peak at 10.91 ppm. The date of ^{1}H NMR is in agreement with the structure of compound **4d**.

All the synthesized chromone hydrazone derivatives **4a**–**4p** were evaluated for their *in vitro* α-glucosidase inhibitory activity. The results were shown in Table 1. Among this series, compounds **4a** (IC_{50} = 26.7 ± 0.24 μM), **4b** (IC_{50} = 39.8 ± 0.30 μM), **4d** (IC_{50} = 20.1 ± 0.19 μM), **4j** (IC_{50} = 45.7 ± 0.23 μM), **4o** (IC_{50} = 30.8 ± 0.32 μM) and **4p** (IC_{50} = 25.2 ± 0.26 μM) showed excellent inhibitory potential as compared to standard acarbose (IC_{50} = 817.38 ± 6.27 μM[29,30]). Compounds **4c**, **4i**, **4k**, **4m** and **4n** also displayed good inhibition with IC_{50} value 96.9 ± 0.34, 60.8 ± 0.28, 96.7 ± 0.37, 95.4 ± 0.43 and 86.3 ± 0.36 μM respectively. Other compounds (**4e**–**4h** and **4l**) displayed low α-glucosidase inhibitory activity. Compound **4d** and **4p** represented the most potent α-glucosidase inhibitory activity with IC_{50} values of 20.1 ± 0.19 and 25.2 ± 0.26 μM, respectively.

Based on the results of α-glucosidase inhibition assay, the structure-activity relationship (SAR) of this class of inhibitors are summarized. Compared the inhibitory activity of **4a** with **4g**, the result was shown that phenylhydrazono group located at the 3-position of the chromone ring resulted in the best activity. The replacement of phenylhydrazono group with benzohydrazide group decreased the activity drastically. Furthermore, the replacement of the right phenyl ring with thiophene (**4e** and **4i**) resulted in a remarkable decrease of inhibitory activity. It is interesting to point out that **4d** and **4p** containing the sulfonamide group at para position of the phenyl ring significantly improved the inhibitory activity, with IC_{50} values of 20.1 ± 0.19 μM and 25.2 ± 0.26 μM, respectively. Among this series of synthesized compounds, **4d** (IC_{50} = 20.1 ± 0.19 μM) with 4-sulfonamide substitution at phenyl part of hydrazide was found to be the most active compound. Additionally, **4p** (IC_{50} = 25.2 ± 0.26 μM) with 4-sulfonamide substitution at phenyl part of hydrazide and 7-hydroxyl on the chromone ring, was found to be the second most active compound. The binding interactions of the most active analogs were confirmed through molecular docking studies.