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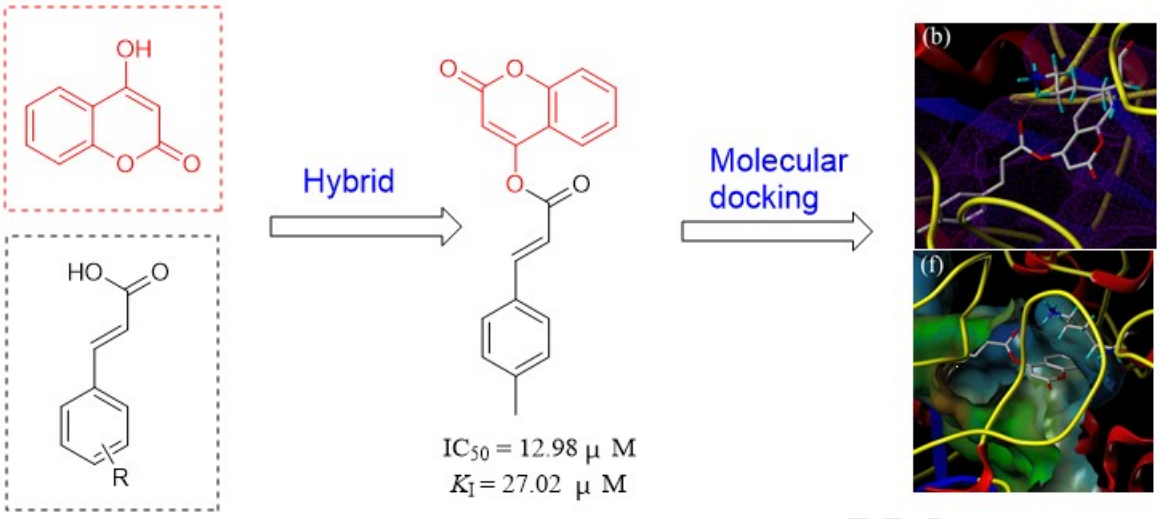

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Synthesis and Biological Evaluation of Coumarin Derivatives as α-glucosidase Inhibitors

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Abstract

In this study, two series of coumarin derivatives **5a~i** and **6a~i** were synthesized, and their inhibitory activity against α-glucosidase was determined. The results indicated that most of the synthesized derivatives exhibited prominent inhibitory activities against α-glucosidase. Among them, compounds **5a** and **5b** showed the strongest inhibition with the IC_{50} values of 19.64 μM and 12.98 μM, respectively. Enzyme kinetic studies of compounds **5a** and **5b** proved that their inhibition was reversible and a mixed type. The K_I and K_{IS} values of compound **5a** were calculated to be 27.39 μM and 13.02 μM, respectively, and the corresponding values for compound **5b** being 27.02 μM and 13.65 μM, respectively. The docking studies showed that compound **5b** could be inserted into the active pocket of α-glucosidase and form hydrogen bonds with LYS293 to enhance the binding affinity.

Key words: Coumarin; cinnamic acid; synthesis; α-glucosidase; enzyme inhibition; molecular docking

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1. Introduction

α-Glucosidase (EC 3.2.1.20), an exo-acting glycoside hydrolase, possesses key functions in the carbohydrate quality control and in particular plays essential roles in the process of sugar metabolism [1-4]. α-Glucosidase can hydrolyze the α-glycosidic bonds from the non-reducing end of carbohydrate substrates [5-8]. The cleavage of α-glucosidic bonds also relates to the number of monosaccharide units, cleavage site position, and configuration of hydroxyl groups in the substrates [9-12]. α-Glucosidase inhibitors can be used not only as research tools to clarify the mechanism of action of α-glucosidase at molecular levels, but also as evolved agents against carbohydrate-mediated diseases, such as cancer, diabetes, HIV, obesity and hepatitis [13-17]. The mechanism of action of α-glucosidase inhibitors is closely related to their affinity with the carbohydrate-binding region of α-glucosidase [18-20]. The biological importance of *α*-glucosidase encourages researchers to discover new, effective agents against *α*-glucosidase [21-23]. To date, a large amount of naturally occurring and synthetic agents toward *α*-glucosidase are produced in laboratories, but only a few are used in further applications [1-25]. Because mammalian α-glucosidase is not commercially available, α-glucosidase from *Saccharomyces cervisiae* has been generally used as a target protein for screening the activity of inhibitors.

It has been reported that coumarin and its derivatives have a wide range of biological activities [26,27], such as anti-oxidation [28,29], anti-inflammatory [30], anti-clotting [31], anti-bacterial [32], anti-cytotoxic [33,34], anti-cancer [35], anti-HIV [36,37] and treatment of dyslipidemia [38]. Recent studies have shown that many herbal and synthetic derivatives containing coumarin fractions can be used as α-glucosidase inhibitors [39,40]. On the other hand, cinnamic acid, a natural product extracted from cinnamon oil, has been used as fragrance and medicine [41], and this compound and its derivatives have received increasing attention in the treatment of type II diabetes in recent years [42].

Meanwhile, it is well recognized that modifying the structural skeletons of natural products is an important way to find lead compounds with certain level of biological

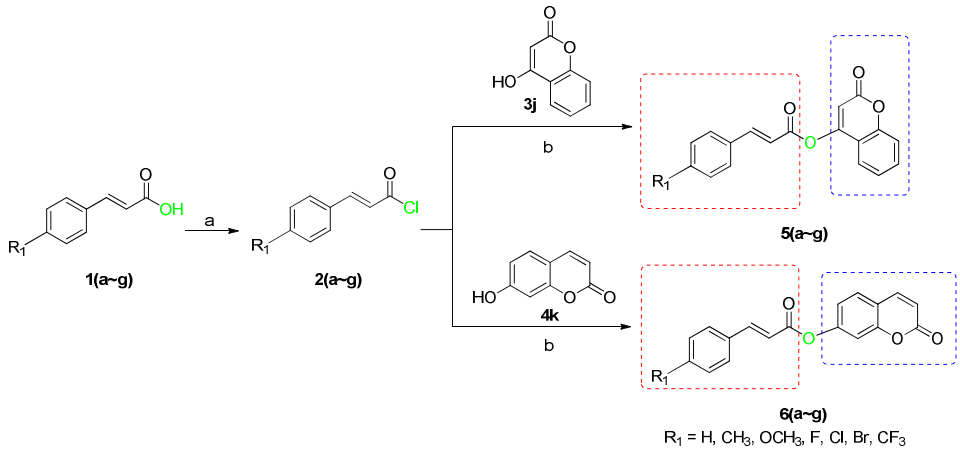
activity [43]. On the other hand, hybridization appears as an effective strategy to increase the biological activity or pharmacological efficacy of the hybrid molecule and to overcome the resistance [44,45]. To date, numerous effective agents have been developed based on these two methods. Inspired by these results and aiming to develop more effective α-glucosidase inhibitors, we integrated the above two strategies to design and synthesize two series of coumarin derivatives **5a~i** and **6a~i** by conjugating substituted cinnamic acids with 4-hydroxycoumarin or 7-hydroxycoumarin. We evaluated their inhibition effect and mechanism of action against α-glucosidase, and also carried out molecular docking studies. Here we report our findings.

2. Results and Discussion

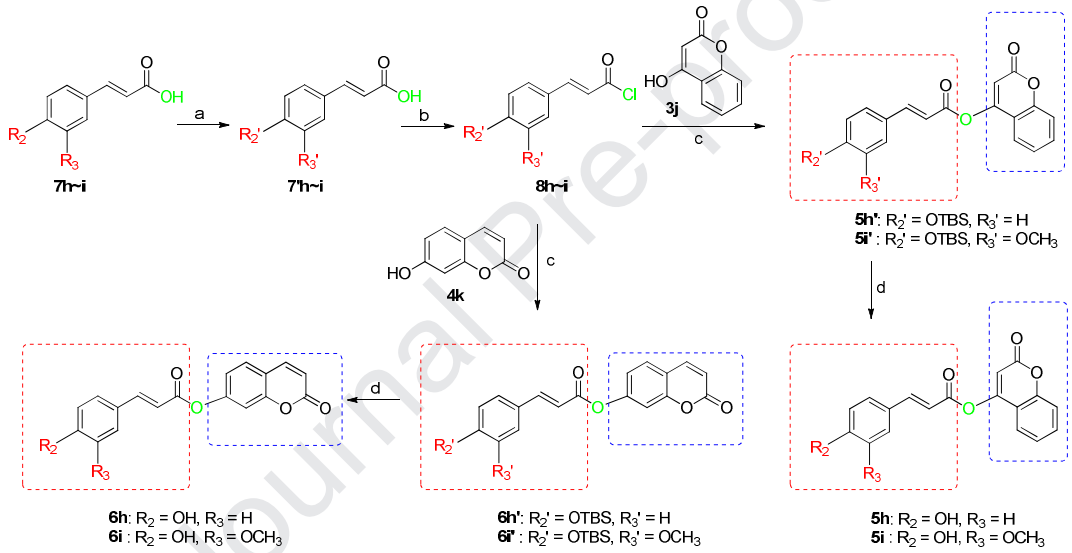
2.1. Chemistry

In this study, substituted cinnamic acids and coumarins were used as starting materials to synthesize coumarin derivatives. The synthetic route of coumarin derivatives **5a~g** and **6a~g** was shown in Scheme 1. Compounds **1a~g** were converted into intermediates **2a~g**, which were esterified with compound **3j** or **4k** to afford compounds **5a~g** and **6a~g**, respectively.

Because of the influence of the hydroxyl groups in substituted cinnamic acids **7h~i**, coumarin derivatives **5h~i** and **6h~i** were synthesized with a circuitous route as depicted in Scheme 2. Protection of the hydroxyl groups in compounds **7h~i** with tert-butyldimethylchlorosilane (TBSCl) afforded compounds **7'h~i**. Treatment of compounds **7'h~**i with thionylchloride gave compounds **8h~i**, which reacted with compound **3j** or **4k** to afford compounds **5h'~i'** and **6h'~i'**, respectively. Finally, compounds **5h~i** and **6h~i** were obtained by deprotecting the TBSCl groups.



Scheme 1. Synthesis of compounds **5a~g** and **6a~g**. Reagents and conditions: (a) $SOCl_2$, DMF, DCM, 0 °C ~ rt, 5h; (b) DIPEA, DCM, 0 °C ~ rt, 4h.



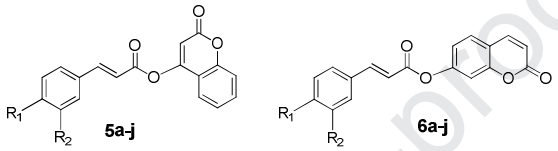
Scheme 2. Synthesis of compounds **5h~i** and **6h~i**. Reagents and conditions: (a) TBSCl, imidazole, DMAP, DMF, 0 °C ~ rt; K_2CO_3, THF, MeOH; (b) $SOCl_2$, DMF, DCM, 0 °C ~ rt, 5h; (c) DIPEA, DCM, 0 °C ~ rt, 4h; (d) HF, THF, rt.

2.2. α-Glucosidase inhibition assay

It has been reported that coumarin and its derivatives can achieve glycemic control by inhibiting the activity of α-glucosidase [46-49]. Therefore, the *in vitro* activity of compounds **5a~i** and **6a~i** against α-glucosidase was investigated. The inhibitory activity of these compounds at the concentration of 100 μM was screened and subsequently their IC_{50} values were evaluated. The results were shown in Table 1 and indicated that most of the synthetic coumarin derivatives exhibited higher inhibitory

potency than cinnamic acid and coumarins. This may be surmised to the better interaction of these conjugates. Among them, compounds **5a** and **5b** showed the strongest inhibition with the IC_{50} values of 19.64 μM and 12.98 μM, respectively, which are obvious higher than the parent pieces, cinnamic acid (1.5×10^4μM) and 4-hydroxycoumarin (9.0×10^3μM), and have similar inhibition activity compared with the positive control ursolic acid (11.38 μM), a widely accepted inhibitor again α-glucosidase from *Saccharomyces cervisiae* [14,50]. Fig. 1 showed the concentration inhibition curves of compounds **5a** and **5b** against α-glucosidase.

Table 1. Inhibitory activity of coumarin derivatives toward α-glucosidase.



Compound	R_1	R_2	Inhibition at 100 μM (%)	IC_{50} (μM)
5a	H	H	83.51	19.64
5b	CH_3	H	89.92	12.98
5c	OCH_3	H	73.15	36.88
5d	F	H	68.50	41.73
5e	Cl	H	33.10	>100
5f	Br	H	60.99	69.30
5g	CF_3	H	41.87	>100
5h	OH	H	33.19	>100
5i	OH	OCH_3	19.51	>100
6a	H	H	45.65	>100
6b	CH_3	H	54.74	94.52
6c	OCH_3	H	20.25	>100
6d	F	H	26.23	>100
6e	Cl	H	29.93	>100
6f	Br	H	30.10	>100
6g	CF_3	H	38.22	>100
6h	OH	H	13.11	>100
6i	OH	OCH_3	20.26	>100
Cinnamic acid				1.5×10^4
3J				4.0×10^5

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4K	9.0×10^3
Ursolic acidb	11.38

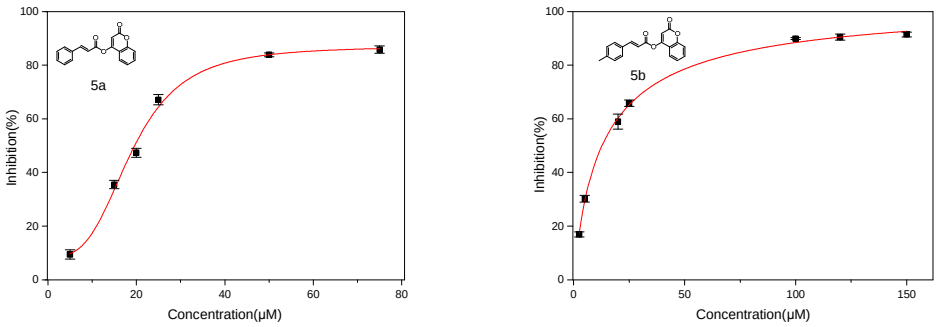

Fig. 1 The α-glucosidase inhibition effects of compounds **5a** and **5b**.

2.3. Structure activity relationships (SAR) analysis

Based on the data in Table 1, the SAR of compounds **5a~i** and **6a~i** against α-glucosidase was analyzed. Firstly, the influence of linking positions at coumarin ring was investigated. Since the inhibition of compounds **5a~i** against α-glucosidase was much higher than that of compounds **6a~i** with the same substituent groups, this result revealed that conjugation of substituted cinnamic acids with 4-hydroxycoumarin would be a better choice than with 7-hydroxycoumarin.

Secondly, the influence of the substituents on cinnamic acid was evaluated by taking compound **5a** as a lead structure. It was observed that introduction of CH_3 group (to give compound **5b**) was favorable to increase the inhibitory activity and the introduction of OCH_3, F, or Br group (to afford compounds **5c**, **5d** and **5f**, respectively) showed slightly negative effect on the inhibitory activity. Cl or CF_3 group as the substituent (that is compounds **5e** and **5g**) led to obviously low inhibitory activity, suggesting that an electron-withdrawing group was not favorable to the activity. Additionally, the presence of a hydroxyl group in compounds **5h** and **5i** also gave low inhibitory activity. Among the substituents, a methyl group at the 4-position of the phenyl ring of cinnamic acid was the most favorable to increase the inhibitory activity against α-glucosidase. Taken together, the above findings suggest that particular attentions should be paid attention to an electron-donating group rather than an electron-withdrawing group.

*2.4. α-Glucosidase inhibitory mechanism of compounds **5a** and **5b***

To ascertain the inhibition mechanism of compounds **5a** and **5b** on α-glucosidase, the plots of the initial velocity against the concentrations of α-glucosidase in the presence of compound **5a** or **5b** of varying concentrations were constructed. As shown in Fig. 2, the plots gave a family of straight lines at each concentration of compound **5a** or **5b**, and these lines passed through the origin. Moreover, the slopes of the lines extended a descent with the increase in the concentrations of compounds **5a** and **5b**. These findings suggest that the inhibition of α-glucosidase by compounds **5a** and **5b** is reversible.

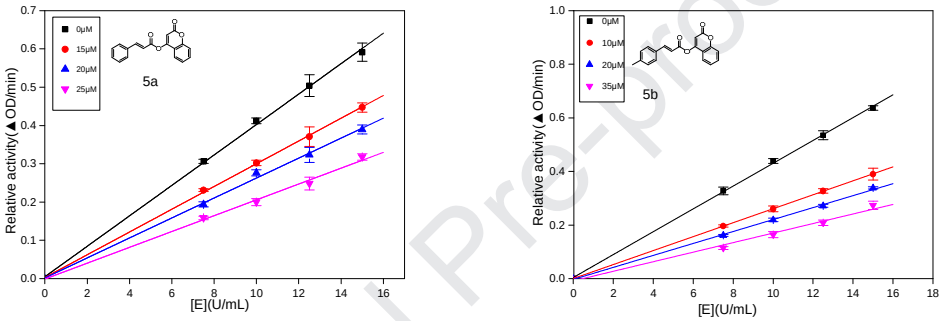

Fig. 2 Plots of the relative activity against the concentrations of α-glucosidase in the presence of compound **5a** (0, 15, 20 and 25 μM) or **5b** (0, 10, 20 and 35 μM).

To further explore the inhibition kinetic behavior of compounds **5a** and **5b**, their activity was determined at the different concentrations of 4-nitrophenyl-β-D-galactopyranoside (PNPG) in the presence or absence of compound **5a** or **5b**, and analyzed using Lineweaver-Burk double reciprocal plots. For both compounds **5a** and **5b**, the plots of 1/*V* *vs* 1/[S] gave straight lines with different slopes intersecting one another in the second quadrant. The values of V_m and K_m descended with the increase in the concentrations of compound **5a** or **5b**, which suggested that compounds **5a** and **5b** induced mixed-type inhibition on α-glucosidase. In other words, compounds **5a** and **5b** are able to bind with both free enzyme and enzyme-substrate complex to reduce the catalytic activity of α-glucosidase. To gain further insight into this, we determined the equilibrium constants of compounds **5a** and **5b** with free enzyme (K_I)

and the enzyme-substrate complex (K_{IS}), by plotting the apparent K_m/V_{max} and $1/V_{max}$ against the concentrations of compounds **5a** and **5b**. The K_I and K_{IS} values of compound **5a** were determined to be 27.39 μM and 13.02 μM, respectively, and the K_I and K_{IS} of compound **5b** were 27.02 μM and 13.65 μM, respectively.

*2.5. Molecular docking of compound **5b***

Molecular docking studies have two purposes, namely specific structural modeling and accurate prediction of activity [51]. The sybyl programe [52] was applied to study the interaction of compound **5b** with the active site of α-glucosidase to understand the inhibition mechanism. As described in our previous work [3,4], oligo-1,6-glucosidase from *Saccharomyces cerevisiae* (PDB: 1UOK) was selected as the target protein. Because compound **5b** was a hybride of 4-methylcinnamic acid and 4-hydroxycoumarin, its electrophilic and lipophilic potentials were changed compared with the parent pieces, 4-methylcinnamic acid and 4-hydroxycoumarin. Thereby the inhibition mode and docking site of compound **5b** may be apparently changed. As shown in Fig. 3a~b, compound **5b** well nested into the active pocket of α-glucosidase and formed a hydrogen bond with the amino acid sequences of LYS293 to enhance the affinity with α-glucosidase. Meanwhile, the electrophilic and lipophilic potential interactions between **5b** and the active pocket were analyzed. As indicated in Fig. 3c, the exterior of the active pocket is more electrophilic than the interior. So, the coumarin fraction of compound **5b**, which is more electrophilic than 4-methylphenyl fraction, was located in the lipophilic potential region (Fig. 3d). Similarly, the lipophilic potential interaction between compound **5b** and the active pocket was presented in Fig. 3e~f. The integration with the methylated phenyl ring of the cinnamic acid part is closer through the van der Waals force, and the coumarin fraction was near the hydrophilic region for its higher hydrophilicity than 4-methylphenyl fraction.

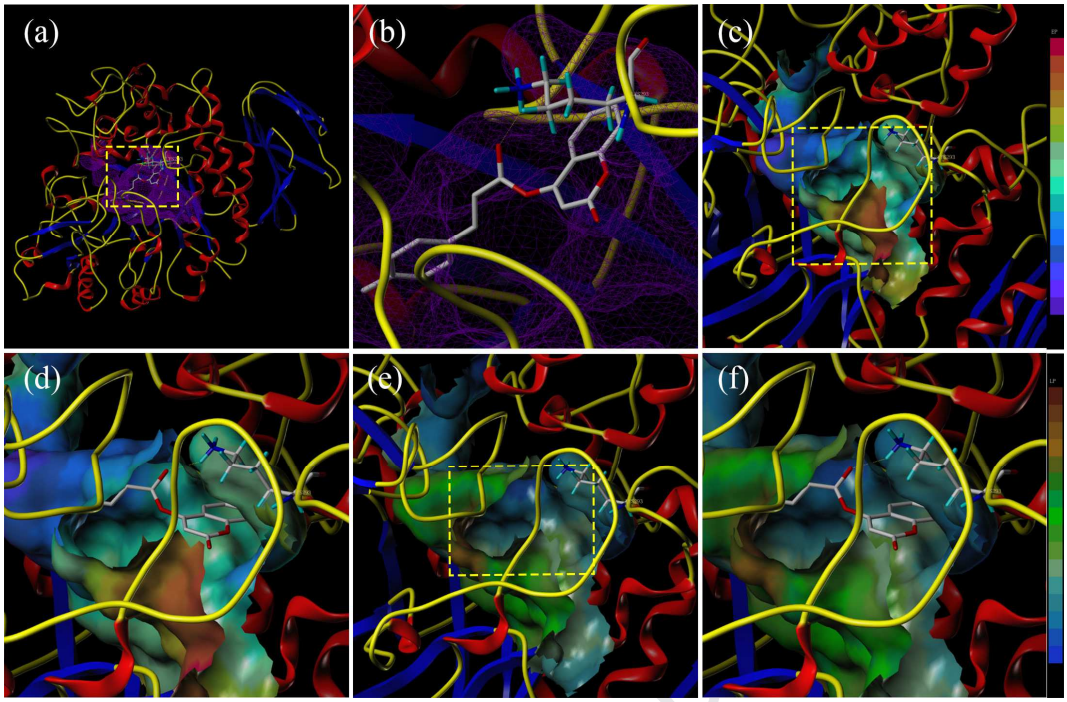

Fig. 3 Molecular docking of compound **5b** with α-glucosidase.

3. Conclusion

In summary, two series of coumarin derivatives were synthesized from the conjugation of substituted cinnamic acid with 4-hydroxycoumarin and 7-hydroxycoumarin, and their inhibitory activity toward α-glucosidase was evaluated. The results show that most of the synthesized derivatives showed prominent inhibitory potency than cinnamic acid and coumarin, and introduction of an electron-donating group is conducive to the α-glucosidase inhibitory activity. Enzyme kinetic studies indicated that their inhibition was reversible and a mixed type. Molecular docking study also confirmed that the synthesized derivatives could be effectively inserted into the active pocket of α-glucosidase. The present findings suggest that coumarin derivatives conjugated with a suitable cinnamic acid at the C-7 position could be promising inhibitors for α-glucosidase. Further structural optimization is under active investigation in our laboratories.

4. Materials and Methods

4.1. Chemistry

α-Glucosidase from *Saccharomyces cerevisiae* (EC 3.2.1.20) and PNPG were supplied by Sigma-Aldrich. All the other commercially available reagents were used without further purification. ^{1}H NMR and ^{13}C NMR were recorded on an NMR spectrometer (DPX-500 MHz) with chemical shifts (*d*) given in parts per million (ppm) relative to TMS as an internal standard. Mass spectrometry was determined on a (LCQ^{TM}) LC-MS supplied by Thermo Fisher Scientific (Shanghai) Co., Ltd. Melting points were measured on a Micro melting point instrument supplied by Shanghai Yidian Physical Optical Instrument Co., Ltd, and the temperature was not corrected.

4.2. General procedures

*4.2.1. Synthesis of compounds **5a~g** and **6a~g***

$SOCl_2$ (2.4 mmol) and DMF (2 drops) were added to a solution of compounds **1a~g** (2.0 mmol) in anhydrous DCM (5 mL) at 0 °C. The reaction mixture was stirred at room temperature for 5 h, and then concentrated to afford cinnamoyl chlorides **2a~g**. Then to a solution of compound **3J** or **4k** (1.6 mmol) and DIPEA (3.2 mmol) in anhydrous DCM (5 mL) was added slowly a solution of compounds **2a~g** in anhydrous DCM (5 mL) at 0 °C. After 30 min, the reaction mixture was warmed to the room temperature and stirring continued until the reaction was completed. Then the reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution and extracted with ethyl acetate. The organic layer was washed subsequently with water and brine, dried over anhydrous Na_2SO_4 and concentrated. The obtained residues were purified by column chromatography to give compounds **5a~g** and **6a~g**.

2-oxo-2H-chromen-4-yl cinnamate 5a. White solid; yield 66.3 %; mp: 156-157 □; ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.98 (d, *J* = 15.9 Hz, 1H), 7.72 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.66 - 7.57 (m, 3H), 7.52 - 7.43 (m, 3H), 7.39 (dd, *J* = 8.4, 1.1 Hz, 1H), 7.33 (dd, *J* =7.4, 1.0 Hz, 1H), 6.69 (d, *J* = 15.9 Hz, 1H), 6.61 (s, 1H); ^{13}C NMR (126 MHz, Chloroform-*d*) δ 162.77, 161.59, 158.67, 153.73, 149.36, 133.55, 132.78, 131.60, 129.22, 128.69, 124.35, 122.88, 117.15, 115.68, 115.35, 105.25; ESI-MS: *m/z* 315.57

([M+Na]$^+$); IR (cm^{-1}) (KBr) *v* 2924 (=C-H, aromatic), 1706 (C=O, ester), 1612 (C=C), 1385, 1328 (3C-H, alkene), 1116 (C-O-C, ester), 940, 841, 763 (9C-H, aromatic).

2-oxo-2H-chromen-4-yl(*E*)-3-(*p*-tolyl)acrylate 5b. White solid; yield 43.5 %; mp: 139-140 □; ^{1}H NMR (500 MHz, Chloroform-*d)* δ 7.95 (d, *J* = 16.0 Hz, 1H), 7.72 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.59 (ddd, *J* = 8.6, 7.3, 1.6 Hz, 1H), 7.55 - 7.51 (m, 2H), 7.38 (dd, *J* = 8.3, 1.1 Hz, 1H), 7.32 (td, *J* = 7.7, 1.1 Hz, 1H), 7.27 (d, *J* = 6.7 Hz, 2H), 6.63 (d, *J* = 15.9 Hz, 1H), 6.60 (s, 1H), 2.42 (s, 3H); ^{13}C NMR (126 MHz, Chloroform-*d*) δ 162.95, 161.64, 158.74, 153.73, 149.40, 142.37, 132.74, 130.86, 129.96, 128.72, 124.32, 122.92, 117.13, 115.75, 114.14, 105.18, 21.65; ESI-MS: *m/z* 329.07 ([M+Na]$^+$); IR (cm^{-1}) (KBr) *v* 2923 (=C-H, aromatic), 1714 (C=O, ester), 1616 (C=C), 1385 (3C-H, alkene), 1326 (CH_3), 1127 (C-O-C, ester), 937, 846, 810, 759 (8C-H, aromatic).

2-oxo-2H-chromen-4-yl (*E*)-3-(4-methoxyphenyl)acrylate 5c. White solid; yield 52.8 %; mp: 149-151 □; ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.93 (d, *J* = 15.9 Hz, 1H), 7.72 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.61 - 7.57 (m, 3H), 7.38 (dd, *J* = 8.4, 1.1 Hz, 1H), 7.32 (td, *J* = 7.6, 1.1 Hz, 1H), 6.99 - 6.95 (m, 2H), 6.59 (s, 1H), 6.53 (d, *J* = 15.9 Hz, 1H), 3.88 (s, 3H); ^{13}C NMR (126 MHz, Chloroform-*d*) δ 163.11, 162.49, 161.70, 158.82, 153.73, 149.07, 132.71, 130.59, 126.32, 124.30, 122.94, 117.12, 115.81, 114.67, 112.51, 105.11, 55.52; ESI-MS: *m/z* 344.98 ([M+Na]$^+$); IR (cm^{-1}) (KBr) *v* 2925 (=C-H, aromatic), 1728 (C=O, ester), 1609 (C=C), 1381 (3C-H, alkene), 1293 (C-O-C, ether), 1112 (C-O-C, ester), 946, 837, 765 (8C-H, aromatic).

2-oxo-2H-chromen-4-yl (*E*)-3-(4-fluorophenyl)acrylate 5d. White solid; yield 54.5 %; mp: 146-147 □; ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.94 (d, *J* = 15.9 Hz, 1H), 7.70 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.66 - 7.62 (m, 2H), 7.60 (ddd, *J* = 8.7, 7.4, 1.6 Hz, 1H), 7.39 (dd, *J* = 8.4, 1.1 Hz, 1H), 7.32 (td, *J* = 7.7, 1.1 Hz, 1H), 7.16 (t, *J* = 8.6 Hz, 2H), 6.61 (d, *J* = 16.2 Hz, 2H); ^{13}C NMR (126 MHz, Chloroform-*d*) δ 165.68, 163.66, 162.66, 161.55, 158.63, 153.73, 147.96, 132.81, 130.76, 130.69, 129.86, 129.83, 124.35, 122.84, 117.17, 116.58, 116.41, 115.64, 115.10, 115.08, 105.27; ESI-MS: *m/z* 333.39 ([M+Na]$^+$); IR (cm^{-1}) (KBr) *v* 2923 (=C-H, aromatic), 1711

(C=O, ester), 1619 (C=C), 1387 (3C-H, alkene), 1331 (C-F), 1133 (C-O-C, ester), 939, 837, 758 (8C-H, aromatic).

2-oxo-2H-chromen-4-yl(*E*)-3-(4-chlorophenyl)acrylate 5e. White solid; yield 62.3 %; mp: 184-185 □; ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.92 (d, *J* = 15.9 Hz, 1H), 7.70 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.63 - 7.55 (m, 3H), 7.47 - 7.42 (m, 2H), 7.39 (dd, *J* = 8.3, 1.1 Hz, 1H), 7.35 - 7.30 (m,1H), 6.66 (d, *J* = 16.0 Hz, 1H), 6.60 (s, 1H); ^{13}C NMR (126 MHz, Chloroform-*d*) δ 162.55, 161.51, 158.58, 153.73, 147.80, 137.68, 132.83, 132.01, 129.81, 129.56, 124.36, 122.82, 117.19, 115.92, 115.60, 105.31; ESI-MS: *m/z* 348.84 ([M+Na]$^{+}$); IR (cm^{-1}) (KBr) *v* 2922 (=C-H, aromatic), 1721 (C=O, ester), 1625 (C=C), 1382, 1317 (3C-H, alkene), 1131 (C-O-C, ester), 940, 868, 821 (8C-H, aromatic), 755 (C-Cl).

2-oxo-2H-chromen-4-yl(*E*)-3-(4-bromophenyl)acrylate 5f. White solid; yield 61.7 %; mp: 194-195 □; ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.90 (d, *J* = 15.9 Hz, 1H), 7.70 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.60 (dq, *J* = 8.7, 2.3, 1.6 Hz, 3H), 7.53 - 7.47 (m, 2H), 7.39 (dd, *J* = 8.4, 1.1 Hz, 1H), 7.32 (td, *J* = 7.7, 1.1 Hz, 1H), 6.68 (d, *J* = 15.9 Hz, 1H), 6.60 (s, 1H); ^{13}C NMR (126 MHz, Chloroform-*d*) δ 162.54, 161.51, 158.57, 153.73, 147.88, 132.84, 132.53, 132.51, 132.43, 129.97, 126.10, 124.36, 122.82, 117.18, 116.03, 115.59, 105.30; ESI-MS: *m/z* 393.05 ([M+Na]$^{+}$); IR (cm^{-1}) (KBr) *v* 2922 (=C-H, aromatic), 1755 (C=O, ester), 1623 (C=C), 1380, 1314 (3C-H, alkene), 1128 (C-O-C, ester), 938, 867, 818 (8C-H, aromatic), 754 (C-Br).

2-oxo-2H-chromen-4-yl (*E*)-3-(4-(trifluoromethyl)phenyl)acrylate 5g. White solid; yield 58.9 %; mp: 165-166 □; ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.99 (d, *J* = 16.0 Hz, 1H), 7.78 - 7.68 (m, 5H), 7.65 - 7.58 (m, 1H), 7.40 (d, *J* = 8.3 Hz, 1H), 7.33 (t, *J* = 7.6 Hz, 1H), 6.77 (d, *J* = 16.0 Hz, 1H), 6.61 (s, 1H); ^{13}C NMR (126 MHz, Chloroform-*d*) δ 162.25, 161.44, 158.47, 153.74, 147.27, 136.80, 133.05, 132.90, 132.79, 128.78, 126.24, 126.21, 126.18, 126.14, 124.40, 122.77, 118.02, 117.22, 115.50, 105.41; ESI-MS: *m/z* 382.78 ([M+Na]$^{+}$); IR (cm^{-1}) (KBr) *v* 2924 (=C-H, aromatic), 1754 (C=O, ester), 1626 (C=C), 1383 (3C-H, alkene), 1323 (3C-F), 1117 (C-O-C, ester), 941, 834, 755 (8C-H, aromatic).

2-oxo-2*H*-chromen-7-ylcinnamate 6a. White solid; yield 65.4 %; mp: 152-154 □; ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.91 (d, *J* = 16.0 Hz, 1H), 7.72 (d, *J* = 9.6 Hz, 1H), 7.64 - 7.58 (m, 2H) , 7.52 (d, *J* = 8.4 Hz, 1H), 7.44 (dd, *J* = 5.1, 1.9 Hz, 3H), 7.21 (d, *J* = 2.2 Hz, 1H), 7.15 (dd, *J* = 8.4, 2.2 Hz, 1H), 6.63 (d, *J* = 16.0 Hz, 1H), 6.41 (d, *J* = 9.5 Hz, 1H); ^{13}C NMR (126 MHz, Chloroform-*d*) δ 164.71, 160.45, 154.77, 153.42, 147.76, 142.93, 133.92, 131.10, 129.11, 128.58, 128.47, 118.52, 116.66, 116.44, 116.07, 110.53; ESI-MS: *m/z* 314.96 ([M+Na]$^{+}$); IR (cm^{-1}) (KBr) *v* 2925 (=C-H, aromatic), 1725 (C=O, ester), 1623 (C=C), 1410, 1312 (4C-H, alkene), 1134 (C-O-C, ester), 986, 864, 757, 692 (8C-H, aromatic).

2-oxo-2*H*-chromen-7-yl(*E*)-3-(p-tolyl)acrylate 6b. White solid; yield 43.7%; mp: 174-176 □; ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.88 (d, *J* = 15.9 Hz, 1H), 7.71 (d, *J* = 9.5 Hz, 1H), 7.51 (dd, *J* = 9.6, 7.9 Hz, 3H), 7.24 (d, *J* = 8.0 Hz, 2H), 7.21 (d, *J* = 2.2 Hz, 1H), 7.14 (dd, *J*= 8.4, 2.2 Hz, 1H), 6.58 (d, *J* = 16.0 Hz, 1H), 6.41 (d, *J* = 9.6 Hz, 1H), 2.40 (s, 3H); ^{13}C NMR (126 MHz, Chloroform-*d*) δ 164.89, 160.47, 154.77, 153.51, 147.79, 142.94, 141.73, 131.22, 129.85, 128.56, 128.49, 118.56, 116.61, 116.01, 115.27, 110.54, 21.59; ESI-MS: *m/z* 328.97 ([M+Na]$^{+}$); IR (cm^{-1}) (KBr) *v* 2923 (=C-H, aromatic), 1723 (C=O, ester), 1619 (C=C), 1404 (4C-H, alkene), 1260 (CH_3), 1129 (C-O-C, ester), 987, 811, 747 (7C-H, aromatic).

2-oxo-2*H*-chromen-7-yl(*E*)-3-(4-methoxyphenyl)acrylate 6c. White solid; yield 53.7 %; mp: 196-198 □; ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.86 (d, *J* = 15.9 Hz, 1H), 7.71 (d, *J* = 9.5 Hz, 1H), 7.58 - 7.54 (m, 2H) , 7.51 (d, *J* = 8.5 Hz, 1H), 7.20 (d, *J* = 2.2 Hz, 1H), 7.14 (dd, *J* = 8.4, 2.2 Hz, 1H), 6.97 - 6.93 (m, 2H), 6.49 (d, *J* = 15.9 Hz, 1H), 6.41 (d, *J* = 9.6 Hz, 1H), 3.87 (s, 3H); ^{13}C NMR (126 MHz, Chloroform-*d*) δ 165.04, 162.06, 160.48, 154.77, 153.59, 147.45, 142.95, 130.27, 128.53, 126.68, 118.59, 116.56, 115.97, 114.55, 113.72, 110.55, 55.47; ESI-MS: *m/z* 345.10 ([M+Na]$^{+}$); IR (cm^{-1}) (KBr) *v* 2925 (=C-H, aromatic), 1736 (C=O, ester), 1610 (C=C), 1417 (4C-H, alkene), 1260 (C-O-C, ether), 1136 (C-O-C, ester), 995, 887, 825 (7C-H, aromatic).

2-oxo-2*H*-chromen-7-yl(*E*)-3-(4-fluorophenyl)acrylate 6d. White solid; yield 63.8 %; mp: 208-210 □; ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.87 (d, *J* = 16.0 Hz, 1H), 7.72 (d, *J* = 9.5 Hz, 1H), 7.63 - 7.57 (m, 2H) , 7.53 (d, *J* = 8.4 Hz, 1H), 7.21 (d, *J* = 2.2 Hz, 1H), 7.17 - 7.10 (m, 3H), 6.56 (d, *J* = 16.0 Hz, 1H), 6.42 (d, *J* = 9.5 Hz, 1H); ^{13}C NMR (126 MHz, Chloroform-*d*) δ 164.58, 160.43, 154.77, 153.36, 146.39, 142.91, 130.47, 130.40, 128.60, 118.48, 116.69, 116.43, 116.25, 116.19, 116.10, 110.51; ESI-MS: *m/z* 333.11 ([M+Na]$^{+}$); IR (cm^{-1}) (KBr) *v* 2924 (=C-H, aromatic), 1734 (C=O, ester), 1615 (C=C), 1411 (4C-H, alkene), 1235 (C-F), 1137 (C-O-C, ester), 993, 835 (7C-H, aromatic).

2-oxo-2*H*-chromen-7-y(*E*)-3-(4-chlorophenyl)acrylate 6e. White solid; yield 41.7%; mp: 201-203 □; ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.85 (d, *J* = 16.0 Hz, 1H), 7.72 (d, *J* = 9.6 Hz, 1H), 7.53 (dd, *J* = 8.4, 5.5 Hz, 3H), 7.45 - 7.37 (m, 2H), 7.20 (d, *J* = 2.2 Hz, 1H), 7.14 (dd, *J* = 8.4, 2.2 Hz, 1H), 6.60 (d, *J* = 16.0 Hz, 1H), 6.41 (d, *J* = 9.6 Hz, 1H); ^{13}C NMR (126 MHz, Chloroform-*d*) δ 164.46, 160.40, 154.77, 153.31, 146.23, 142.89, 137.11, 132.39, 129.60, 129.43, 128.61, 118.44, 117.03, 116.72, 116.13, 110.49; ESI-MS: *m/z* 349.31 ([M+Na]$^{+}$); IR (cm^{-1}) (KBr) *v* 2924 (=C-H, aromatic), 1726 (C=O, ester), 1620 (C=C), 1406 (4C-H, alkene), 1273, 1125 (C-O-C, ester), 817 (7C-H, aromatic), 755 (C-Cl).

2-oxo-2*H*-chromen-7-yl(*E*)-3-(4-bromophenyl)acrylate 6f. White solid; yield 64.6%; mp: 217-218 □; ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.83 (d, *J* = 16.0 Hz, 1H), 7.72 (d, *J* = 9.6 Hz, 1H), 7.61 - 7.56 (m, 2H), 7.52 (d, *J* = 8.4 Hz, 1H), 7.49 - 7.43 (m, 2H), 7.20 (d, *J* = 2.2 Hz, 1H), 7.14 (dd, *J* = 8.4, 2.2 Hz, 1H), 6.62 (d, *J* = 16.0 Hz, 1H), 6.42 (d, *J* = 9.5 Hz, 1H); ^{13}C NMR (126 MHz, Chloroform-*d*) δ 164.45, 160.40, 154.76, 153.30, 146.30, 142.89, 132.81, 132.40, 129.78, 128.61, 125.50, 118.44, 117.15, 116.73, 116.13, 110.49; ESI-MS: *m/z* 393.33 ([M+Na]$^{+}$); IR (cm^{-1}) (KBr) *v* 2924 (=C-H, aromatic), 1723 (C=O, ester), 1615 (C=C), 1404 (4C-H, alkene), 1268, 1122 (C-O-C, ester), 986, 847, 812 (7C-H, aromatic), 600 (C-Br).

2-oxo-2*H*-chromen-7-yl (*E*)-3-(4-(trifluoromethyl)phenyl)acrylate 6g. White solid; yield 45.3 %; mp: 178-180 □; ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.92 (d, *J* = 16.0

Hz, 1H), 7.75 - 7.67 (m, 5H), 7.54 (d, *J* = 8.5 Hz, 1H) , 7.22 (d, *J* = 2.1 Hz, 1H), 7.15 (dd, *J* = 8.4, 2.2 Hz, 1H), 6.71 (d, *J* = 16.0Hz, 1H), 6.42 (d, *J* = 9.5 Hz, 1H); ^{13}C NMR (126 MHz, Chloroform-*d*) δ 164.15, 160.35, 154.77, 153.17, 145.73, 142.87, 128.66, 128.56, 126.13, 126.10, 126.07, 126.04, 119.10, 118.37, 116.81, 116.21, 110.47; ESI-MS: *m/z* 382.73 ([M+Na]$^+$); IR (cm^{-1}) (KBr) *v* 2924 (=C-H, aromatic), 1727 (C=O, ester), 1619 (C=C), 1411, 1328 (4C-H, alkene), 1270 (3C-F), 1119, 1068 (C-O-C, ester), 985, 864, 830 (7C-H, aromatic).

*4.2.2 Synthesis of compounds **5h~i** and **6h~i***

Compounds **7h~i** (2 mmol), imidazole (9 mmol), TBSCl (6 mmol) and DMAP (0.2 mmol) were dissolved in dry DMF (5 mL) in sequence under ice bath and the resulting solution was stirred for 3 h. After concentrated, the obtained residues were dissolved in a solution of K_2CO_3 (0.2 g) in MeOH/THF (1/2, 12 mL). The mixture was stirred for 3 h and concentrated under reduced pressure. The obtained residues were partitioned between ethyl acetate and water. The organic layer was separated, washed with water and brine, and dried over anhydrous Na_2SO_4. Removal of the organic layer under vacuum gave compounds **7h'~i'**. Then compounds **7h'~i'** (2.0 mmol), $SOCl_2$ (2.4 mmol) and DMF(2 drops) were added to dry DCM (5 mL) at 0 □, and the resulting solution was stirred at room temperature for 5 h, followed by concentration to give compounds **8h~i**. To a solution of compound **3J** or **4k** (1.6 mmol) and DIPEA (3.2 mmol) in dry DCM (5 mL) at 0 □ was added slowly a solution of compounds **8h~i** in dry DCM (5 mL). Then the reaction mixture was warmed to room temperature and stirred until the reaction was completed on TLC. The reaction was quenched with saturated aqueous $NaHCO_3$ solution, followed by extraction with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous Na_2SO_4 and concentrated. The obtained residues were purified by column chromatography to give compounds **5h~i** and **6h~i**.

2-oxo-2*H*-chromen-4-yl(*E*)-3-(4-hydroxyphenyl)acrylate 5h. White solid; yield 29.7 %; mp: 170-171 □; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.27 (s, 1H), 7.91 (d, *J* = 15.9 Hz, 1H), 7.80 (dd, *J* = 8.0, 1.8 Hz, 1H) , 7.71 (td, *J* = 6.9, 5.5, 2.0 Hz, 3H), 7.53 -

7.47 (m, 1H), 7.41 (tt, *J* = 7.6, 1.4 Hz, 1H), 6.88 - 6.82 (m, 2H), 6.81 - 6.74 (m, 1H), 6.63 (d, *J* = 1.5 Hz, 1H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 163.36, 160.97, 160.79, 158.92, 153.19, 149.19, 133.33, 131.42, 124.87, 124.83, 123.35, 116.84, 116.07, 115.48, 111.65, 105.26; ESI-MS: *m/z* 330.72 ([M+Na]$^+$); IR (cm^{-1}) (KBr) *v* 3435 (O-H), 2925 (=C-H, aromatic), 1737 (C=O, ester), 1596, 1511 (C=C), 1384 (3C-H, alkene), 1146 (C-O-C, ester), 894, 847, 755 (8C-H, aromatic).

2-oxo-2*H*-chromen-4-yl (*E*)-3-(4-hydroxy-3-methoxyphenyl)acrylate 5i. Light yellow solid; yield 40.0%; mp: 177-178 □; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.89 (s, 1H), 7.91 (d, *J* = 15.9 Hz, 1H), 7.81 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.73 (ddd, *J* = 8.6, 7.3, 1.6 Hz, 1H), 7.53 - 7.49 (m, 2H), 7.45 - 7.41 (m, 1H), 7.29 (dd, *J* = 8.2, 2.0 Hz, 1H), 6.90 - 6.83 (m, 2H), 6.64 (s, 1H), 3.85 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 163.79, 161.18, 159.31, 153.58, 150.95, 149.93, 148.55, 133.73, 125.72, 125.23, 124.96, 123.69, 117.24, 116.10, 115.87, 112.26, 112.22, 105.62, 56.27; ESI-MS: *m/z* 359.46 ([M+Na]$^+$); IR (cm^{-1}) (KBr) ν 3431 (O-H), 2925 (=C-H, aromatic), 1723 (C=O, ester), 1621 (C=C), 1385 (3C-H, alkene), 1274 (C-O-C, ether), 1117 (C-O-C, ester), 944, 851, 759 (7C-H, aromatic).

2-oxo-2*H*-chromen-7-yl(*E*)-3-(4-hydroxyphenyl)acrylate 6h. White solid; yield 29.0%; mp: 242-244 □; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.20 (s, 1H), 8.10 (d, *J* = 9.6 Hz, 1H), 7.85 - 7.78 (m, 2H), 7.70 - 7.66 (m, 2H), 7.37 (d, *J* = 2.3 Hz, 1H), 7.24 (dd, *J* = 8.4, 2.2 Hz, 1H), 6.86 - 6.82 (m, 2H), 6.67 (d, *J* = 15.9 Hz, 1H), 6.50 (d, *J* = 9.6 Hz, 1H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 165.35, 160.96, 160.26, 154.64, 153.59, 147.99, 144.37, 131.41, 129.81, 125.36, 119.25, 117.07, 116.39, 115.96, 113.02, 110.67; ESI-MS: *m/z* 330.98 ([M+Na]$^+$); IR (cm^{-1}) (KBr) *v* 3424 (O-H), 2924 (=C-H, aromatic), 1736 (C=O, ester), 1598 (C=C), 1389 (4C-H, alkene), 1128 (C-O-C, ester), 817 (7C-H, aromatic).

2-oxo-2*H*-chromen-7-yl (*E*)-3-(4-hydroxy-3-methoxyphenyl)acrylate 6i. White solid; yield 59.3%; mp: 213-215 □; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.79 (s, 1H), 8.10 (d, *J* = 9.6 Hz, 1H), 7.80 (dd, *J* = 12.2, 3.7 Hz, 2H), 7.45 (d, *J* = 2.0 Hz, 1H), 7.37 (d, *J* = 2.2 Hz, 1H), 7.24 (dd, *J* = 8.3, 2.2 Hz, 2H), 6.83 (d, *J* = 8.1 Hz, 1H) , 6.75

(d, *J* = 15.9 Hz, 1H), 6.49 (d, *J* = 9.6 Hz, 1H), 3.84 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 165.38, 160.26, 154.64, 153.60, 150.51, 148.51, 148.33, 144.38, 129.83, 125.84, 124.38, 119.23, 117.06, 116.07, 115.95, 113.31, 112.03, 110.63, 56.23; ESI-MS: *m/z* 359.65 ([M+Na]$^+$); IR (cm^{-1}) (KBr) ν 3433 (O-H), 2924 (=C-H, aromatic), 1709 (C=O, ester), 1607 (C=C), 1420 (4C-H, alkene), 1232 (C-O-C, ether), 1128 (C-O-C, ester), 983, 849 (6C-H, aromatic).

4.3. Inhibitory activity toward α-glucosidase

The inhibitory activity of compounds **5a~i** and **6a~i** against α-glucosidase and their inhibition mechanism of action were investigated according to the method of Worawalai with a slight modification [53]. Those compounds were dissolved in DMSO. α-Glucosidase enzyme and PNPG were dissolved in 0.1 M potassium phosphate buffer (pH 6.8). Then 10 μL of α-glucosidase (final concentration 0.1 U/mL), 130 μL of phosphate buffer and 10 μL of the test compounds were added into 96-well plates, in succession. After incubated at 37 □ for 10 min, 50 μL of PNPG (final concentration 1 mmol/L) was added into the mixture, followed by incubation at 37 □ for 30 min. The enzymatic activity was quantified by measuring the absorbance at 405 nm using Multimodel Reader. The inhibition percentage was calculated by the formula: % Inhibition = $[(A_1 – A_0) / A_0] \times 100\%$, where A_1 and A_0 are the absorbance with and without the test compound, respectively. The IC_{50} value was determined from a plot of the inhibition percentage *vs* the concentrations of test compounds. The experiment was performed in duplicate and the man values were taken.

4.4. Kinetics of enzyme inhibition

The enzyme inhibition kinetics experiments were performed using similar assays as described above, in the presence of different concentrations of test compound and α-glucosidase or PNPG. The enzyme inhibitory kinetics was analyzed with the plot of enzyme concentrations *vs* the concentrations of test compounds, and the substrate inhibitory kinetics was assessed with the plots of substrate concentrations *vs* the concentrations of test compounds using the Lineweaver-Burk plot.

4.5. Molecular modeling

Sybyl-2.1.1 (Tripos, shanghai, China) was used to simulate the interaction between compound **5b** and α-glucosidase. After hydrogen atoms were added, compound **5b** was energy minimized using MM2 program, with the energy convergence criterion of 0.001 kcal/mol by using Gasteiger-Hückle charges and optimizing the energy gradient with 2500 times. The crystal structure of α-glucosidase was retrieved from RCSB Protein Database (PDB: 1UOK). The α-glucosidase protein was prepared by procedure of termini treatment, including removing H_2O, adding hydrogens, adding charges, fixing side chain amides, and stageding minimization. The active pocket of α-glucosidase was simulated by automatic mode. Then the docking between compound **5b** and α-glucosidase was carried out in the default format.

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Highlights

1. Coumarin derivatives **5** (**a ~ i**) and **6** (**a ~ i**) were synthesized.
2. The synthetic compounds were screened for α-glucosidase inhibitory activity.
3. Kinetic studies determined the mechanism of synthetic compounds on α-glucosidase.
4. In silico studies were performed to confirm the binding interactions of synthetic compounds with the enzyme active site.

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Declaration of interests

√ The authors declare that they have no known competing financialinterestsor personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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