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Bioorganic & Medicinal Chemistry 14 (2006) 5683–5690
Bioorganic & Medicinal Chemistry

Synthesis and pharmacological activities of xanthone derivatives as α-glucosidase inhibitors

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Received 13 March 2006; revised 6 April 2006; accepted 7 April 2006
Available online 2 May 2006

Abstract—Considerable interest has been attracted in xanthone and its derivatives because of their large variety of pharmacological activities. In this project, a series of hydroxylxanthones and their acetoxy and alkoxy derivatives were synthesized and evaluated as α-glucosidase inhibitors, aimed at clarifying the structure–activity correlation. The results indicated that these xanthone derivatives were capable of inhibiting in vitro α-glucosidase with moderate to good activities. Among them, polyhydroxylxanthones exhibited the highest activities and thus may be exploitable as a lead compound for the development of potent α-glucosidase inhibitors.

1. Introduction

It is well known that α-glucosidase (EC.3.2.1.20) catalyzes the final step of carbohydrate digestion in biological systems. This biological importance of α-glucosidase prompts various efforts to develop new agents capable of efficiently inhibiting α-glucosidase. These agents, namely α-glucosidase inhibitors, have wide application, for example, in elucidating the action mechanism of α-glucosidase at molecular levels and in developing chemotherapeutic agents for clinic use in the treatment of carbohydrate mediated diseases such as diabetes, cancer, HIV, hepatitis, and certain forms of hyperlipoproteinemia and obesity.[1–5] Therefore in the past two decades, there has been increasing interest in the development of inhibitors that can probe the structure and function of α-glucosidase. To date, many new and effective α-glucosidase inhibitors have been reported, such as acarbose and voglibose from microorganisms and 1-deoxynojirimycin isolated from plants.[6,7] Recently, flavones (Fig. 1) and their related derivatives, thanks to their strong inhibitory activities, have attracted considerable attentions as a new class of α-glucosidase inhibitors.[6,8,9] These flavone-based compounds feature two fused aromatic rings and a conjugated phenyl substituent. Studies on hydroxyflavones and other polyphenols have shown that phenolic hydroxyl groups play a determinant role in their α-glucosidase inhibitory activities.[10,11]

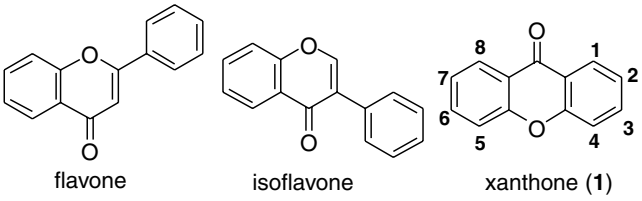

Figure 1. Structures of flavone, isoflavone, and xanthone.

Our concern in this field is to design and synthesize novel α-glucosidase inhibitors, by using xanthones as building motifs. Xanthones (**1**, Fig. 1), readily isolated from some medicinal plants, have been reported to exhibit several important biological activities, such as anti-tumor,[12,13] anti-inflammatory,[14] anti-thrombotic,[15] and eukaryote kinase effects.[16] Recent studies have indicated that some xanthone derivatives, such as mangiferin, a xanthone C-glycoside, serve as potent α-glucosidase inhibitors,[17–19] however, few systematic studies of the interaction of xanthones and their derivatives with α-glucosidase have been reported. Consequently, their structure–activity relationships remain to be established. As shown in Figure 1, xanthones having three linear fused aromatic rings may be viewed as flavone derivatives in which the phenyl group is fused with the two fused aromatic rings. This structural 'similarity', together with the aforementioned studies on hydroxyflavones

Keywords: Xanthone analogues; Synthesis; α-Glucosidase; Inhibitory activity.
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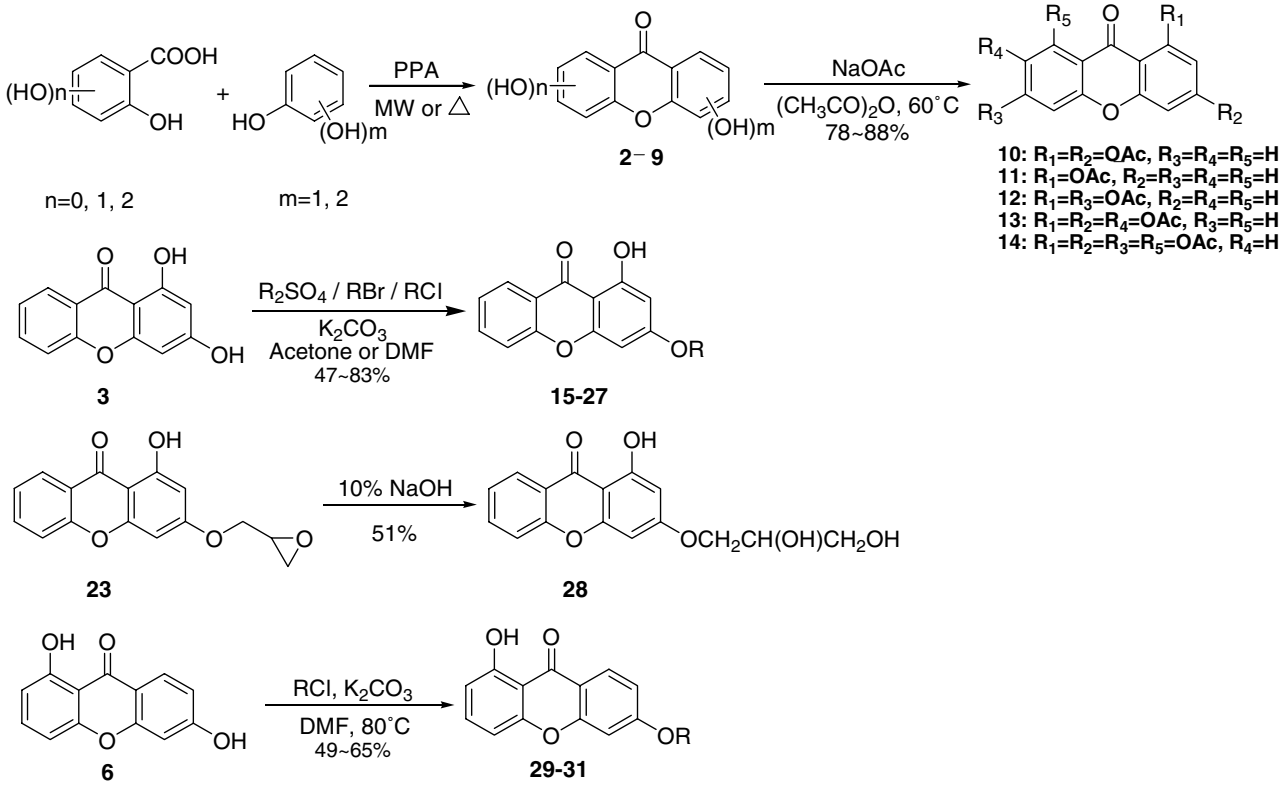
doi:10.1016/j.bmc.2006.04.014



Scheme 1. Synthetic route for xanthone derivatives **2**–**31**.

and other polyphenols, makes us aware that hydroxyxanthones and their appropriately modified derivatives may serve as new α-glucosidase inhibitors. With this rational in mind, we describe herein the synthesis and α-glucosidase inhibitory activities of a series of hydroxyxanthones **2**–**9** and their acetoxy and alkoxy derivatives **10**–**31** (Scheme 1 and Table 1), aiming at clarifying the structure–activity correlation involved in the inhibition process of α-glucosidase.

2. Results and discussion

2.1. Chemistry

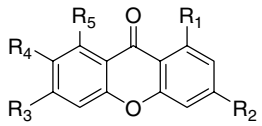
The synthetic route of hydroxylxanthones **2**–**9** and their acetoxy and alkoxy derivatives **10**–**31** is shown in Scheme 1. Compounds **2**–**9** were synthesized in 4–35% yield from the condensation of salicylic acid or hydroxyl salicylic acid with polyhydric phenols in the presence of polyphosphoric acid (PPA) as a condensing agent.[20] It should be noted that microwave irradiation can efficiently accelerate these reactions in slightly improved yields. Acetoxyxanthones **10**–**14** were obtained in good to high yields (78–88%) from the acetylation of their corresponding hydroxylxanthones by acetic anhydride in the presence of freshly fused sodium acetate.[21,22] According to the protocols described in the literatures,[22–24] alkylation of **3** with dimethyl sulfate and alkyl halides in acetone or DMF afforded **15**–**27** in moderate to good yields (47–83%).[25] Similar procedures smoothly produced compounds **29**–**31**. Hydrolyzation of **23** in 10% aqueous NaOH afforded ring-opened compound **28** in 51% yield. All these xanthone derivatives were characterized by NMR, mass, IR, and elemental analyses (see Section 4) and are summarized in Table 1.

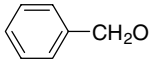
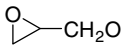
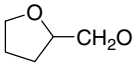
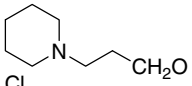
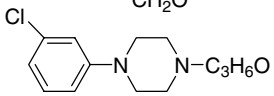
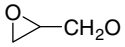
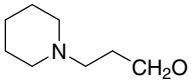
2.2. α-Glucosidase inhibitory activity

The α-glucosidase inhibitory activities of xanthone derivatives **2**–**31** were evaluated by using methods similar to those described in the literatures.[8,26–28] The obtained IC_{50} values, together with that of parent xanthone (**1**) for comparison, are shown in Table 1.

Several interesting structure–activity relationships can be extracted from the analyses of the IC_{50} values of hydroxylxanthones **2**–**9**. The first observation is that all the hydroxylxanthones exhibit much higher inhibitory activities than the parent xanthone. The parent xanthone **1** was inactive under our assay conditions. However hydroxyl derivatives **2**–**9** showed up to 21-fold higher inhibitory activities. This result is in agreement with the fact that hydroxyl xanthones always possess a variety of biological activities,[12–14,29] and suggests that modification of xanthones with hydroxyl groups is an efficient approach to increase their inhibitory activities. Second, inhibitory activities show significant dependence on the number of hydroxyl groups. For example, compound **8** bearing three hydroxyl groups has 12-fold stronger activity than compound **2** bearing one hydroxyl group. The data listed in Table 1 indicate that inhibitory activities increase in the order of tetrahydroxyl (i.e., compound **9**) ≈ trihydroxyl (i.e., compounds **6**–**8**) > bishydroxyl (i.e., compounds **3**–**5**) > monohydroxyl (i.e., compound **2**)

Table 1. Structures of compounds **1**–**31** and their α-glucosidase inhibitory activities (IC_{50}, μM)[a]



Compound	R_1	R_2	R_3	R_4	R_5	IC_{50}	Compound	R_1	$R_{3–5}$	R_2	IC_{50}
1	H	H	H	H	H	>200	**17**	OH	H	OC_4H_9	130.1
2	OH	H	H	H	H	177.4	**18**	OH	H	OC_5H_{11}	120.9
3	OH	OH	H	H	H	160.8	**19**	OH	H	OC_7H_{15}	113.8
4	OH	H	H	H	OH	91.5	**20**	OH	H	OC_8H_{17}	123.7
5	OH	H	OH	H	H	131.4	**21**	OH	H	$OC_{10}H_{21}$	115.6
6	OH	OH	H	H	OH	81.8	**22**	OH	H		98.2
7	OH	OH	OH	H	H	41.5	**23**	OH	H		66.6
8	OH	OH	H	OH	H	14.7	**24**	OH	H		53.0
9	OH	OH	OH	H	OH	17.1	**25**	OH	H		115.4
10	OAc	OAc	H	H	H	31.9	**26**	OH	H		61.8
11	OAc	H	H	H	H	>200	**27**	OH	H	OCH_2CH_2OH	>200
12	OAc	H	OAc	H	H	138.9	**28**	OH	H	$OCH_2CH(OH)CH_2OH$	>200
13	OAc	OAc	H	OAc	H	46.5	Compound	R_1	$R_{2,4–5}$	R_3	IC_{50}
14	OAc	OAc	OAc	H	OAc	49.7	**29**	OH	H		63.5
15	OH	OCH_3	H	H	H	172.9	**30**	OH	H		132.7
16	OH	OC_2H_5	H	H	H	110.8	**31**	OH	H	OCH_2CH_2OH	>200

[a] Determined against yeast α-glucosidase in 50 mM phosphate buffer (pH 6.8) at 37 °C. A classical α-glucosidase inhibitor, 1-deoxynojirimycin,[5] was adopted as a positive control with an IC_{50} value of 26.4 μM. The experiments were performed in triplicate and repeated at least three times, and the mean values were taken.

derivatives, suggesting that the presence of more phenolic hydroxyl groups gives favorable effect on α-glucosidase and that three and more hydroxyl groups are necessary to achieve significant inhibitory activities. Compounds **8** and **9** became slightly more active than 1-deoxynojirimycin. Third, the position of hydroxyl groups has obvious effect on the inhibitory activities of trihydroxyxanthones. Hydroxyl group at C7 (i.e., compound **8**) was more favorable to the activity than that at C6 (i.e., compound **7**), which in turn was more favorable than that at C8 (i.e., compound **6**). However, bishydroxylxanthones **3**–**5** show comparable activities.

It is reported that acetylation of phenolic compounds has some impact on their biological activities.[30,31] To test this possibility, we prepared acetoxyxanthones **10**–**14** from their corresponding hydroxylxanthones and evaluated their inhibitory activities. It can be seen that compound **10** exhibits at least 5-fold higher activity than **3**, however, compounds **11**–**14** show much lower activities than their corresponding hydroxylxanthones. This result indicated that the introduction of acetoxy groups was not crucial for the improvement of the inhibitory activities of xanthones.

Since acetylation of compound **3** led to an obvious increase in the activity, it will be interesting to investigate the effect of other groups as side chain. To achieve this goal, a series of various alkoxy groups were introduced to the C3-position of **3** to afford compounds **15**–**28** (Table 1). These substituents included straight alkyl, hydroxyalkyl, and heterocyclic groups, which are frequently used in drug design. It can be seen that the introduction of straight alkoxy chains, that is, compounds **16**–**21** resulted in a slight increase in the activities, but compound **15** having a methoxy group was an exception. However, compounds **15**–**21** exhibited comparable IC_{50} values, suggesting that the introduction of straight alkoxy groups at C3 was not essential for the increase of inhibitory activities. That compounds **27** and **28** bearing hydroxyl groups at the side chains showed extremely weak inhibitory activities, suggesting that hydroxyl groups on the parent xanthone backbones were more potent in the improvement of inhibitory

activities than those at the side chain (vide supra). Additionally, the derivatives having heterocyclic groups and benzyl group at the C3 position, that is, compounds **22**–**26** showed enhanced inhibitory activities. It is noteworthy that the compound **23** having oxirane ring was more active than its ring-opened form **28**. For comparison, the introduction of heterocyclic group and hydroxy-containing side chain onto C6 position was carried out, leading to compounds **29**–**31**. Their IC_{50} values were comparable to those of **23**, **25**, and **27**, respectively, which revealed that the attaching of similar side chains has comparable influence on the activities (vide supra).

3. Conclusions

A series of hydroxylxanthones and their acetoxy and alkoxy derivatives have been successfully synthesized in moderate to high yields. The results revealed that these xanthone derivatives were capable of inhibiting α-glucosidase with moderate to good activities, indicating that structural modification of xanthones is a practical approach to increase their inhibitory activities. Among all the derivatives, polyhydroxylxanthones show the highest activities, and thus may be exploitable as potentially potent α-glucosidase inhibitors. Further efforts aiming at developing potent α-glucosidase inhibitors based on appropriately modified polyhydroxylxanthones are continuing in our laboratories, which will be reported in due course.

4. Experimental

NMR spectra were recorded on a Varian INOVA 500 MB or Mercury – Plus 300 NMR spectrometer in either $CDCl_3$ or CD_3COCD_3 and tetramethylsilane was used as an internal standard. Mass spectra were measured on a Bruker REFLEX III ionization time-of-flight mass spectrometer or on a Shimadzu LCMS-2010A liquid chromatograph mass spectrometer. IR spectra were obtained on a Bruker EQUINOX55 Fourier transformation infrared spectrometer. Elemental analyses were carried out on an Elementar Vario EL series elemental analyzer. Melting points were determined on a WRS-1B digital melting point apparatus and are uncorrected. UV spectra were recorded on a Shimadzu UV-3150 scanning spectrophotometer.

p-Nitrophenyl (PNP) glycoside and α-glucosidase (from Baker's yeast) used in this study were purchased from Sigma (St. Louis, MO, USA). Xanthone (**1**) was purchased from Sigma–Aldrich (Sintra, Portugal). All other reagents were of analytical quality and used upon received. Microwave reactions were carried out in a CEM Discover 300W focused microwave reactor.

4.1. Synthesis of hydroxylxanthones 2–9

General procedures: a mixture of salicylic acid or polyhydric salicylic acid (0.5 mmol), polyhydric phenols (0.5 mmol), and polyphosphoric acid (3–5 mL) was irradiated at 80–140 °C in a sealed tube for 2–5 min or heated at 80–140 °C in an oil bath for 4 h. The reaction mixture was cooled and poured over crushed ice and then the resulting mixture was extracted with ethyl acetate (15 mL). The extract was washed with saturated $NaHCO_3$ (30 mL), dried over Na_2SO_4, and evaporated under reduce pressure to give **2**–**9** as yellow solids.

4.1.1. 1-Hydroxyxanthone (2).[20,32] Yield 29% from salicylic acid and resorcinol. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 12.64 (s, 1H), 8.28 (dd, J = 8.0, 2.0 Hz, 1H), 7.76–7.73 (m, 1H), 7.60 (t, J = 8.0 Hz, 1H), 7.47 (d, J = 8.0 Hz, 1H), 7.41–7.38 (m, 1H), 6.93 (d, J = 8.0 Hz, 1H), 6.80 (d, J = 8.0 Hz, 1H).

4.1.2. 1,3-Dihydroxyxanthone (3).[20,32] Yield 35% from salicylic acid and phloroglucinol. ^{1}H NMR (500 MHz, d_6-acetone) δ: 12.92 (s, 1H), 9.89 (br, 1H), 8.22–8.20 (m, 1H), 7.87–7.83 (m, 1H), 7.56–7.53 (m, 1H), 7.49–7.45 (m, 1H), 6.45 (d, J = 2.5 Hz, 1H), 6.28 (d, J = 2.5 Hz, 1H).

4.1.3. 1,8-Dihydroxyxanthone (4)[33] **and 1,6-dihydroxyxanthone (5).**[34] Yield 4% and 19%, respectively, simultaneously obtained from 2,6-dihydroxybenzoic acid and resorcinol. Compound **4** has ^{1}H NMR (300 MHz, d_6-acetone) δ: 11.74 (s, 2H), 7.78 (t, J = 8.4 Hz, 2H), 7.05 (d, J = 8.1 Hz, 2H), 6.84 (d, J = 8.1 Hz, 2H). Compound **5** has ^{1}H NMR (300 MHz, d_6-acetone) δ: 12.86 (s, 1H), 9.89 (br, 1H), 8.12 (d, J = 8.4 Hz, 1H), 7.66 (t, J = 8.1, 8.4 Hz, 1H), 7.01 (dd, J = 2.7, 9.0 Hz, 1H), 6.96 (d, J = 9.0 Hz, 1H), 6.93 (d, J = 2.7 Hz, 1H), 6.76 (d, J = 8.1 Hz, 1H).

4.1.4. 1,3,8-Trihydroxyxanthone (6).[22] Yield 31% from 2,6-dihydroxybenzoic acid and phloroglucinol. ^{1}H NMR (300 MHz, d_6-acetone) δ: 11.86 (s, 1H), 11.83 (s, 1H), 9.93 (br, 1H), 7.68 (t, J = 8.4 Hz, 1H), 6.94 (dd, J = 8.4, 1.5 Hz, 1H), 6.77 (dd, J = 8.4, 1.5 Hz, 1H), 6.44 (d, J = 1.8 Hz, 1H), 6.29 (d, J = 1.8 Hz, 1H).

4.1.5. 1,3,6-Trihydroxyxanthone (7).[34] Yield 25% from 2,4-dihydroxybenzoic acid and phloroglucinol. ^{1}H NMR (300 MHz, d_6-acetone) δ: 13.09 (s, 1H), 9.74 (br, 2H), 8.05 (d, J = 8.4 Hz, 1H), 6.96 (dd, J = 8.4, 2.1 Hz, 1H), 6.87 (d, J = 2.1 Hz, 1H), 6.39 (d, J = 2.1 Hz, 1H), 6.24 (d, J = 2.1 Hz, 1H).

4.1.6. 1,3,7-Trihydroxyxanthone (8).[34] Yield 21% from 2,5-dihydroxybenzoic acid and phloroglucinol. ^{1}H NMR (300 MHz, d_6-acetone) δ: 12.96 (s, 1H), 9.64 (br, 1H), 8.93 (br, 1H), 7.57 (d, J = 2.7 Hz, 1H), 7.44 (d, J = 8.7 Hz, 1H), 7.35 (dd, J = 8.7, 2.7 Hz, 1H), 6.41 (d, J = 2.7 Hz, 1H), 6.26 (d, J = 2.7 Hz, 1H).

4.1.7. 1,3,6,8-Tetrahydroxyxanthone (9).[35] Yield 17% as a white solid from 2,4,6-trihydroxybenzoic acid and phloroglucinol. ^{1}H NMR (300 MHz, d_6-acetone) δ: 11.96 (s, 2H), 9.89 (br, 2H), 6.38 (d, J = 2.4 Hz, 2H), 6.25(d, J = 2.4 Hz, 2H).

4.2. Synthesis of acetoxyxanthones 10–14

General procedures: to a solution of hydroxylxanthone (0.2 mmol) in acetic anhydride (5–8 mL) was added

freshly fused sodium acetate (0.25–0.9 mmol). The mixture was stirred at 60 °C for 3–5 h. Solvent was evaporated under reduced pressure. The residue was partitioned between water (30 mL) and $CHCl_3$ (15 mL). The organic layer was separated. Flash column chromatography on a silica gel column (petroleum ether/acetone, 8:1) afforded **10**–**14** as white solids.

4.2.1. 1,3-Diacetoxyxanthone (10).[32] Yield 88% from **3**. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.23 (dd, J = 8.1, 1.8 Hz, 1H), 7.73–7.66 (m, 1H), 7.43 (d, J = 8.7 Hz, 1H), 7.39–7.33 (m, 1H) 7.26 (d, J = 2.4 Hz, 1H), 6.83 (d, J = 2.4 Hz, 1H), 2.49 (s, 3H), 2.36 (s, 3H).

4.2.2. 1-Acetoxyxanthone (11).[32] Yield 82% from **2**. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.22 (dd, J = 8.1, 1.8 Hz, 1H), 7.72–7.64 (m, 2H), 7.44 (d, J = 7.8 Hz, 1H), 7.39 (dd, J = 8.1, 0.9 Hz, 1H), 7.36–7.30 (m, 1H), 6.98 (dd, J = 8.1, 0.9 Hz, 1H), 2.49 (s, 3H).

4.2.3. 1,6-Diacetoxyxanthone (12).[36] Yield 85% from **5**. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.24 (d, J = 8.7 Hz, 1H), 7.67 (t, J = 8.1 Hz, 1H), 7.38 (d, J = 8.1 Hz, 1H), 7.25 (d, J = 2.1 Hz, 1H), 7.08 (dd, J = 8.7, 2.1 Hz, 1H), 6.78 (d, J = 8.1 Hz, 1H), 2.48 (s, 3H), 2.35 (s, 3H).

4.2.4. 1,3,7-Triacetoxyxanthone (13).[37] Yield 78% from **8**. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.92 (dd, J = 2.1, 0.9 Hz, 1H), 7.48–7.44 (m, 2H), 7.27 (d, J = 2.4 Hz, 1H), 6.48 (d, J = 2.4 Hz, 1H), 2.48 (s, 3H), 2.36 (s, 3H), 2.34 (s, 3H).

4.2.5. 1,3,6,8-Tetraacetoxyxanthone (14).[38] Yield 80% from **9**. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.20 (d, J = 2.1, 2H), 6.80 (d, J = 2.1 Hz, 2H), 2.43 (s, 6H), 2.35 (s, 6H).

4.3. Synthesis of alkoxyxanthones 15–22

To a solution of **3** (0.2 mmol) and dimethyl sulfate or haloalkane (0.3 mmol) in acetone (6–8 mL) was added K_2CO_3 (0.25 mmol). The mixture was refluxed under stirring for 2–4 h. After cooling, the mixture was filtered and the organic filtrate was concentrated. The crude product was purified by chromatography on a silica-gel column to afford **15**–**22** as yellow solids.

4.3.1. 1-Hydroxy-3-methoxyxanthone (15).[39] Yield 65%. ^{1}H NMR (500 MHz, d_4-methanol) δ: 8.20 (dd, J = 8.0, 1.0 Hz, 1H), 7.82–7.77 (m, 1H), 7.51 (dd, J = 8.0, 0.5 Hz, 1H), 7.42–7.41 (m, 1H), 6.54 (d, J = 2.5 Hz, 1H), 6.34 (d, J = 2.5 Hz, 1H), 3.91 (s, 3H).

4.3.2. 1-Hydroxy-3-ethoxyxanthone (16).[40] Yield 83%. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 12.85 (s, 1H), 8.25 (dd, J = 8.0, 1.0 Hz, 1H), 7.73–7.69 (m, 1H), 7.43 (dd, J = 8.0, 0.5 Hz, 1H), 7.39–7.35 (m, 1H), 6.42 (d, J = 2.5 Hz, 1H), 6.34 (d, J = 2.5 Hz, 1H), 4.13 (q, J = 7.0 Hz, 2H), 1.46 (t, J = 7.0 Hz, 3H).

4.3.3. 1-Hydroxy-3-butoxyxanthone (17). Yield 78%. Mp 118–120 °C; IR (KBr): 3423, 3071, 2927, 2871, 1940, 1833, 1660, 1609, 1466, 1297, 1162, 1079, 823, 758, 609 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 12.86 (s, 1H), 8.21 (dd, J = 8.0, 1.0 Hz, 1H), 7.88–7.84 (m, 1H), 7.55 (dd, J = 8.0, 0.5 Hz, 1H), 7.49–7.46 (m, 1H), 6.54 (d, J = 2.5 Hz, 1H), 6.34 (d, J = 2.5 Hz, 1H), 4.18 (t, J = 6.5 Hz, 2H), 1.84–1.78 (m, 2H), 1.57–1.49 (m, 2H), 1.00 (t, J = 6.5 Hz, 3H); FAB-MS m/z: 285 ([M+H]$^+$); Anal. Calcd for $C_{17}H_{16}O_4$: C, 71.82; H, 5.67. Found: C, 72.03; H, 5.69.

4.3.4. 1-Hydroxy-3-pentyloxyxanthone (18). Yield 71%. Mp 113–116 °C; IR (KBr): 3450, 3090, 3062, 2952, 2862, 1940, 1832, 1669, 1604, 1567, 1468, 1296, 1175, 1075, 821, 758 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 12.83 (s, 1H), 8.24 (d, J = 7.8 Hz, 1H), 7.70 (t, J = 7.8 Hz, 1H), 7.43–7.34 (m, 2H), 6.42 (s, 1H), 6.34 (s, 1H), 4.05 (t, J = 7.2 Hz, 2H), 1.88–1.79 (m, 2H), 1.50–1.27 (m, 4H), 0.92 (t, J = 7.2 Hz, 3H); ESI-MS m/z: 299 ([M+H]$^+$); Anal. Calcd for $C_{18}H_{18}O_4$: C, 72.47; H, 6.08. Found: C, 72.58; H, 6.28.

4.3.5. 1-Hydroxy-3-heptyloxyxanthone (19). Yield 79%. Mp 111–113 °C; IR (KBr): 3450, 3090, 3062, 2966, 2855, 1939, 1831, 1667, 1604, 1567, 1467, 1208, 1075, 821, 757 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 12.82 (s, 1H), 8.24 (d, J = 7.8 Hz, 1H), 7.70 (t, J = 7.8 Hz, 1H), 7.42–7.35 (m, 2H), 6.42 (s, 1H), 6.34 (s, 1H), 4.05 (t, J = 6.6 Hz, 2H), 1.89–1.79 (m, 2H), 1.52–1.27 (m, 8H), 0.92 (t, J = 6.6 Hz, 3H); ESI-MS m/z: 327 [M+H]$^+$; Anal. Calcd for $C_{20}H_{22}O_4$: C, 73.60; H, 6.79. Found: C, 73.88; H, 6.98.

4.3.6. 1-Hydroxy-3-octyloxyxanthone (20).[41] Yield 83% ^{1}H NMR (300 MHz, $CDCl_3$) δ: 12.83 (s, 1H), 8.24 (dd, J = 7.8, 1.2 Hz, 1H), 7.73–7.67 (m, 1H), 7.43–7.34 (m, 2H), 6.42 (d, J = 1.8 Hz, 1H), 6.34 (d, J = 1.8 Hz, 1H), 4.05 (t, J = 6.9 Hz, 2H), 1.88–1.79 (m, 2H), 1.56–1.26 (m, 10H), 0.91 (t, J = 6.6 Hz, 3H).

4.3.7. 1-Hydroxy-3-decyloxyxanthone (21). Yield 69%. Mp 124–126 °C; IR (KBr): 3422, 3063, 2922, 2854, 1937, 1829, 1660, 1604, 1568, 1469, 1327,1292, 1167, 1078, 821, 793, 671 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 12.83 (s, 1H), 8.24 (d, J = 8.1 Hz, 1H), 7.70 (t, J = 8.1 Hz, 1H), 7.44–7.34 (m, 2H), 6.42 (s, 1H), 6.35 (s, 1H), 4.05 (t, J = 6.6 Hz, 2H), 1.86–1.77 (m, 2H), 1.58–1.29 (m, 14H), 0.90 (t, J = 6.3 Hz, 3H); FAB-MS m/z: 369 ([M+H]$^+$); Anal. Calcd for $C_{23}H_{28}O_4$: C, 74.97; H, 7.66. Found: C, 74.75; H, 7.81.

4.3.8. 1-Hydroxy-3-benzyloxyxanthone (22). Yield 83%. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 12.85 (s, 1H), 8.26 (dd, J = 8.0, 1.5 Hz, 1H), 7.78–7.69 (m, 1H), 7.46–7.34 (m, 7H), 6.51 (d, J = 2.5 Hz, 1H), 6.44 (d, J = 2.5 Hz, 1H), 5.16 (s, 2H).

4.4. Synthesis of alkoxyxanthones 23–26 and 29–31

To a solution of **3** or **5** (0.2 mmol) and haloalkane (0.3 mmol) in DMF (6–8 mL) was added K_2CO_3 (0.25 mmol). The mixture was stirred at 60–80 °C for 4–8 h. Solvent was evaporated under reduced pressure. The residue was treated with 1 N HCl (30 mL) and extracted with ethyl acetate (15 mL). The organic layer

was washed with water (30 mL) and concentrated. Purification by chromatography on a silica-gel column (petroleum ether/EtOAc, 12:1) afforded **23**–**27** and **29**–**31** as yellow solids.

4.4.1. 1-Hydroxy-3-(2-oxiranylmethoxy)xanthone (23).[42] Yield 51% from **3** and 2-(chloromethyl)oxirane. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 12.86 (s, 1H), 8.26 (dd, J = 8.0, 1.5 Hz, 1H), 7.74–7.70 (m, 1H), 7.44 (d, J = 8.0 Hz, 1H), 7.40–7.36 (m, 1H), 6.47 (d, J = 2.0 Hz, 1H), 6.37 (d, J = 2.0 Hz, 1H), 4.34 (dd, J = 11.0, 3.0 Hz, 1H), 4.03 (q, J = 5.5 Hz, 1H), 3.41–3.37 (m, 1H), 2.94 (dd, J = 4.5, 4.0 Hz, 1H), 2.78 (q, J = 2.5 Hz, 1H).

4.4.2. 1-Hydroxy-3-((tetrahydrofuran-2-yl)methoxy)xanthone (24). Yield 48% from **3** and 2-(chloromethyl)-tetrahydrofuran. Mp 158–160 °C; IR (KBr): 3426, 3070, 2949, 2879, 1658, 1567, 1464, 1365, 1296, 1220, 1161,1080, 926, 824, 759, 606 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 12.83 (s, 1H), 8.23 (dd, J = 7.5, 1.8 Hz, 1H), 7.73–7.66 (m, 1H), 7.43–7.33 (m, 2H), 6.45 (d, J = 2.4 Hz, 1H), 6.36 (d, J = 2.4 Hz, 1H), 4.35–4.27 (m, 1H), 4.16–4.06 (m, 2H), 3.97–3.92 (m, 1H), 3.89–3.82 (m, 1H), 2.21–2.06 (m, 1H), 2.01–1.93 (m, 2H), 1.84–1.75 (m, 1H); ESI-MS m/z: 313 ([M+H]$^+$); Anal. Calcd for $C_{18}H_{16}O_5$: C, 69.22; H, 5.16. Found: C, 69.21; H, 5.16.

4.4.3. 1-Hydroxy-3-(2-(1-piperidinyl)ethoxy)xanthone (25). Yield 68% from **3** and 1-(2-chloroethyl)piperidine. Mp 114–116 °C; IR (KBr): 3450, 3092, 3064, 2930, 2834, 2790, 1964, 1821, 1659, 1605, 1466, 1317, 1172,1075, 829, 759 cm^{-1}; ^{1}H NMR (500 MHz, d_4-methanol) δ: 8.21 (dd, J = 8.0, 2.0 Hz, 1H), 7.82–7.78 (m, 1H), 7.52 (d, J = 8.0 Hz, 1H), 7.45–7.41 (m, 1H), 6.57 (d, J = 2.5 Hz, 1H), 6.38 (d, J = 2.5 Hz, 1H), 4.27 (t, J = 5.5 Hz, 2H), 2.88 (t, J = 5.5 Hz, 2H), 2.64 (br, 4H), 1.70–1.64 (m, 4H), 1.53–1.50 (m, 2H); FAB-MS m/z: 340 ([M+H]$^+$); Anal. Calcd for $C_{20}H_{21}NO_4$: C, 70.78; H, 6.24; N, 4.13. Found: C, 70.67; H, 6.38; N 4.05.

4.4.4. 1-Hydroxy-3-(3-(4-(3-chlorophenyl)piperazin-1-yl)propoxy)xanthone (26). Yield 50% from **3** and 1-(3-chlorophenyl)-4-(3-chloropropyl)piperazine. Mp 258–260 °C; IR (KBr): 3120, 3065, 2947, 2824, 2758, 1664, 1601, 1568, 1467, 1324, 1291, 1163, 1081, 950, 782, 760, 676 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 12.83 (s, 1H), 8.25 (dd, J = 8.1, 1.5 Hz, 1H), 7.74–7.67 (m, 1H), 7.44–7.34 (m, 2H), 7.16 (t, J = 8.1 Hz, 1H), 6.88 (t, J = 2.4 Hz, 1H), 6.83–6.77 (m, 2H), 6.46 (d, J = 2.4 Hz, 1H), 6.36 (d, J = 2.4 Hz, 1H), 4.17 (t, J = 6.3 Hz, 2H), 3.25 (t, J = 5.7 Hz, 4H), 2.70–2.59 (m, 6H), 2.12–2.03 (m, 2H); FAB-MS m/z: 465 ([M+H]$^+$); Anal. Calcd for $C_{26}H_{25}ClNO_5$: C, 67.17; H, 5.42; N, 6.03. Found: C, 66.94; H, 5.70; N, 5.88.

4.4.5. 1-Hydroxy-3-(2-hydroxyethoxy)xanthone (27). Yield 51% from **3** and 2-chloroethanol. Mp 147–149 °C; IR (KBr): 3350, 3071, 2941, 2874, 1728, 1603, 1450, 1378, 1230, 1048, 884, 802, 679, 614 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 12.86 (s, 1H), 8.24 (dd, J = 7.8, 1.5 Hz, 1H), 7.73–7.67 (m, 1H), 7.44–7.34 (m, 2H), 6.58 (d, J = 2.4 Hz, 1H), 6.38 (d, J = 2.4 Hz, 1H), 4.34 (t, J = 5.4 Hz, 2H), 3.95 (t, J = 5.4 Hz, 2 H); ESI-MS m/z: 273 ([M+H]$^+$); Anal. Calcd for $C_{15}H_{12}O_5$: C, 66.17; H, 4.44. Found: C, 66.35; H, 4.42.

4.4.6. 1-Hydroxy-3-(2,3-dihydroxypropoxy)xanthone (28). A mixture of **23** (28.4 mg, 0.1 mmol) and 10% NaOH (10 mL) was heated on an oil bath until the solid was dissolved. The mixture was acidified with 1 N hydrochloric acid and extracted with ethyl acetate. Evaporation of the solvent and flash column chromatography (petroleum ether/EtOAc, 6:1) yielded **28** (15.4 mg, 51%) as a yellow solid. Mp 161–162 °C; IR (KBr): 3342, 3065, 2926, 1660, 1568, 1466, 1324, 1172, 1034, 822, 755, 671 cm^{-1}; ^{1}H NMR (500 MHz, d_6-acetone) δ: 12.88 (s, 1H), 8.23–8.21 (m, 1H), 7.89–7.85 (m, 1H), 7.58–7.56 (m, 1H), 7.51–7.47 (m, 1H), 6.60 (d, J = 2.5 Hz, 1H), 6.38 (d, J = 2.5 Hz, 1H), 4.28 (dd, J = 10.0, 4.0 Hz, 1H), 4.24 (d, J = 5.5 Hz, 1H), 4.07–4.02 (m, 1H), 3.86 (t, J = 4.0 Hz, 2H); FAB-MS m/z: 303 ([M+H]$^+$); Anal. Calcd for $C_{16}H_{14}O_6$: C, 63.57; H, 4.67. Found: C, 63.85; H, 4.57.

4.4.7. 1-Hydroxy-6-(oxiran-2-ylmethoxy)xanthone (29)[42]. Yield 55% from **6** and 2-(chloromethyl)oxirane. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 12.75 (s, 1H), 8.13 (d, J = 8.7 Hz, 1H), 7.52 (t, J = 8.7 Hz, 1H), 6.93 (dd, J = 8.7, 2.1 Hz, 1H), 6.88–6.84 (m, 2H), 6.76 (d, J = 7.8 Hz, 1H), 4.33 (dd, J = 11.0, 3.0 Hz, 1H), 4.13 (q, J = 5.5 Hz, 1H), 3.45–3.36 (m, 1H), 2.96 (dd, J = 4.5, 4.0 Hz, 1H), 2.76 (q, J = 2.5 Hz, 1H).

4.4.8. 1-Hydroxy-6-(2-(1-piperidinyl)ethoxy)xanthone (30). Yield 64% from **6** and 1-(2-chloroethyl)piperidine. Mp 110–112 °C; IR (KBr): 3391, 3074, 2966, 2850, 2790, 1916, 1647, 1608, 1574, 1448, 1379, 1262, 1231, 1105, 1053, 800, 763, 677 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 12.75 (s, 1H), 8.13 (d, J = 8.7 Hz, 1H), 7.52 (t, J = 8.7 Hz, 1H), 6.93 (dd, J = 8.7, 2.1 Hz, 1H), 6.88–6.84 (m, 2H), 6.76 (d, J = 7.8 Hz, 1H), 4.22 (t, J = 6.0 Hz, 2H), 2.84 (t, J = 6.0 Hz, 2H), 2.54 (t, J = 5.4 Hz, 4H), 1.67–1.59 (m, 4H), 1.50–1.45 (m, 2H); FAB-MS m/z: 340 ([M+H]$^+$); Anal. Calcd for $C_{20}H_{21}NO_4 \cdot 0.25H_2O$: C, 69.85; H, 6.30; N, 4.07. Found: C, 70.10; H, 6.34; N, 3.89.

4.4.9. 1-Hydroxy-6-(2-hydroxyethoxy)xanthone (31). Yield 49% from **6** and 2-chloroethanol. Mp 140–142 °C; IR (KBr): 3350, 3071, 2941, 2874, 1728, 1603, 1450, 1378, 1230, 1048, 884, 802, 679, 614 cm^{-1}; ^{1}H NMR (300 MHz, d_6-acetone) δ: 12.82 (s, 1H), 8.15 (d, J = 8.7 Hz, 1H), 7.68 (t, J = 8.7 Hz, 1H), 7.13–7.07 (m, 2H), 6.98 (d, J = 7.2 Hz, 1H), 6.78 (d, J = 8.7 Hz, 1H), 4.32 (t, J = 5.4 Hz, 2H), 3.97 (t, J = 5.4 Hz, 2H); ESI-MS m/z: 273 ([M+H]$^+$); Anal. Calcd for $C_{15}H_{12}O_5$: C, 66.17; H, 4.44. Found: C, 66.01; H, 4.53.

4.5. Enzyme assays

The inhibitory activities of all the xanthone derivatives were measured by using the methods similar to those described previously.[8,26–28] Typically, α-glucosidase activity was assayed in 50 mM phosphate buffer (pH 6.8)

containing 5% v/v dimethylsulfoxide and the PNP glycoside was used as a substrate. The inhibitors were pre-incubated with the enzyme at 37 °C for 0.5 h. The substrate was then added and the enzymatic reaction was carried out at 37 °C for 60 min. The reaction was monitored spectrophotometrically by measuring the absorbance at 400 nm. The assay was performed in triplicate with five different concentrations around the IC_{50} values that were roughly estimated in the first round of experiments, and the mean values were taken.

Acknowledgments

The project was partially supported by the Innovative Research Fund from the School of Chemistry and Chemical Engineering, Sun Yat-sen University.

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25. By the same method described for **15**–**22**, 1-hydroxy-3-tetradececyloxyxanthone (yield 66%) was obtained as a yellow solid. Mp 129–131; IR (KBr): 3455, 3063, 2920, 2852, 1660, 1603, 1567, 1469, 1326, 1292, 1167, 1077, 1033, 820, 757, 671 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 12.83 (s, 1H), 8.24 (d, J = 7.8 Hz, 1H), 7.71 (t, J = 7.8 Hz, 1H), 7.44–7.34 (m, 2H), 6.42 (d, J = 1.5 Hz, 1H), 6.34 (d, J = 1.5 Hz, 1H), 4.06 (t, J = 6.6 Hz, 2H), 1.88–1.78 (m, 2H), 1.56–1.28 (m, 22H), 0.90 (t, J = 6.9 Hz, 3H); FAB-MS m/z: 425 $[M+H]^+$; Anal. Calcd for $C_{23}H_{28}O_4$: C, 76.38; H, 8.55. Found: C, 76.42; H, 8.79. 1-hydroxy-3-hexadececyloxyxanthone (yield 63%) was obtained as a yellow solid. Mp 136–138 °C; IR (KBr): 4045, 3106, 2920, 2852, 1937, 1829, 1660, 1603, 1469, 1326, 1291, 1166, 1077, 1030, 792, 721, 671 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 12.83 (s, 1H), 8.24 (dd, J = 7.8, 1.5 Hz, 1H), 7.73–7.67 (m, 1H), 7.44–7.34 (m, 2H), 6.42 (d, J = 2.1 Hz, 1H), 6.34 (d, J = 2.1 Hz, 1H), 4.05 (t, J = 6.6 Hz, 2H), 1.88–1.78 (m, 2H), 1.56–1.27 (m, 26H), 0.89 (t, J = 7.2 Hz, 3H); ESI-MS m/z: 453 $[M+H]^+$; Anal. Calcd for $C_{29}H_{40}O_4$: C, 76.95; H, 8.91. Found: C, 76.80; H, 9.08. 1-hydroxy-3-tetradececyloxyxanthone (yield 71%) was obtained as a yellow solid. Mp 141–143 °C; IR (KBr): 4040, 3109, 2920, 2852, 1937, 1829, 1665, 1603, 1471, 1326, 1290, 1166, 1077, 1033, 792, 721, 671 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 12.83 (s, 1H), 8.24 (dd, J = 7.8, 1.5 Hz, 1H), 7.73–7.67 (m, 1H), 7.44–7.34 (m, 2H), 6.42 (d, J = 2.1 Hz, 1H), 6.34 (d, J = 2.1 Hz, 1H), 4.05 (t, J = 6.6 Hz, 2H), 1.88–1.78 (m, 2H), 1.56–1.27 (m, 30H), 0.89 (t, J = 7.2 Hz, 3H); FAB-MS m/z: 481 $[M+H]^+$; Anal. Calcd for $C_{31}H_{44}O_4$: C, 77.46; H, 9.23. Found: C, 77.39; H, 9.28. Their inhibitory activities were not determined for their insolubility under our assay conditions.
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