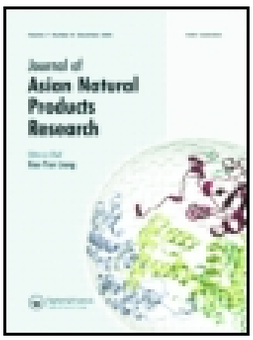

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Syntheses of xanthone derivatives and their bioactivity investigation

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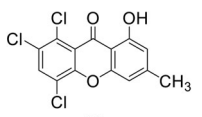
ABSTRACT

Sixteen substituted 1-hydroxy-3-methylxanthones were synthesized in one step. The yields ranged from 33 to 76%. Then, the antitumor, antioxidant, anti-tyrosinase, anti-pancreatic lipase, and antifungal activities of compounds **1**–**16** were evaluated. Compounds **10**–**12** and **14** inhibited tyrosinase and pancreatic lipase activity to a certain extent, respectively. Compound **16** exhibited obvious cytotoxicity against fifteen cancer cells, moderate antioxidant activity, and moderate inhibitory activity against *Candida albicans*. In particular, compound **16** exhibited strong inhibitory activity against A-549 and A549/Taxol cells. These results demonstrated that compounds **10**–**12**, **14**, and **16** are promising leads for further structural modification.



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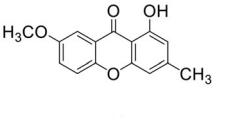

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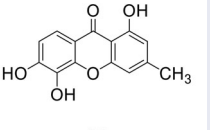

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Xanthone; antitumor activity; anti-tyrosinase; antioxidation; pancreatic lipase; antifungal activity

1. Introduction

Many natural xanthones are found in some plants and microorganisms, such as mangosteen. This class of compound exhibits various biological activities and the compounds are important organic synthesis intermediates. Some natural xanthones have been isolated from the root, fruit, and twigs of *Cratoxylum cochinchinense*, including cochinchinones E–G, 7-geranyloxy-1,3-dihydroxyxanthone, and celebixanthone [1]. 7-Geranyloxy-1,3-dihydroxyxanthone and celebixanthone both strongly inhibited MCF-7, HeLa, and HT-29 cells with IC_{50} values of 0.32–0.40 and 0.2 μg/ml,

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respectively [1]. Three prenylated xanthones, jacareubin, 1,3,5-trihydroxy-2-(3,3-dimethylallyl)-xanthone, and l,3,5,6-tetrahydroxy-2-(3,3-dimethylallyl)xanthone, were isolated from the tropical tree *Calophyllum brasiliensis*. They inhibited the mycelial growth of *Postia placenta* at 0.25 mg/ml [2]. Other natural xanthones have been isolated from *Garcinia mangostana* L. and been shown to have cancer chemopreventive and antioxidant action, including 8-hydroxycudraxanthone G, mangostingone, garcinones D–E, α-mangostin, and γ-mangostin. Moreover, α-mangostin inhibited 7,12-dimethylbenzo[α]anthracene-induced preneoplastic lesions in a mouse mammary organ culture assay with an IC_{50} of 1.0 μg/ml (2.44 μM) [3].

Some substituted 1,3-dihydroxyxanthones have been synthesized and shown to exhibit a variety of biological activities. 7-Chloro-1,3-dihydroxyxanthone exhibited obvious cytotoxicity against a hepatoma cell line (SMMC-7721) and a cervical carcinoma cell line (HeLa) with IC_{50} values of 6.14 and 13.73 μM, respectively; 1,3,5,6-tetrahydroxyxanthone exhibited strong cytotoxicity against a T-cell leukemia cell line (MT-4) with an IC_{50} of 9.05 μM and obvious antioxidant activity with 47.1% inhibition [4]. Both 1,3-dihydroxy-6-trifluoromethylxanthone and 7-(2,4-difluorophenyl)−1,3-dihydroxyxanthone exhibited obvious cytotoxicity against some tumor cell lines, including lung cancer A-549 cells, Taxol-resistant lung cancer A549 cells, and hepatoma SMMC-7721 cells, as well as showing anti-tyrosinase activity with inhibition of 11.3 and 19.3%, respectively [4,5].

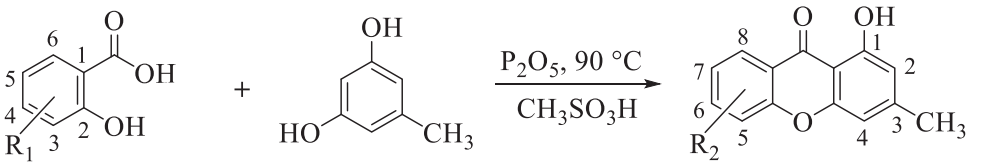
The activity is determined by the different substituents and their positions on the xanthone core. The hydroxyl group at the C3 position of 1,3-dihydroxyxanthone is replaced by a methyl group to obtain 1-hydroxy-3-methylxanthone. To further study the structure–activity relationship of xanthones, sixteen substituted 1-hydroxy-3-methylxanthones were designed and synthesized, then their antitumor, antioxidant, anti-tyrosinase, anti-pancreatic lipase, and antifungal activities were assessed.

2. Results and discussion

2.1. Synthesis

Compounds **1–16** were synthesized in Eaton's reagent in one step according to a previously reported method (Schemes 1) [4]. Owing to the formation of an intermolecular hydrogen bond, a substituted salicylic acid was substituted at the C4 position of 3,5-dihydroxytoluene, followed by dihydroxy dehydration and cyclization to give a substituted 3-methyl-1-hydroxyxanthone. These xanthones contain a hydroxyl group with a chemical shift of approximately 12.0 ppm, indicating that the hydroxyl group is close to the electron-withdrawing carbonyl group. Therefore, it must be at the C1 position on the xanthone, which strongly proves the above selective substitution.

Theoretically, the product of the reaction of 3,5-diiodosalicylic acid with 3,5-dihydroxytoluene is 1-hydroxy-5,7-diiodo-3-methylxanthone. However, the two iodines in this predicted product were replaced by the hydrogen of methanesulfonic acid to give 1-hydroxy-3-methylxanthone (**12**). Theoretically, 3-hydroxysalicylic acid reacts with 3,5-dihydroxytoluene to give 1,5-dihydroxy-3-methylxanthone. However, the hydrogen of the hydroxyl group at the C5 position of this product was substituted by the methyl group of methanesulfonic acid, providing 1-hydroxy-5-methoxy-3-



1. R_1: 3-F, R_2: 5-F
2. R_1: 4-F, R_2: 6-F
3. R_1: 5-F, R_2: 7-F
4. R_1: 5-F, 6-F; R_2: 7-F, 8-F
5. R_1: 5-(2,4-difluorophenyl) R_2: 7-(2,4-difluorophenyl)
6. R_1: 4-CF_3, R_2: 6-CF_3
7. R_1: 3-Cl, R_2: 5-Cl
8. R_1: 4-Cl, R_2: 6-Cl
9. R_1: 5-Cl, R_2: 7-Cl
10. R_1: 3-Cl, 5-Cl, 6-Cl; R_2: 5-Cl, 7-Cl, 8-Cl
11. R_1: 3-Br, 5-Br; R_2: 5-Br, 7-Br
12. R_1: 3-I, 5-I; R_2: 5-H, 7-H
13. R_1: 3-OH, R_2: 5-OCH_3
14. R_1: 5-OH, R_2: 7-OCH_3
15. R_1: 6-OH, R_2: 8-OH
16. R_1: 3-OH, 4-OH; R_2: 5-OH, 6-OH

Scheme 1. Synthetic route of compounds **1-16**.

methylxanthone (**13**) as the product. 5-Hydroxysalicylic acid reacted with 3,5-dihydroxytoluene to give 1-hydroxy-7-methoxy-3-methylxanthone (**14**) for the same reason. 6-Hydroxysalicylic acid reacted with 3,5-dihydroxytoluene to give 1,8-dihydroxy-3-methylxanthone (**15**). Because the two phenolic hydroxyl groups of compound **15** and the adjacent carbonyl formed intramolecular hydrogen bonds, these two hydroxyl groups were not converted to methoxy groups.

2.2. Biological activity

2.2.1. Antitumor activity

The *in vitro* cytotoxic activity of compounds **1**–**15** was evaluated against five human cancer cell lines, including a promyelocytic leukemia cell line (HL-60), a lung cancer cell line (A-549), a hepatocarcinoma cell line (SMMC-7721), a breast cancer cell line (MCF-7), and a colon cancer cell line (SW480). The *in vitro* cytotoxic activity of compound **16** was evaluated against sixteen human cancer cell lines and two normal human cell lines, including hepatoma cell lines (SMMC-7721, HepG-2, Huh-7, SK-HEP-1, MHCC97H, and PLC/PRF/5), a normal liver cell line (L02), lung cancer cell lines (A-549, NCI-H460, NCI-H520, and SPC-A-1), a Taxol-resistant lung cancer cell line (A549/Taxol), a normal lung epithelial cell line (BEAS-2B), a leukemia cell line (HL-60), breast cancer cell lines (MCF-7 and MDA-MB-231), a colon cancer cell line (SW480), and a cervical carcinoma cell line (HeLa). Two anticancer drugs, cisplatin and Taxol, were co-assayed as the positive control. The results of compounds **1-15** are listed in Table 1, and the results of compound **16** are listed in Tables 1–3. The inhibition of the compound was greater than 50% and the IC_{50} value (concentration required to inhibit tumor cell proliferation by 50%) relative to the corresponding tumor cell line was determined subsequently. These results of IC_{50} values are listed in Tables 4–6.

Table 1. The inhibitory activities of compounds **1-16** at 40 μM against cancer cell lines.

	Cell inhibition (%)					
Compd	HL-60	A-549	SMMC-7721	MCF-7	SW480	HeLa
1	17.88 ± 0.87	15.20 ± 1.50	11.72 ± 0.61	27.53 ± 2.05	13.34 ± 0.42	–
2	14.32 ± 1.92	18.65 ± 0.84	16.39 ± 1.97	32.22 ± 1.52	14.15 ± 1.77	–
3	10.94 ± 2.72	11.75 ± 1.99	16.58 ± 1.07	16.41 ± 1.17	4.25 ± 2.61	–
4	3.73 ± 1.37	14.11 ± 1.16	10.43 ± 0.30	13.01 ± 3.46	1.76 ± 2.33	–
5	16.62 ± 1.44	18.38 ± 1.20	46.44 ± 1.09	24.00 ± 2.15	8.58 ± 1.14	–
6	9.79 ± 2.62	0.86 ± 2.24	−0.97 ± 3.03	−3.66 ± 1.26	8.60 ± 3.16	–
7	11.77 ± 1.66	19.98 ± 1.84	7.15 ± 0.36	17.69 ± 1.13	3.36 ± 4.36	–
8	7.77 ± 0.75	21.65 ± 3.47	8.41 ± 2.15	18.47 ± 3.35	4.06 ± 3.14	–
9	11.84 ± 2.59	−1.14 ± 1.47	12.35 ± 1.24	3.66 ± 0.12	8.34 ± 1.10	–
10	4.61 ± 1.03	9.65 ± 1.59	5.13 ± 1.76	8.61 ± 0.61	12.41 ± 3.24	–
11	7.92 ± 2.33	8.98 ± 2.25	5.42 ± 0.95	18.00 ± 1.17	10.72 ± 3.12	–
12	15.79 ± 3.32	11.35 ± 1.73	13.11 ± 3.32	13.20 ± 2.47	16.22 ± 1.97	–
13	12.18 ± 1.26	5.94 ± 0.13	25.25 ± 1.51	27.05 ± 0.38	2.40 ± 3.08	–
14	8.07 ± 0.87	9.88 ± 0.64	12.88 ± 2.87	11.00 ± 2.33	14.48 ± 2.58	–
15	16.81 ± 1.59	1.55 ± 0.52	10.69 ± 1.30	1.71 ± 2.92	9.37 ± 0.77	–
16	75.20 ± 0.22	85.15 ± 0.49	88.17 ± 0.50	86.53 ± 4.89	82.01 ± 0.26	75.54 ± 0.40

Note: "–" means not being determinated.

Table 2. The inhibitory activities of compound **16** at 40 μM against liver cell lines.

	Cell inhibition (%)					
Compd	HepG2	Huh-7	SK-HEP-1	MHCC97H	PLC/PRF/5	L02
16	68.16 ± 0.83	77.71 ± 0.69	56.95 ± 1.87	12.21 ± 1.27	54.18 ± 2.37	75.41 ± 0.83

Table 3. The inhibitory activities of compound **16** at 40 μM against cancer and normal lung epithelial cell lines.

	Cell inhibition (%)					
Compd	NCI-H460	NCI-H520	MDA-MB-231	SPC-A-1	A549/Taxol	BEAS-2B
16	59.89 ± 2.37	77.28 ± 0.55	59.08 ± 0.08	88.27 ± 0.38	86.03 ± 0.56	53.99 ± 2.22

Table 4. IC_{50} values of compound **16** against corresponding cancer cell lines.

	IC_{50} (μM)				
Compd	HL-60	A-549	SMMC-7721	MCF-7	SW480
16	14.98 ± 0.15	9.37 ± 0.52	14.22 ± 0.65	21.81 ± 1.61	17.20 ± 0.82
Cisplatin	3.22 ± 0.10	15.59 ± 0.26	10.66 ± 0.26	15.29 ± 1.11	15.45 ± 0.32
Taxol	<0.008	<0.008	0.81 ± 0.075	<0.008	<0.008

Table 5. IC_{50} values of compound **16** against cancer and normal liver cell lines.

	IC_{50} (μM)					
Compd	HepG2	Huh-7	SK-HEP-1	PLC/PRF/5	HeLa	L02
16	12.57 ± 0.11	21.39 ± 0.66	28.83 ± 1.82	34.16 ± 3.02	18.76 ± 0.17	19.63 ± 0.43
Cisplatin	2.80 ± 0.10	13.27 ± 0.38	8.60 ± 0.54	11.13 ± 0.13	4.97 ± 0.20	8.84 ± 0.20
Taxol	<0.008	0.080 ± 0.005	<0.008	<0.008	<0.008	<0.008

Compounds **1**–**15** inhibited the five tested cancer cells by less than 50%. Among them, compound **5** exhibited the strongest cytotoxicity against SMMC-7721 cells with 46.44%, inhibition. Compound **16** exhibited moderate-to-strong cytotoxicity against

Table 6. IC_{50} values of compound **16** against cancer and normal lung epithelial cell lines.

	IC_{50} (μM)					
Compd	NCI-H460	NCI-H520	MDA-MB-231	SPC-A-1	A549/Taxol	BEAS-2B
16	30.44 ± 1.89	15.09 ± 0.56	28.84 ± 0.28	14.12 ± 0.45	6.41 ± 0.51	31.15 ± 2.61
Cisplatin	17.35 ± 0.36	14.41 ± 0.89	26.68 ± 1.38	11.86 ± 0.66	11.77 ± 0.92	>40
Taxol	<0.008	<0.008	<0.008	<0.008	0.40 ± 0.03	>5

Table 7. Screening result of DPPH radical scavenging activity of compound **16**.

Compd	Conc (μM)	Antioxidant (%)
Trolox	25	71.04 ± 1.05
16	50	62.28 ± 3.05

15 of the 16 tested cancer cell lines, including SMMC-7721, HepG-2, Huh-7, SK-HEP-1, PLC/PRF/5, A-549, NCI-H460, NCI-H520, SPC-A-1, A549/Taxol, HL-60, MCF-7, MDA-MB-231, SW480, and HeLa. Compound **16** inhibited the above cell lines by 52 to 89%, with IC_{50} values ranging from 5.90 to 37.18 μM. In particular, compound **16** exhibited strong cytotoxicity against A-549 and A549/Taxol cells with IC_{50} values of 9.37 and 6.41 μM (<10 μM), respectively. The IC_{50} values for cisplatin against A-549 and A549/Taxol cell lines were 15.59 and 11.77 μM, respectively. Thus, compound **16** was more cytotoxic against the two cancer cells than cisplatin. Compound **16** inhibited L02 and BEAS-2B cells by 75% and 54% with IC_{50} values of 19.63 and 31.15 μM, respectively. Compound **16** exhibited moderate cytotoxicity against both L02 and BEAS-2B cells. Thus, it could be considered for targeted administration to reduce its cytotoxicity against normal liver and lung cells.

Among the sixteen 3-methyl-1-hydroxyxanthones prepared in this work, only compound **16** contains two adjacent phenolic hydroxyl groups at the C5 and C6 positions. Therefore, this structural motif contributes to its superior and broad-spectrum antitumor activity.

2.2.2. DPPH radical scavenging activity

The antioxidant activity assay results are presented in Table 7. Compound **16** containing two ortho-hydroxyl groups exhibited the strongest antioxidant activity [4]. Therefore, only compound **16** was detected. Trolox was used as a positive control. Compound **16**, named 1,5,6-trihydroxy-3-methylxanthone, exhibited stronger antioxidant activity than the positive control with inhibition of approximately 62.3% versus approximately 47.1% for 1,3,5,6-tetrahydroxyxanthone [4]. Therefore, substituting the hydroxyl group at the C3 position of 1,3,5,6-tetrahydroxyxanthone for a methyl group greatly improved the antioxidant activity.

2.2.3. Anti-tyrosinase activity

The anti-tyrosinase activity assay results are presented in Table 8. All compounds were compared against kojic acid. Compounds **10–12** inhibited tyrosinase activity to a certain extent, with inhibition of 14.9, 11.4, and 11.2%, respectively. Compounds **1**, **3–6**, **9–13**, and **15** exhibited minimal anti-tyrosinase activity, whilst the other compounds did not present any anti-tyrosinase activity. Compound **10**, named 1,2,4-trichloro-8-hydroxy-6-methylxanthone, exhibited the best inhibitory activity of 14.9%, versus 22%

Table 8. Anti-tyrosinase activities of compounds **1-16**.

Compd	Conc (μM)	Inhibition (%)
kojic acid	35	51.45 ± 0.15
1	50	8.53 ± 3.85
2	50	−6.55 ± 2.51
3	50	9.09 ± 0.87
4	50	9.01 ± 0.33
5	100	7.68 ± 1.82
6	100	10.99 ± 4.68
7	50	−1.70 ± 1.09
8	50	−2.16 ± 0.87
9	100	5.66 ± 0.78
10	50	14.87 ± 0.55
11	50	11.40 ± 1.09
12	50	11.17 ± 0.33
13	50	9.71 ± 0.87
14	95	0.046 ± 1.43
15	100	9.15 ± 1.30
16	50	−6.09 ± 0.98

Table 9. Anti-pancreatic lipase activities of compounds **1-16**.

Compd	Conc (μM)	Inhibition (%)
Orlistat	0.005	76.84 ± 0.49
1	50	13.40 ± 1.26
2	50	16.59 ± 0.44
3	50	0.81 ± 2.09
4	50	9.83 ± 0.97
5	100	−5.29 ± 0.23
6	100	−19.02 ± 0.17
7	50	−9.24 ± 0.19
8	50	−0.34 ± 1.48
9	100	−13.30 ± 2.68
10	50	15.87 ± 2.91
11	50	1.02 ± 7.03
12	50	15.83 ± 2.47
13	50	3.11 ± 3.40
14	95	36.83 ± 1.14
15	100	−13.34 ± 0.91
16	50	12.95 ± 3.54

for 1,2,4-trichloro-6,8-dihydroxyxanthone [5]. The inhibitory activities of these two analogs were comparable in view of their different concentrations, indicating that trichlorine-substituted xanthones were useful for their anti-tyrosinase activity. The elucidated structure–anti-tyrosinase activity relationship of these compounds will be beneficial for structural modification.

2.2.4. Anti-pancreatic lipase activity

The anti-pancreatic lipase activity assay results are presented in Table 9. All compounds were compared with orlistat. Compound **14** inhibited pancreatic lipase activity by >35% whilst compounds **1–2**, **4**, **10**, **12**, and **16** also exhibited minimal anti-pancreatic lipase activity. However, the other compounds were inactive.

2.2.5. Antifungal activity

The antifungal activity assay results are presented in Table 10. Amphotericin B was used as a positive control. Amphotericin B completely inhibited *Candida albicans*

Table 10. Inhibitory activity of compound **16** against *Candida albicans*.

Compd	Conc (μg/ml)	Inhibition (%)
amphotericin B	0.25	100.15 ± 0.21
16	52	79.75 ± 2.23

whilst compound **16** presented 79.8% inhibition. It exhibited moderate inhibitory activity against *Candida albicans*.

3. Experimental

3.1. Chemistry

Melting points were determined on a micro-melting point apparatus and are uncorrected (Shanghai Precision Scientific Instrument Co., Ltd, Shanghai, China). IR spectra were recorded with KBr pellets (Bruker, Bremen, Germany). ^{1}H and ^{13}C NMR spectra were determined in acetone-d_6 at 500 MHz for ^{1}H and 125 MHz for ^{13}C (Bruker, Fällanden, Switzerland). Low-resolution mass spectra were recorded on an ABI mass spectrometer (American Applied Biosystems, Carlsbad, USA). High-resolution mass (HRMS) data were recorded via a positive or negative ion electron impact mass spectrometry using a time-of-flight analyzer (Bruker Daltonics Inc, Boston, USA). The chemical reagents purchased (Shanghai Aladdin Biochemical Technology Co., Ltd, Shanghai, China) were of the highest commercially available purity and were used directly.

3.2. General procedure for preparation of substituted 1-hydroxy-3-methylxanthones

A mixture of phosphorus pentoxide (0.36 g, 2.5 mmol) and methanesulfonic acid (10 ml) was heated at 110 °C until a clear solution was obtained. The temperature was then lowered to 90 °C and a mixture of 3,5-dihydroxytoluene (0.13 g, 1.0 mmol) and substituted salicylic acid (1.0 mmol) was added. Heating was then continued for several hours. The reaction progress was monitored by thin-layer chromatography (TLC) until the reaction was balanced, then the reaction mixture was poured into iced-water. The crude product was collected by filtration or extracted with ethyl acetate, washed with water, dried, and purified by medium pressure preparative chromatography with ethyl acetate/petroleum ether to afford the target xanthone.

3.2.1. 5-Fluoro-1-hydroxy-3-methyl-9H-xanthen-9-one (1)

Yellow solid; yield 51%; mp: 183–184 °C; IR (KBr) ν_{max} 720, 789, 843, 883, 1090, 1291, 1500, 1609, 1648, 2848, 2922, 3072, 3453 cm^{-1}; ^{1}H NMR (500 MHz, acetone-d_6) δ 2.46 (s, 3H, -CH_3), 6.70 (s, 1H, H-2), 6.95 (s, 1H, H-4), 7.47 (td, 1H, J = 4.5, 8.1 Hz, H-7), 7.75 (t, 1H, J = 8.1 Hz, H-6), 8.02 (d, 1H, J = 8.1 Hz, H-8), 12.41 (s, 1H, 1-OH); ^{13}C NMR (125 MHz, acetone-d_6) δ 22.4, 108.4, 112.5, 121.66, 121.69, 122.1, 122.2, 123.3, 124.8 and 124.8 (C-7, $^{3}J_{CF}$ = 6.8 Hz), 150.9, 152.6, 156.6, 162.5, 181.8; HRESIMS: *m/z* 243.0466 [M - H]$^{-}$ (calcd for $C_{14}H_8FO_3$, 243.0463).

3.2.2. 6-Fluoro-1-hydroxy-3-methyl-9H-xanthen-9-one (2)

Yellow solid; yield 56%; mp: 150–152 °C; IR (KBr) ν_{max} 666, 770, 787, 827, 844, 954, 1101, 1155, 1261, 1449, 1608, 1656, 2838, 2958, 3078, 3425 cm^{-1}; ^1H NMR (500 MHz, acetone-d_6) δ 2.44 (s, 3H, -CH_3), 6.66 (s, 1H, H-2), 6.85 (s, 1H, H-4), 7.30 (td, 1H, $^4J_{HH}$ = 2.3 Hz, $^3J_{HH}$ = 8.5 Hz, H-7), 7.38 (dd, 1H, $^4J_{HH}$ = 2.3 Hz, $^3J_{HF}$ = 9.7 Hz, H-5), 8.29 (dd, 1H, $^4J_{HF}$ = 6.5 Hz, $^3J_{HH}$ = 8.5 Hz, H-8), 12.46 (s, 1H, 1-OH); ^{13}C NMR (125 MHz, acetone-d_6) δ 22.4, 105.3, 105.5, 107.2, 108.2, 112.3, 113.6 and 113.8 (C-7, $^2J_{CF}$ = 23.3 Hz), 129.3, 129.4, 150.4, 157.2, 162.5, 166.7 and 168.8 (C-6, $^1J_{CF}$ = 252.8 Hz), 181.6; HRESIMS: *m/z* 243.0461 $[M - H]^-$ (calcd for $C_{14}H_8FO_3$, 243.0463).

3.2.3. 7-Fluoro-1-hydroxy-3-methyl-9H-xanthen-9-one (3)

Yellow solid; yield 58%; mp: 160–161 °C; IR (KBr) ν_{max} 547, 573, 782, 820, 1215, 1279, 1366, 1477, 1493, 1619, 1652, 2827, 2971, 3085, 3453 cm^{-1}; ^1H NMR (500 MHz, acetone-d_6) δ 2.43 (s, 3H, -CH_3), 6.64 (s, 1H, H-2), 6.84 (s, 1H, H-4), 7.65 (dd, 1H, $^4J_{HF}$ = 4.4 Hz, $^3J_{HH}$ = 9.2 Hz, H-5), 7.67-7.71 (m, 1H, H-6), 7.81 (dd, 1H, $^4J_{HH}$ = 3.1 Hz, $^3J_{HF}$ = 8.2 Hz, H-8), 12.34 (s, 1H, 1-OH); ^{13}C NMR (125 MHz, acetone-d_6) δ 22.4, 108.2, 110.7, 110.9, 112.0, 121.3 and 121.3 (C-5, $^3J_{CF}$ = 8.1 Hz), 122.1, 124.5, 124.7, 150.7, 157.0 and 158.6 (C-7, $^1J_{CF}$ = 196.5 Hz), 160.6, 162.3, 181.7; HRESIMS: *m/z* 243.0464 $[M - H]^-$ (calcd for $C_{14}H_8FO_3$, 243.0463).

3.2.4. 1,2-Difluoro-8-hydroxy-6-methyl-9H-xanthen-9-one (4)

Light yellow solid; yield 52%; mp: 205–207 °C; IR (KBr) ν_{max} 796, 836, 893, 1201, 1292, 1477, 1510, 1615, 1651, 3060, 3430 cm^{-1}; ^1H NMR (500 MHz, acetone-d_6) δ 2.45 (s, 3H, -CH_3), 6.68 (s, 1H, H-7), 6.88 (s, 1H, H-5), 7.66 (dd, 1H, $^4J_{HF}$ = 6.4 Hz, $^2J_{HH}$ = 10.2 Hz, H-4), 8.05 (t, 1H, J = 10.2 Hz, H-3), 12.28 (s, 1H, 8-OH); ^{13}C NMR (125 MHz, acetone-d_6) δ 22.4, 107.0, 108.1, 108.3, 112.3, 112.4, 113.5, 113.7, 147.4 and 149.4 (C-1, $^1J_{CF}$ = 245.5 Hz), 149.4 and 150.8 (C-2, $^1J_{CF}$ = 173.4 Hz), 153.9, 157.2, 162.3, 181.0; HRESIMS: *m/z* 261.0367 $[M - H]^-$ (calcd for $C_{14}H_7F_2O_3$, 261.0369).

3.2.5. 7-(2,4-Difluorophenyl)-1-hydroxy-3-methyl-9H-xanthen-9-one (5)

Yellow solid; yield 60%; mp: 210–212 °C; IR (KBr) ν_{max} 805, 829, 1144, 1207, 1255, 1279, 1480, 1611, 1656, 2974, 3058, 3080, 3431 cm^{-1}; ^1H NMR (500 MHz, acetone-d_6) δ 2.46 (s, 3H, -CH_3), 6.68 (s, 1H, H-2), 6.92 (s, 1H, H-4), 7.20-7.26 (m, 2H, H-3′, H-5′), 7.71-7.73 (m, 2H, H-5, H-6′), 8.07 (d, 1H, J = 8.7 Hz, H-6), 8.35 (s, 1H, H-8), 12.51 (s, 1H, 1-OH); ^{13}C NMR (125 MHz, acetone-d_6) δ 22.5, 105.1, 105.3 and 105.5 (C-3′, $^2J_{CF}$ = 26.5 Hz), 108.4, 112.1, 112.9 and 113.1 (C-5′, $^2J_{CF}$ = 21.5 Hz), 113.1, 119.4, 121.3, 126.3, 131.8, 132.9 and 132.9 (C-7, $^3J_{CF}$ = 4.4 Hz), 133.0, 137.3 and 137.3 (C-6′, $^3J_{CF}$ = 2.9 Hz), 150.6, 156.5, 157.1, 162.5, 164.5, 182.3; HRESIMS: *m/z* 337.0685 $[M - H]^-$ (calcd for $C_{20}H_{11}F_2O_3$, 337.0682).

3.2.6. 1-Hydroxy-3-methyl-6-(trifluoromethyl)-9H-xanthen-9-one (6)

Yellow solid; yield 62%; mp: 180–182 °C; IR (KBr) ν_{max} 799, 903, 928, 994, 1065, 1205, 1317, 1357, 1445, 1496, 1566, 1615, 1651, 2858, 2931, 3079, 3438 cm^{-1}; ^1H NMR (500 MHz, acetone-d_6) δ 2.46 (s, 3H, CH_3-), 6.70 (s, 1H, H-2), 6.91 (s, 1H, H-4), 7.78 (d, 1H, J = 8.3 Hz, H-7), 7.94 (s, 1H, H-5), 8.42 (d, 1H, J = 8.3 Hz, H-8),

12.29 (s, 1H, HO-1); ^{13}C NMR (125 MHz, acetone-d_6) δ 22.5, 107.8, 108.4, 108.5, 112.4 (C-5, C-8a), 116.6 (q, $^{3}J_{CF}$ = 4.1 Hz, C-7), 121.2 (q, $^{4}J_{CF}$ = 3.4 Hz, C-8), 123.9, 128.1, 151.2, 156.6, 157.1, 162.5, 181.7; HRESIMS: *m/z* 293.0430 [M - H]$^-$ (calcd for $C_{15}H_8F_3O_3$, 293.0431).

3.2.7. 5-Chloro-1-hydroxy-3-methyl-9H-xanthen-9-one (7)

Yellow solid; yield 71%; mp: 208–209 °C; IR (KBr) ν_{max} 724, 784, 805, 843, 945, 1083, 1213, 1284, 1484, 1602, 1655, 2839, 2920, 3069, 3433 cm^{-1}; ^{1}H NMR (500 MHz, acetone-d_6) δ 2.47 (s, 3H, -CH_3), 6.70 (s, 1H, H-2), 6.96 (s, 1H, H-4), 7.48 (t, 1H, J = 8.0 Hz, H-7), 7.99 (dd, 1H, J = 0.9, 8.0 Hz, H-6), 8.18 (dd, 1H, J = 0.9, 8.0 Hz, H-8), 12.37 (s, 1H, 1-OH); ^{13}C NMR (125 MHz, acetone-d_6) δ 22.0, 107.3, 108.5, 112.5, 119.0, 122.8, 125.31, 125.33, 136.6, 150.9, 152.5, 156.6, 162.5, 182.0; HRESIMS: *m/z* 259.0165 [M - H]$^-$ (calcd for $C_{14}H_8ClO_3$, 259.0167).

3.2.8. 6-Chloro-1-hydroxy-3-methyl-9H-xanthen-9-one (8)

Orange solid; yield 73%; mp: 165–167 °C; IR (KBr) ν_{max} 573, 665, 724, 795, 861, 926, 1078, 1206, 1280, 1368, 1435, 1600, 1652, 2853, 2919, 3071, 3440 cm^{-1}; ^{1}H NMR (500 MHz, acetone-d_6) δ 2.44 (s, 3H, -CH_3), 6.66 (s, 1H, H-2), 6.86 (s, 1H, H-4), 7.50 (dd, 1H, J = 1.9, 8.6 Hz, H-7), 7.66 (d, 1H, J = 1.9 Hz, H-5), 8.21 (d, 1H, J = 8.6 Hz, H-8), 12.40 (s, 1H, 1-OH); ^{13}C NMR (125 MHz, acetone-d_6) δ 22.4, 107.5, 108.3, 112.3, 118.7, 120.1, 125.8, 128.1, 141.9, 150.7, 156.9, 157.3, 162.5, 181.8; HRESIMS: *m/z* 259.0168 [M - H]$^-$ (calcd for $C_{14}H_8ClO_3$, 259.0167).

3.2.9. 7-Chloro-1-hydroxy-3-methyl-9H-xanthen-9-one (9)

Yellow solid; yield 76%; mp: 193–194 °C; IR (KBr) ν_{max} 536, 721, 813, 1081, 1207, 1279, 1367, 1468, 1623, 1650, 2850, 2925, 3064, 3433 cm^{-1}; ^{1}H NMR (500 MHz, acetone-d_6) δ 2.45 (s, 3H, CH_3-), 6.67 (s, 1H, H-2), 6.89 (s, 1H, H-4), 7.65 (d, 1H, J = 9.0 Hz, H-5), 7.88 (dd, 1H, J = 2.5, 9.0 Hz, H-6), 8.13 (d, 1H, J = 2.5 Hz, H-8), 12.32 (s, 1H, HO-1); ^{13}C NMR (125 MHz, acetone-d_6) δ 22.5, 107.4, 108.4, 112.2, 121.2, 122.4, 125.4, 130.1, 136.6, 150.9, 155.6, 157.0, 162.4, 181.4; HRESIMS: *m/z* 261.0311 [M + H]$^+$ (calcd for $C_{14}H_{10}ClO_3$, 261.0313).

3.2.10. 1,2,4-Trichloro-8-hydroxy-6-methyl-9H-xanthen-9-one (10)

Yellow solid; yield 66%; mp: 254–256 °C; IR (KBr) ν_{max} 739, 836, 1004, 1091, 1207, 1254, 1444, 1625, 1651, 2841, 2923, 3062, 3437 cm^{-1}; ^{1}H NMR (500 MHz, acetone-d_6) δ 2.41 (s, 3H, -CH_3), 6.72 (s, 1H, H-7), 6.95 (s, 1H, H-5), 8.44 (s, 1H, H-3), 12.19 (s, 1H, 8-OH); ^{13}C NMR (125 MHz, acetone-d_6) δ 21.9, 96.6, 99.8, 109.2, 112.1, 135.2 (C-1, C-9a), 150.0 (C-2, C-3), 164.7, 168.5, 173.7, 177.6, 195.0; HRESIMS: *m/z* 350.9349 [M + Na]$^+$ (calcd for $C_{14}H_7Cl_3NaO_3$, 350.9353).

3.2.11. 5,7-Dibromo-1-hydroxy-3-methyl-9H-xanthen-9-one (11)

Yellow solid; yield 53%; mp: 232–234 °C; IR (KBr) ν_{max} 534, 725, 803, 831, 1078, 1206, 1260, 1354, 1467, 1590, 1626, 1647, 2846, 2918, 3066, 3435 cm^{-1}; ^{1}H NMR (500 MHz, acetone-d_6) δ 2.42 (s, 3H, -CH_3), 6.73 (s, 1H, H-2), 6.99 (s, 1H, H-4), 8.19 (d, 1H, J = 2.4 Hz, H-8), 8.43 (d, 1H, J = 2.4 Hz, H-6), 12.04 (s, 1H, 1-OH); ^{13}C NMR

(125 MHz, acetone-d_6) δ 22.0, 106.1, 107.9, 111.8, 112.5, 116.4, 122.6, 127.1, 140.5, 150.3, 151.4, 157.3, 160.5, 179.5; HRESIMS: *m/z* 380.8771 [M - H]$^-$ (calcd for $C_{14}H_7Br_2O_3$, 380.8767).

3.2.12. 1-Hydroxy-3-methyl-9H-xanthen-9-one (12)

Yellow solid; yield 55%; mp: 127–130 °C; IR (KBr) ν_{max} 670, 760, 824, 924, 1080, 1205, 1290, 1377, 1482, 1611, 1656, 2852, 2922, 3048, 3428 cm^{-1}; ^{1}H NMR (500 MHz, acetone-d_6) δ 2.42 (s, 3H, -CH_3), 6.61 (d, 1H, J = 0.5 Hz, H-2), 6.81 (d, 1H, J = 0.5 Hz, H-4), 7.47 (t, 1H, J = 8.0 Hz, H-7), 7.54 (d, 1H, J = 8.0 Hz, H-5), 7.84-7.88 (m, 1H, H-6), 8.20 (dd, 1H, J = 1.7, 8.0 Hz, H-8), 12.54 (s, 1H, 1-OH); ^{13}C NMR (125 MHz, acetone-d_6) δ 21.6, 106.6, 107.4, 111.0, 117.9, 120.4, 124.3, 125.5, 135.9, 149.4, 156.1, 156.2, 161.7, 181.6; HRESIMS: *m/z* 227.0709 [M + H]$^+$ (calcd for $C_{14}H_{11}O_3$, 227.0703).

3.2.13. 1-Hydroxy-5-methoxy-3-methyl-9H-xanthen-9-one (13)

Yellowish solid; yield 64%; mp: 245–248 °C; IR (KBr) ν_{max} 523, 731, 810, 890, 970, 1088, 1166, 1274, 1364, 1492, 1609, 1648, 3013, 3428 cm^{-1}; ^{1}H NMR (500 MHz, acetone-d_6) δ 2.46 (s, 3H, -CH_3), 3.52 (s, 3H, -OCH_3), 6.71 (s, 1H, H-2), 7.05 (s, 1H, H-4), 7.55 (t, 1H, J = 8.0 Hz, H-7), 7.89 (dd, 1H, J = 1.4, 8.0 Hz, H-6), 8.20 (dd, 1H, J = 1.4, 8.0 Hz, H-8), 12.37 (s, 1H, 1-OH); ^{13}C NMR (125 MHz, acetone-d_6) δ 22.4, 38.7, 107.5, 108.6, 112.5, 122.5, 123.2, 124.8, 125.1, 130.8, 138.6, 150.9, 156.5, 162.5, 181.9; HRESIMS: *m/z* 255.0664 [M - H]$^-$ (calcd for $C_{15}H_{11}O_4$, 255.0663).

3.2.14. 1-Hydroxy-7-methoxy-3-methyl-9H-xanthen-9-one (14)

Yellow solid; yield 67%; mp: 172–174 °C; IR (KBr) ν_{max} 538, 849, 977, 1176, 1212, 1368, 1475, 1613, 1650, 2854, 2920, 3063, 3436 cm^{-1}; ^{1}H NMR (500 MHz, acetone-d_6) δ 2.45 (s, 3H, CH_3-), 3.40 (s, 3H, -OCH_3), 6.68 (s, 1H, H-2), 6.90 (s, 1H, H-4), 7.72 (d, 1H, J = 9.1 Hz, H-5); 7.84 (dd, 1H, J = 2.9, 9.1 Hz, H-6), 8.12 (d, 1H, J = 2.9 Hz, H-8), 12.34 (s, 1H, HO-1); ^{13}C NMR (125 MHz, acetone-d_6) δ 22.4, 37.7, 108.4, 112.2, 119.2, 121.0, 122.0, 130.9, 131.2, 146.4, 150.9, 155.3, 157.0, 162.4, 181.7; HRESIMS: *m/z* 255.0659 [M - H]$^-$ (calcd for $C_{15}H_{11}O_4$, 255.0663).

3.2.15. 1,8-Dihydroxy-3-methyl-9H-xanthen-9-one (15)

Yellow solid; yield 56%; mp: 201–203 °C; IR (KBr) ν_{max} 819, 917, 1061, 1208, 1231, 1289, 1482, 1602, 1631, 1661, 2852, 2920, 3022, 3431 cm^{-1}; ^{1}H NMR (500 MHz, acetone-d_6) δ 2.45 (s, 3H, CH_3-), 6.67 (s, 1H, H-2), 6.79 (d, 1H, J = 8.4 Hz, H-7), 6.86 (s, 1H, H-4), 6.99 (d, 1H, J = 8.4 Hz, H-5), 7.74 (t, 1H, J = 8.4 Hz, H-6), 11.63 (s, 1H, HO-8), 11.77 (s, 1H, HO-1); ^{13}C NMR (125 MHz, acetone-d_6) δ 22.4, 108.0 (C-2, C-4), 108.5, 111.4, 112.2, 112.3, 138.7, 151.4, 157.1, 157.2, 161.9, 162.2, 186.7; MS-ESI, m/z 241 [M - H]$^-$. HRESIMS: *m/z* 241.0508 [M - H]$^-$ (calcd for $C_{14}H_9O_4$, 241.0506).

3.2.16 1,5,6-Trihydroxy-3-methyl-9H-xanthen-9-one (16)

Brown solid; yield 33%; mp: 309–312 °C; IR (KBr) ν_{max} 460, 788, 886, 1055, 1162, 1210, 1282, 1464, 1586, 1612, 1656, 2853, 2924, 3076, 3181, 3401, 3514 cm^{-1}; ^{1}H NMR (500 MHz, acetone-d_6) δ 2.41 (s, 3H, -CH_3), 6.59 (s, 1H, H-2), 6.80 (s, 1H,

H-4), 7.00 (d, 1H, $J = 8.8$ Hz, H-7), 7.65 (d, 1H, $J = 8.8$ Hz, H-8), 8.73 (s, 1H, 5-OH), 9.25 (s, 1H, 6-OH), 12.83 (s, 1H, 1-OH); ^{13}C NMR (125 MHz, acetone-d_6) δ 22.3, 106.8, 108.0, 111.6, 111.7, 113.9, 114.9, 117.6, 147.1, 149.2, 152.4, 157.0, 162.7, 182.1; HRESIMS: *m/z* 257.0454 $[M - H]^-$ (calcd for $C_{14}H_9O_5$, 257.0455).

3.3. Bioassay

3.3.1. Cytotoxicity assay

The human cell lines SMMC-7721, HepG-2, Huh-7, SK-HEP-1, MHCC97H, PLC/PRF/5, L02, A-549, NCI-H460, NCI-H520, SPC-A-1, A549/Taxol, BEAS-2B, HL-60, MCF-7, MDA-MB-231, SW480 and HeLa were used in the cytotoxic assay. These cell lines were obtained from ATCC (Manassas, VA, USA). Cells were cultured in RMPI-1640 or DMEM medium (Biological industries, Kibbutz Beit-Haemek, Israel), supplemented with 10% fetal bovine serum (Biological Industries) at 37 °C in a humidified atmosphere with 5% CO_2. The cytotoxicity assay was evaluated by MTS (Promega, Madison, WI, USA) assay [6]. Briefly, cells were seeded into each well of a 96-well cell culture plate. After 12 h of incubation at 37 °C, the test compound (40 μM) was added. After incubation for 48 h, cells were subjected to the MTS assay. Compounds with a growth inhibition of 50% were further evaluated at concentrations of 0.064, 0.32, 1.6, 8, and 40 μM in triplicate. Cisplatin and Taxol (Sigma, St. Louis, MO, USA) served as positive controls. The IC_{50} value of each compound was calculated using the method of Reed and Muench [7]. The results were expressed as average ± standard deviation.

3.3.2. Mushroom tyrosinase in vitro inhibition

The sample or kojic acid standard (final concentration: 35 μM) was mixed with L-DOPA (final concentration: 1.25 mM) in a 96-well microplate. Each test particle was assayed in triplicate. The reaction was initiated by adding tyrosinase (final concentration: 25 U/ml). The plate was incubated at room temperature on a shaker for 5 min. The plates were read at 490 nm. The results were expressed as average ± standard deviation. The effect of tyrosinase inhibition was calculated by using the following equation:

$$\text{Tyrosinase } (\%) = (1 - \text{mean OD of sample}/\text{mean OD of untreated control}) \times 100\%$$

3.3.3. In vitro antioxidant capacity

Sample or the trolox standard (final concentration, 25 μM) was added to 96-well microplates. Each test particle was assayed in triplicate. The reaction was initiated by adding DPPH solution (final concentration, 50 μM) at 30 °C for 1 h. The plates were read at 515 nm. The results were expressed as average ± standard deviation. The antioxidant effect was calculated by using following equation:

$$\text{Antioxidant } (\%) = (1 - \text{mean OD of sample}/\text{mean OD of untreated control}) \times 100\%$$

3.3.4. Measurement of inhibitory activity against lipase

Porcine pancreatic lipase (PPL), Dulbecco's phosphate-buffered saline (D-PBS), and anhydrous calcium chloride were purchased from Aladdin Reagent (Shanghai, China), Hyclone (Logan, Utah, USA), and Chengdu Kelon Chemical Reagent Factory (Chengdu, China), respectively. *p*-Nitrophenyl butyrate (p-NPB), Tris, and orlistat were purchased from Sigma-Aldrich (Shanghai, China). The test compounds were thoroughly mixed with the PPL solution and then added to a 96-well microplate. Each test compound was assayed in triplicate. The test mixture was kept at 37 °C for 15 min then p-NPB was added to the well and mixed evenly. This new mixture was kept at 37 °C for 15 min. The plates were read at 400 nm with 630 nm as the reference wavelength. At the same time, the blank control well and the orlistat positive control well were set [8–10]. The results were expressed as the average ± standard deviation. The inhibitory activity was calculated using the following equation:

$$\text{PPL activity inhibition } (\%) = (1 - \text{mean OD of sample}/\text{OD value of control well}) \times 100\%$$

3.3.5. Antifungal activity

Candida albicans ATCC 10231 was purchased from Microbiologics (Minnesota, USA). Amphotericin B and DMSO were purchased from Sigma-Aldrich, and agar powder was purchased from Aladdin Reagent (Shanghai, China). A dimethyl sulfoxide (DMSO) solution containing the sample (final concentration, 200 μM) was added to a 96-well microplate. Subsequently, a dimethyl sulfoxide (DMSO) solution containing *Candida albicans* (final concentration, 1×105 CFU/ml) was added to each well. Each test compound was assayed in triplicate. This mixture was incubated at 37 °C for 24 h. The plates were read at 625 nm. At the same time, the blank control well and the positive control well containing amphotericin B were set [11,12]. The results were expressed as the average ± standard deviation. The inhibitory activity was calculated by using the following equation:

$$\text{Antifungal activity inhibition } (\%) = (1 - \text{mean OD of sample}/\text{OD value of control well}) \times 100\%$$

Disclosure statement

The authors declare no conflict of interest.

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