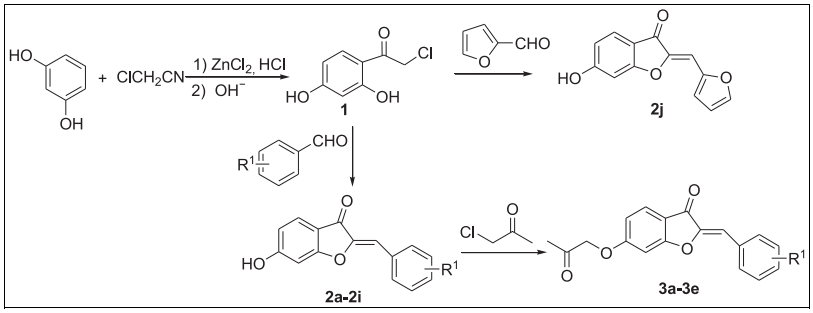
Yong-Tuan Bao,[a] Min Zhang,[a] Ting Li,[a] Hui-Feng Xiao,[a] Ting Zhao,[a] Xiao-Hua Xu,[b] and Liu-Qing Yang[a]*

[a]School of Chemistry and Chemical Engineering, Jiangsu University, Zhenjiang 212013, Jiangsu, China
[b]State Key Laboratory of Elemento-Organic Chemistry, Research Institute of Elemento-Organic Chemistry, Nankai University, Tianjin 300071, China
*E-mail: yangliuqing@ujs.edu.cn

Received April 12, 2015
DOI 10.1002/jhet.2497
Published online 15 July 2015 in Wiley Online Library (wileyonlinelibrary.com).



A series of 6-hydroxyaurone derivatives were synthesized in satisfactory yields and characterized by IR, ^{1}H NMR, ^{13}C NMR, and HRMS or elemental analysis. The structure of compound **3e** was further confirmed by X-ray crystal analysis. Bioassay results indicated that some of the target compounds displayed moderate herbicidal activity against the dicotyledonous plant *Brassica campestris* L. at 100 μg·mL^{-1}, and some compounds also showed significant antiproliferative activity against tumor cell lines Hela, HepG-2, and MCF-7.

J. Heterocyclic Chem., **53**, 637 (2016).

INTRODUCTION

Aurones, 2-benzylidene-3(*2H*)-benzofuranone (Fig. 1), as a class of flavonoids [1], are common structures found in flowers, seeds, leafs, and heartwood of higher plants [2], as well as in marine organisms [3]. They are not only responsible for yellow and orange flower pigmentation [4], but also play an important role in protecting plant from rot [5,6], insects [7], and phytoalexin [8,9]. In addition, the therapeutic potential of aurones for humans is very promising [1,10], with a wide range of activity including antitumor [11–13], antioxidant [14,15], antileishmanial [16], and antimicrobial [17] activities whereas they possess enzyme inhibitory [18], or enzyme-inducing [19] properties. Thus numerous efforts have been devoted to modification of the scaffold of aurone to obtain new chemical entity with desired biological activity.

Most of the aurones existing in nature are 4,6-substituted [10] and the previous research presented that 4,6-dihydroxylated aurones demonstrated moderate to good herbicidal activity against the dicotyledonous plant *Brassica campestris* L. [20,21]. However, there are few reports concerning the herbicidal activity of aurones with a substituent only on 6-position of ring A, especially with a 6-hydroxyl group [22]. To continue our study on the ornamentation of aurone [20–22], herein we describe the synthesis, structural characterization, and herbicidal evaluation of 6-hydroxyaurone derivatives, as well as their antiproliferative activity against human liver carcinoma (HepG-2), cervix epithelioid carcinoma (HeLa), and breast cancer cell line (MCF-7).

RESULTS AND DISCUSSION

Synthesis. As shown in Scheme 1, 2-chloro-1-(2,4-dihydroxyphenyl)ethanone (**1**) was prepared from resorcinol and 2-chloroacetonitrile in the presence of dry hydrogen chloride gas and anhydrous zinc chloride followed by hydrolyzation in good yield according to a reported method [21]. Reaction of compound **1** with the requisite aromatic aldehyde in the presence of potassium hydroxide gave 6-hydroxyaurone analogues **2** in exclusively the (*Z*)-configuration which was confirmed according to reference [21]. Accordingly, alkylation of 6-hydroxyaurones **2** with 1-chloroacetone under basic conditions afforded their corresponding methylketone derivatives **3**. All of the target compounds **2** and **3** were characterized by ^{1}H NMR, ^{13}C NMR, and HRMS or elemental analysis.

Crystal structure. Light yellow single crystals of compound **3e** suitable for analysis were obtained by slowly evaporating from ethyl acetate and petroleum ether at room temperature for a few days. A single crystal with dimensions of 0.20 mm × 0.20 mm × 0.20 mm was put on a Rigaku Saturn 724 CCD area-detector diffractometer with a graphite-monochromated Mo Ka radiation ($\lambda = 0.71073$ Å) at 293(2) K using a muti-scan mode in the ranges of $3.21^\circ \le \theta \le 25.36^\circ$. The structure of compound **3e** was solved by direct method with SHELXS-97 and refined with SHELXTL-97 [23]. Figure 2 shows the molecular structure of compound **3e** with atomic numbering scheme. The torsion angles O(3)–C(11)–C(12)–C(13) and C(10)–C(11)–C(12)–C(13) are 2.4(3)° and −174.6(2)°, respectively,

© 2015 HeteroCorporation

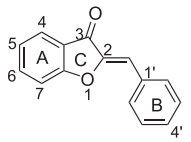


Figure 1. Chemical structure and numbering of the aurone scaffold.

which indicates that the exocyclic C=C double bond is in (*Z*)-configuration.

Herbicidal activity. The herbicidal activity of the target compounds against *B. campestris* and *E. crus-galli* has been investigated according to the method described in the experimental section, and the results were listed in Table 1.

As shown in Table 1, some of the target compounds possessed moderate herbicidal activity against dicotyledonous plant (*B. campestris*). For example, compounds **2b**, **2g**, and **3e** displayed >50% inhibitory activity against *B. campestris* at the concentration of 100 $\mu g \cdot mL^{-1}$. Furthermore, most of target compounds exhibited stronger inhibitory activity against dicotyledonous plant (*B. campestris*) than that of monocotyledonous plant (*E. crus-galli*). The results revealed that 6-hydroxyaurones possessed the same selectivity as 4,6-dihydroxyaurones, but showed slightly lower herbicidal activity than the latter [21].

From the data listed in Table 1, it was also found that, in the case of 6-hydroxyaurones (**2a–2j**), introducing substituents on ring B of aurones increased the inhibitory activity against *B. campestris*. Compared with compound **2a** (R^1 = H), compounds **2b** (R^1 = 2′-F), **2d** (R^1 = 4′-F), **2e** (R^1 = 3′-CF_3), and **2 g** (R^1 = 3′,5′-$(OCH_3)_2$-4′-OBn) exhibited higher inhibitory activity against *B. campestris* at 100 $\mu g \cdot mL^{-1}$. When the phenyl ring B was replaced by a furan ring, the resulted molecule (**2j**) showed a low herbicidal activity against *B. campestris* at 100 $\mu g \cdot mL^{-1}$, which is consistent with that of 4,6-dimethoxyaurones [21]. In an effort to

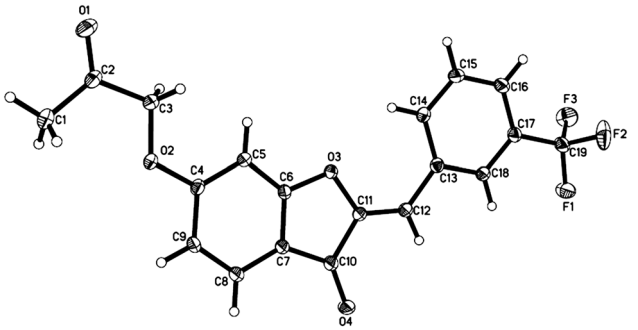


Figure 2. Molecular structure of compound 3e.

study the function of 6-hydroxyl group, modification of 6-hydroxyl group by alkylation with 1-chloroacetone was carried out. And it was found that the alkylation could increase the herbicidal activity, for example, compounds **3c** and **3e** exhibited higher activity than the corresponding **2c** and **2e**. The results indicated that 6-substituted aurones showed herbicidal potential against dicotyledonous plant *B. campestris*, and highly active aurones are expected to be found through further structure modification.

Antitumor activity. The synthesized compounds were subjected to the antiproliferative assay against cancer cell lines HepG-2, HeLa, and MCF-7. And the antiproliferative IC_{50} values were summarized in Table 2.

As shown in Table 2, unsubstituted 6-hydroxyaurone (**2a**) was not active against the cell growth; meanwhile **2j** containing a furan ring was also found inactive. However, aurones bearing substituents on ring B generally exhibited antiproliferative activity against cancer cell. Fluorides **2b–2d** exhibited inhibitory activity against both HepG-2 and Hela proliferation; furthermore, fluoro substituent at the 3′-position of aurone (**2c**) possessed higher activity than 2′,4′-fluorinated compounds. In addition, the introduction

Scheme 1. Synthesis of 6-hydroxyaurone derivatives.

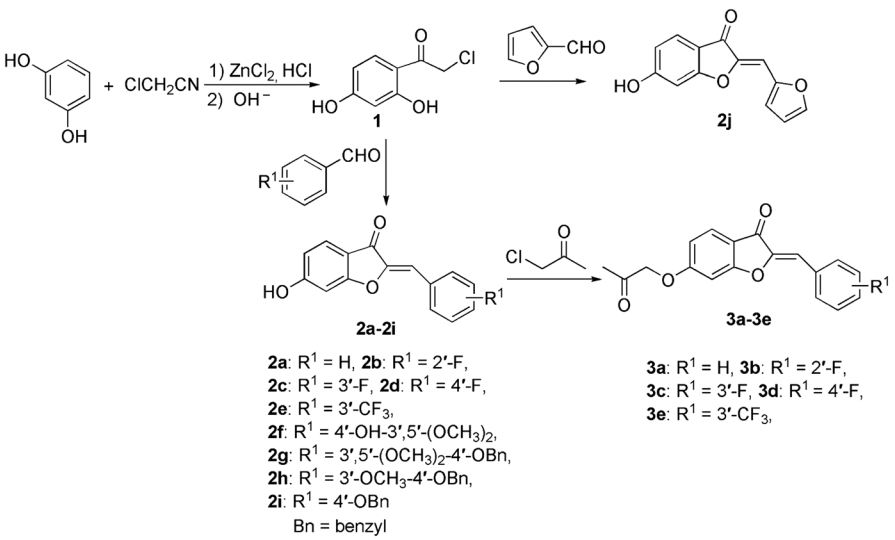


Table 1

Herbicidal activity of the target compounds on rape root and barnyard grass seeding growth (% inhibition, concentration, μg/mL).

	B. campestris		*E. crus-galli*	
Compd	100	1000	100	1000
2a[a]	22.4	75.0	20.0	35.1
2b	52.4	83.2	28.2	45.1
2c[a]	29.0	76.7	10.1	16.2
2d[b]	44.0	78.2	7.0	29.7
2e	48.2	67.1	5.0	27.0
2f[a]	42.6	65.9	5.0	25.8
2g	54.0	77.5	0	36.6
2h	26.4	91.9	4.0	46.7
2i	31.8	91.5	4.8	38.1
2j	26.4	91.9	4.0	46.7
3a	1.9	22.7	0	25.7
3b	8.0	50.9	0	18.9
3c	10.9	60.0	0	21.6
3d	26.2	80.5	3.0	24.3
3e	50.8	78.2	0	24.3

[a]Compounds **2a**, **2c**, and **2f** and their herbicidal activity were reported in ref. [22], while all of the data here of them came from our own work.
[b]Compound **2d** was reported in Ref. [24], but the herbicidal and antitumor activity had not been reported.

Table 2

Antiproliferative action of synthesized compounds against three cancer cell lines (IC_{50}, μg/mL)[a].

Compd	HepG-2	Hela	MCF-7
2a	/	ND	/
2b	12.5	7.7	ND
2c	7.9	9.3	ND
2d	9.1	11.2	ND
2e	8.4	3.3	7.1
2f	ND	/	/
2h	/	/	/
2i	5.0	/	15.5
2j	/	/	/
3b	14.9	9.5	ND

[a]ND, not detected.
[/]No activity.

of 3′-trifluoromethyl group dramatically increased inhibition on the proliferation of HepG-2, Hela, and MCF-7 cells with IC_{50} values 8.4, 3.3, and 7.1 $\mu g \cdot mL^{-1}$, respectively. The introduction of electron-donating groups made the inhibitory activity of **2f** and **2h** completely disappear; however, **2i** possessed the strongest antitumor activity against HepG-2. Comparing **3b** with **2b**, it was also found that the alkylation of 6-hydroxyl group led to decreasing antiproliferative activity against cancer cells. On the basis of these data, it is concluded that these compounds are selective against the proliferation of three cancer cell lines.

In summary, a variety of 6-hydroxyaurone derivatives have been synthesized and tested for their herbicidal activity against *B. campestris* and *E. crus-galli*, as well as their antitumor activity against HepG-2, Hela, and MCF cell lines. The results of preliminary bioassay indicated that some compounds displayed moderate herbicidal activity against dicotyledonous plant *B. campestris* at 100 $\mu g \cdot mL^{-1}$, and some compounds also showed significant antiproliferative activity against tumor cell lines Hela, HepG-2, and MCF-7.

EXPERIMENTAL

Melting points were determined on an X-4 binocular microscope melting point apparatus (Beijing Tech Instruments Co., Beijing, China) and are uncorrected. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker AVANCEII400 MHz instrument at room temperature in $CDC1_3$ or DMSO-d_6. Elemental analysis was carried out with a Perkin–Elmer 240C analyzer. High resolution mass spectra (HRMS) were recorded on a VARIAN 7.0 T direct inlet instrument. Infrared (IR) spectra were measured on a Nicolet Nexus 470 infrared spectrometer as KBr pellets and are reported in terms of frequency of absorption (cm^{-1}). X-ray diffraction was carried out on a Rigaku Saturn 724 CCD diffractometer (Tokyo, Japan). Common reagents and materials were purchased from commercial sources and were used directly without further purification. All solvents were dried and redistilled before use.

Synthetic procedure for 2-chloro-1-(2,4-dihydroxyphenyl) ethanone (1). To a mixture of resorcinol (20.00 g, 181.6 mmol) and 2-chloroacetonitrile (12.70 mL, 200.0 mmol) in anhydrous ether (420 mL) was added dry $ZnCl_2$ (12.56 g, 92.4 mmol). The solution was cooled to below 0°C, and dry HCl gas was bubbled through the reaction for 3 h. The solution was left in the cold-room overnight, and HCl gas was bubbled again for 3 h. Then the solution was left again in the cold-room for 3 days. The precipitate was filtered off and washed three times with ether, then followed by dissolving in 150-mL hot water and refluxed for 3 h. After cooling, the solid was filtered off, washed three times with water, and dried to yield 2-chloro-1-(2,4-dihydroxyphenyl)ethanone (**1**) as a light yellow solid, which was used without further purification, yield 77.2%, m.p. 129–131°C. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 4.98 (s, 2H, CH_2Cl), 6.33 (d, $J = 2.1$ Hz, 1H, H-3), 6.39 (dd, $J = 8.7$, 2.1 Hz, 1H, H-5), 7.72 (d, $J = 8.7$ Hz, 1H, H-6), 10.70 (brs, 1H, OH), 11.67 (brs, 1H, OH); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 47.3, 102.4, 108.4, 111.6, 132.8, 163.1, 164.8, 193.4. MS (ESI, *m/z*) 185.15 (M^-).

General synthetic procedure for 6-hydroxyaurone analogues (2a–2j). To a solution of compound **1** (12.0 mmol) in methanol (5 mL) was added requisite aromatic aldehyde (14.7 mmol) followed by the addition of 10% aqueous KOH solution (30 mL). The solution was stirred at ambient temperature until the starting **1** disappeared by TLC analysis. The solvent was removed under reduced pressure and ice-cold water (30 mL) was added. The crude product was

collected by filtration, washed with ice-cold water (10 mL), and recrystallized from ethanol–dichloromethane (1:1) to give the target compound.

(Z)-2-Phenylmethylene-6-hydroxy-3(2H)-benzofuranone (2a). Light yellow solid, m.p. 262–264°C, yield 89.8%; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 6.73 (dd, J = 2.0, 8.4 Hz, 1H, H-5), 6.79 (s, 1H, =CH), 6.82 (d, J = 1.6 Hz, 1H, H-7), 7.40–7.46 (m, 1H, ArH), 7.46–7.53 (m, 2H, ArH), 7.64 (d, J = 8.4 Hz, 1H, H-4), 7.92–7.97 (m, 2H, ArH); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 98.6, 110.4, 112.8, 113.0, 126.0, 128.9(2C), 129.6, 131.0(2C), 132.1, 147.4, 166.4, 167.8, 181.5; IR (KBr) v: 3417, 3069, 1673, 1644, 1581, 1450, 1375, 1330, 1316, 1285, 1250, 1155, 1131, 1111. HRMS (ESI, m/z) calcd for $[C_{15}H_{10}O_3 + H]^+$ 239.0703, found 239.0706.

(Z)-2-(2-Fulorophenyl)methylene-6-hydroxy-3(2H)-benzofuranone (2b). Yellow solid, m.p. 275–276°C, yield 83.0%; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 6.73 (dd, J = 2.0, 8.4 Hz, 1H, H-5), 6.76 (s, 1H, =CH), 6.79 (d, J = 2.0 Hz, 1H, H-7), 7.29–7.38 (m, 2H, ArH), 7.45–7.52 (m, 1H, ArH), 7.63 (d, J = 8.4 Hz, 1H, H-4), 8.17–8.25 (m, 1H, ArH); 11.31 (s, 1H, OH); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 98.7, 100.2, 112.4, 113.2, 115.7, 119.7, 125.0, 126.1, 131.1, 131.7, 148.3, 160.5, 166.8, 168.0, 181.1; IR (KBr) v: 3423, 3062, 1675, 1650, 1585, 1303,1231, 1136, 1111 cm^{-1}. *Anal.* Calcd. for $C_{15}H_9FO_3$: C 70.31, H 3.54; found: C 70.16, H, 3.65.

(Z)-2-(3-Fulorophenyl)methylene-6-hydroxy-3(2H)-benzofuranone (2c). Light yellow solid, m.p. 272–274°C, yield 74.4%; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 3.83 (s, 3H, CH_3), 3.86 (s, 3H, CH_3), 6.75 (dd, J = 8.4, 1.6 Hz, 1H, H-5), 6.81 (d, J = 1.6 Hz, 1H, H-7), 6.98 (s, 1H, =CH), 7.14–7.25 (m, 2H, ArH), 7.65 (d, J = 8.4 Hz, 1H, ArH), 7.78 (d, J = 8.0 Hz, 1H, H-4), 11.3 (br, 1H, OH); IR (KBr) v: 3452, 2790, 2843, 2361, 2345, 1670, 1580, 1552, 1442, 1392, 1290, 1106, 1037 cm^{-1}. *Anal.* Calcd. for $C_{15}H_9O_3F$: C 70.31, H 3.54; found C 70.26, H 3.70.

(Z)-2-(4-Fulorophenyl)methylene-6-hydroxy-3(2H)-benzofuranone (2d). Yellow solid, m.p. 268–269°C, yield 84.1%; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 6.72 (dd, J = 2.0, 8.4 Hz, 1H, H-5), 6.79 (d, J = 2.0 Hz, 1H, H-7), 6.81 (s, 1H, =CH), 7.28–7.37 (m, 2H, ArH), 7.62 (d, J = 8.4 Hz, 1H, H-4), 7.97–8.04 (m, 2H, ArH), 11.24 (s, 1H, OH); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 98.6, 109.2, 112.7, 113.0, 116.0(2C), 125.9, 128.7, 133.3 (2C), 147.0, 162.4, 166.5, 167.9, 181.3; IR (KBr) v: 3448, 3121, 3068, 1679, 1646, 1589, 1503, 1450, 1372, 1315, 1241, 1136, 1119 cm^{-1}. *Anal.* Calcd. for $C_{15}H_9FO_3$: C 70.31, H 3.54; found: C 70.48, H 3.74.

(Z)-2-(3-Trifuloromethylphenyl)methylene-6-hydroxy-3(2H)-benzofuranone (2e). Yellow solid, m.p. 259–260°C, yield 60.4%; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 6.72 (dd, J = 8.4, 2.0 Hz, 1H, H-5), 6.78 (d, J = 1.6 Hz, 1H, H-7), 6.89 (s, 1H, =CH), 7.63 (d, J = 8.4 Hz, 1H, H-4), 7.67–7.78 (m, 2H, ArH), 8.20–8.28 (m, 2H, ArH), 11.29 (s, 1H, OH); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 98.6, 108.3, 112.4, 113.2, 123.9, 125.6, 126.1, 127.1, 129.6, 129.9, 133.2, 134.3, 148.1, 166.8, 168.0, 181.3; IR (KBr) v: 3450, 3158, 3068, 2868, 1687, 1650, 1587, 1491, 1352, 1299, 1266, 1135, 1090 cm^{-1}. *Anal.* Calcd. for $C_{16}H_9F_3O_3$: C 62.75, H 2.96; found: C 63.02, H 2.86.

(Z)-2-(4-Hydroxy-3,5-dimethoxyphenyl)methylene-6-hydroxy-3(2H)-benzofuranone (2f). Yellow solid, m.p. 218–223°C, yield 90.6%; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 3.84 (s, 6H, 2 × OCH_3), 6.70–6.75 (m, 2H, =CH + H-5), 6.82 (d, J = 1.6 Hz, 1H, H-7), 7.29 (s, 2H, ArH), 7.61 (d, J = 8.4 Hz, 1H, H-4); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 56.1 (2C), 98.6, 109.2(2C), 112.0, 112.8, 113.2, 122.3, 125.7, 138.1, 146.0, 148.0(2C), 165.9, 167.5, 181.2. HRMS (ESI, m/z) calcd for $[C_{17}H_{14}O_6 + H]^+$ 315.0863, found 315.0864.

(Z)-2-(3,5-Dimethoxy-4-benzyloxyphenyl)methylene-6-hydroxy-3(2H)-benzofuranone (2g). Bright yellow solid, m.p. 235–237°C, yield 81.4%; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 3.84 (s, 6H, 2 × OCH_3), 4.97 (s, 2H, CH_2O), 6.69–6.75 (m, 2H, ArH), 6.80 (s, 1H, =CH), 7.27 (s, 2H, ArH), 7.29–7.40 (m, 3H, ArH), 7.43–7.49 (m, 2H, ArH), 7.59 (d, J = 8.4 Hz, 1H, ArH), 11.18 (brs, 1H, OH); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 56.0(2C), 74.1, 98.8, 108.7(2C), 110.9, 112.9, 113.0, 125.9, 127.7, 127.8, 128.0(2C), 128.1(2C), 137.7, 137.9, 146.9, 153.2(2C), 166.5, 167.8, 181.4; IR (KBr) v: 3419, 3029, 3002, 2971, 2940, 2840, 1671, 1637, 1583, 1499, 1450, 1421, 1307, 1276, 1230, 1209, 1152, 1133, 1104 cm^{-1}. HRMS (ESI, m/z) calcd for $[C_{24}H_{20}O_6 + Na]^+$ 427.1152, found 427.1146.

(Z)-2-(3-Methoxy-4-benzyloxyphenyl)methylene-6-hydroxy-3(2H)-benzofuranone (2h). Bright yellow solid, m.p. 255–257°C, yield 80.4%; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 3.84 (s, 3H, OCH_3), 5.17 (s, 2H, CH_2O), 6.72 (d, J = 8.0 Hz, 1H, ArH), 6.77 (s, 1H, =CH), 6.79–6.85 (m, 1H, ArH), 7.16 (d, J = 8.4 Hz, 1H, ArH), 7.30–7.51 (m, 5H, ArH), 7.51–7.66 (m, 3H, ArH), 11.16 (brs, 1H, OH); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 55.6, 69.8, 98.6, 111.1, 112.9, 113.1, 113.5, 114.5, 124.9, 125.1, 125.8, 127.9(2C), 128.0, 128.5(2C), 136.7, 146.3, 149.0, 149.3, 166.2, 167.6, 181.3. HRMS (ESI, m/z) calcd for $[C_{23}H_{18}O_5 + Na]^+$ 397.1046, found 397.1042.

(Z)-2-(4-Benzyloxyphenyl)methylene-6-hydroxy-3(2H)-benzofuranone (2i). Light yellow solid, m.p. 258–260°C, yield 86.7%; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 5.15 (s, 2H, CH_2O), 6.72 (d, J = 8.4 Hz, 1H, ArH), 6.75–6.78 (m, 1H, ArH), 6.78–6.83 (m, 1H, ArH), 7.11 (d, J = 8.4 Hz, 2H, ArH), 7.30–7.50 (m, 5H, ArH), 7.61 (d, J = 8.4 Hz, 1H, ArH), 7.90 (d, J = 8.4 Hz, 2H, ArH), 11.19 (brs, 1H, OH); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 69.4, 98.6, 110.7, 112.9, 113.2, 115.4(2C), 124.8, 125.8, 127.8(2C), 128.0, 128.5(2C), 133.0(2C), 136.6, 146.3, 159.5, 166.3, 167.7, 181.3. HRMS (ESI, m/z) calcd for $[C_{22}H_{16}O_4 + Na]^+$ 367.0941, found 367.0942.

(Z)-2-(2-Furanyl)methylene-6-hydroxy-3(2H)-benzofuranone (2j). Silver brown solid, m.p. 281–282°C, yield 87.5%; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 6.70–6.77 (m, 3H, ArH), 6.78–6.82 (m, 1H, ArH), 7.16 (d, J = 3.6 Hz, 1H, ArH),

7.62 (d, J = 8.4 Hz, 1H, ArH), 7.96–7.98 (m, 1H, ArH), 11.23 (brs, 1H, OH); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 98.6, 99.2, 113.0, 113.2, 113.3, 117.0, 125.9, 145.3, 146.1, 148.1, 166.3, 167.6, 180.9. HRMS (ESI, *m/z*) calcd for $[C_{13}H_8O_4 + Na]^+$ 251.0315, found 251.0316.

General synthetic procedure for compounds 3a–3e. To a solution of requisite **2** (2.1 mmol) and 1-chloroacetone (0.30 mL, 3.8 mmol) in DMF (*N*,*N*-dimethylformamide, 5 mL) was added K_2CO_3 (0.50 g, 3.6 mmol). The mixture was stirred at room temperature for 48 h and then was poured into water (100 mL). The precipitate was collected on a filter, washed well with water, and dried to afford a crude product. Further purification by recrystallization from ethyl acetate and petroleum ether gave a pure product.

(Z)-2-Phenylmethylene-6-(2-oxopropoxy)-3(2H)-benzofuranone (3a). Earth yellow solid, m.p. 123–124°C, yield 70.3%; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.33 (s, 3H, CH_3), 4.68 (s, 2H, CH_2), 6.73 (d, J = 2.0 Hz, 1H, H-7), 6.79 (dd, J = 8.4, 2.0 Hz, 1H, H-5), 6.84 (s, 1H, =CH), 7.38–7.48 (m, 3H, ArH), 7.44 (d, 1H, H-4), 7.88–7.90 (m, 2H, ArH); IR (KBr) v: 3099, 1717, 1611, 1426, 1383, 1279, 1156, 1127, 1095 cm^{-1}. *Anal.* Calcd. for $C_{18}H_{14}O_4$: C 73.46, H 4.79; found: C 73.19, H 5.02.

(Z)-2-(2-Fulorophenyl)methylene-6-(2-oxopropoxy)-3(2H)-benzofuranone (3b). Yellow solid, m.p. 98–99°C, yield 67.3%; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.33 (s, 3H, CH_3), 4.68 (s, 2H, CH_2), 6.71 (d, J = 2.0 Hz, 1H, H-7), 6.78 (dd, J = 8.4, 2.0 Hz, 1H, H-5), 7.09–7.15 (m, 2H, =CH + ArH), 7.22–7.27 (m, 1H, ArH), 7.33–7.40 (m, 1H, ArH), 7.73 (d, J = 8.8 Hz, 1H, H-4), 8.22–8.28 (m, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 26.6, 73.1, 97.6, 103.3, 112.2, 115.6, 115.7, 120.5, 124.4, 126.3, 131.3, 131.7, 148.3, 161.5, 165.2, 168.2, 182.5, 203.4; IR (KBr) v: 3060, 1701, 2890, 1658, 1608, 1485, 1449, 1344, 1270, 1238, 1131, 1100, 1049 cm^{-1}. *Anal.* Calcd. for $C_{18}H_{13}FO_4$: C 69.23, H 4.20; found: C 69.29, H 4.46.

(Z)-2-(3-Fulorophenyl)methylene-6-(2-oxopropoxy)-3(2H)-benzofuranone (3c). Yellow solid, m.p. 112–113°C, yield 68.9%; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.33 (s, 3H, CH_3), 4.70 (s, 2H, CH_2), 6.72 (d, J = 2.4 Hz, 1H, H-7), 6.76 (s, 1H, =CH), 6.79 (dd, J = 2.4, 8.4 Hz, 1H, H-5), 7.05–7.12 (m, 1H, ArH), 7.36–7.44 (m, 1H, ArH), 7.52–7.58 (m, 1H, ArH), 7.64–7.70 (m, 1H, ArH), 7.72 (d, J = 8.4 Hz, 1H, H-4); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 26.5, 73.1, 97.6, 110.6, 112.4, 115.5, 116.6, 117.4, 126.2, 127.2, 130.2, 134.3, 148.0, 162.8, 165.3, 168.2, 182.6, 203.1; IR (KBr) v: 3066, 1720, 1654, 1610, 1443, 1334, 1274, 1235, 1155, 1127, 1047 cm^{-1}. *Anal.* Calcd. for $C_{18}H_{13}FO_4$: C 69.23, H 4.20; found: C 69.16, H 4.23.

(Z)-2-(4-Fulorophenyl)methylene-6-(2-oxopropoxy)-3(2H)-benzofuranone (3d). White solid, m.p. 135–136°C, yield 71.2%; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.33 (s, 3H, CH_3), 4.68 (s, 2H, CH_2), 6.71 (d, J = 2.0 Hz, 1H, H-7), 6.77 (s, 1H, =CH, overlapped by the signal of H-5), 6.75–6.81 (m, 1H, H-5), 7.08–7.17 (m, 2H, ArH), 7.72 (d, J = 8.8 Hz, 1H, H-4), 7.83–7.92 (m, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 26.5, 73.1, 97.6, 111.1, 112.2, 115.7, 116.0 (2C), 126.2, 128.5, 133.3 (2C), 147.2, 163.3, 165.1, 168.1, 182.7, 203.3; IR (KBr) v: 3064, 1720, 1695, 1653, 1603, 1511, 1449, 1344, 1270, 1233, 1157, 1046 cm^{-1}. *Anal.* Calcd. for $C_{18}H_{13}FO_4$: C 69.23, H 4.20; found: C 69.29, H 4.26.

(Z)-2-(3-Trifuloromethylphenyl)methylene-6-(2-oxopropoxy)-3(2H)-benzofuranone (3e). Light yellow solid, m.p. 123–124°C, yield 88.6%; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.34 (s, 3H, CH_3), 4.71 (s, 2H, CH_2), 6.75 (d, J = 2.4 Hz, 1H, H-7), 6.81 (dd, J = 2.4, 8.8 Hz, 1H, H-5), 6.81 (s, 1H, =CH, overlapped by the signal of H-5), 7.54–7.60 (m, 1H, ArH), 7.61–7.66 (m, 1H, ArH), 7.75 (d, J = 8.4 Hz, 1H, ArH), 8.01 (d, J = 7.6 Hz, 1H, ArH), 8.15 (s, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 26.6, 73.1, 97.8, 110.1, 112.5, 115.4, 123.9, 126.0, 126.3, 127.6, 129.3, 131.4, 133.1, 134.2, 148.3, 165.4, 168.3, 182.6, 203.1; IR (KBr) v: 3066, 1724, 1695, 1656, 1603, 1450, 1425, 1326, 1302, 1264, 1170, 1132, 1098, 1075 cm^{-1}. *Anal.* Calcd for $C_{19}H_{13}F_3O_4$: C 62.99, H 3.62; found: C 62.89, H 3.74.

Herbicidal activity. ***Treatment.*** The emulsions of the evaluated compounds were prepared by dissolving them in 100 μL of DMF, adding a few drops of Tween 20 and dispersing in water. The mixture of the same amount of water, DMF, and Tween 20 was used as control. There were three replicates for each treatment.

Inhibition of the root growth of rape (B. campestris). Rape seeds were soaked in distilled water for 4 h before being placed on a filter paper in a 6-cm Petri plate, to which 2 mL of inhibitor solution had been added in advance. Usually, 15 seeds were used on each plate. The plate was placed in a dark room and allowed to germinate for 65 h at 28 (±1)°C. The lengths of 10 rape roots selected randomly from each plate were measured, and the means were calculated. The inhibition rate was calculated from the root length by use of the equation:

$$\text{Inhibition rate } (\%) = [(\text{C-T})/\text{C}] \times 100$$

where C is the average root length during the control assay and T is the average root length after treatment during testing.

Inhibition of the seedling growth of barnyard grass (E. crus-galli). A total of 10 barnyard grass seeds were placed into a 50-mL cup covered with a layer of glass beads and a piece of filter paper at the bottom, to which 5 mL of inhibitor solution had been added in advance. The cup was placed in a bright room, and the seeds were allowed to germinate for 65 h at 28 ± 1°C. The heights of seedlings of above-ground plant parts from each cup were measured, and the means were calculated. The inhibition rate was calculated from the plant height by use of the equation:

$$\text{Inhibition rate } (\%) = [(C - T)/C] \times 100$$

where C is the average plant height during the control assay and T is the average plant height after treatment during testing.

Antiproliferative activity. ***Cell lines and culture conditions.*** Human liver carcinoma (HepG-2), cervix epithelioid carcinoma (HeLa), and breast cancer cell line (MCF-7) were provided by the School of Pharmacy, Jiangsu University, Zhenjiang, China. All cells were grown in Dulbecco's modified eagle minimum essential medium (DMEM) medium supplemented with 10% fetal bovine serum (FBS), 100 units/mL penicillin and 100 μg/mL streptomycin. All cells were incubated at 37°C in a humidified atmosphere with 5% (*v*/*v*) CO_2.

Cell antiproliferative assay. Evaluation of cancer cell growth inhibition was assessed by 3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2*H*-tetrazolium bromide (MTT) assay. Exponentially growing cancer cells were seeded into 96-well culture plates (4×10^3 cells/well) and incubated at 37°C in a humidified incubator with 5% CO_2 for 24 h. Cells were incubated with different concentrations of sample for another 48 h. Untreated cells were used as negative control. Then, MTT solution (100 μL/well, 1 mg/mL) was added to each well and incubated again for 4 h. After the removal of MTT, the precipitate was solubilized in dimethyl sulfoxide (DMSO) (100 μL/well), and the absorbance was measured on a microplate ELISA reader (Spectra MAX 190, Molecular Devices Corporation, USA) at a wavelength of 570 nm. The inhibition ratio of the tumor cells proliferation was determined as follows:

$$\text{Inhibition rate } (\%) = \left(1\text{-Abs}_{sample}/\text{Abs}_{control}\right) \times 100.$$

IC_{50} values of some compounds against HepG-2, Hela, and MCF-7 were calculated with SPSS 16.0 version (SPSS Inc., Chicago, USA).

Acknowledgments. We are grateful for financial support by the Natural Science Foundation of Jiangsu Province (BK20140536), and Jiangsu University (09JDG064).

REFERENCES AND NOTES

[1] Boumendjel, A. Curr Med Chem 2003, 10, 2621.
[2] Perrier, E.; Okombi, S.; Rival, D.; Boumendjel, A.; Mariotte, A.-M. EP 1709964, 2006; Chem Abstr 2006, 145, 425283.
[3] Atta-Ur-Rahman; Choudhary M. I.; Hayat, S.; Khan, A. M.; Ahmed, A. Chem Pharm Bull 2001, 49, 105.
[4] Ono, E.; Fukuchi-Mizutani, M.; Nakamura, N.; Fukui, Y.; Yonekura-Sakakibara, K.; Yamaguchi, M.; Nakayama, T.; Tanaka, T.; Kusumi, T.; Tanaka, Y. Proc Natl Acad Sci U S A 2006, 103, 11075.
[5] Gomez-Garibay, F.; Reyes-Chilpa, R.; Quijano, L.; Pardo, J. S. C.; Castillo, T. R. Phytochemistry 1990, 29, 459.
[6] Reyes-Chilpa, R.; Viveros-Rodriguez, N.; Gomez-Garibay, F.; Alavez-Solano, D. J Chem Ecol 1995, 21, 455.
[7] Morimoto, M.; Fukumoto, H.; Nozoe, T.; Hagiwara, A.; Komai K J Agric Food Chem 2007, 55, 700.
[8] Pare, P. W.; Dmitrieva, N.; Mabry, T. J. Phytochemistry 1991, 30, 1133.
[9] Farag, M. A.; Deavours, B. E.; de Fatima, A.; Naoumkina, M.; Dixon, R. A.; Sumner, L. W. Plant Physiol 2009, 151, 1096.
[10] Haudecoeur, R.; Boumendjel, A. Curr Med Chem 2012, 19, 2861.
[11] Cheng, H. M.; Zhang, L. W.; Liu, Y. X.; Chen, S. P.; Cheng, H.; Lu, X.; Zheng, Z. X.; Zhou, G. C. Eur J Med Chem 2010, 45, 5950.
[12] Schoepfer, J.; Fretz, H.; Chaudhuri, B.; Muller, L.; Seeber, E.; Meijer, L.; Lozach, O.; Vangrevelinghe, E.; Furet, P. J Med Chem 2002, 45, 1741.
[13] Sim, H. M.; Loh, K. Y.; Yeo, W. K.; Lee, C. Y.; Go, M. L. ChemMedChem 2011, 6, 713.
[14] Venkateswarlu, S.; Panchagnula, G. K.; Subbaraju, G. V. Biosci Biotechnol Biochem 2004, 68, 2183.
[15] Nenadis, N.; Sigalas, M. P. Food Res Int 2011, 44, 114.
[16] Roussaki, M.; Lima, S. C.; Kypreou, A.-M.; Kefalas, P.; da Silva, A. C.; Detsi, A. Int J Med Chem 2012, DOI: 10.1155/2012/196921.
[17] Shin, S. Y.; Shin, M. C.; Shin, J. S.; Lee, K. T.; Lee, Y. S. Bioorg Med Chem Lett 2011, 21, 4520.
[18] Haudecoeur, R.; Ahmed-Belkacem, A.; Yi, W.; Fortune, A. F.; Brillet, R.; Belle, C.; Nicolle, E.; Pallier, C.; Pawlotsky, J.-M.; Boumendjel, A. J Med Chem 2011, 54, 5395.
[19] Lee, C. Y.; Chew, E. H.; Go, M. L. Eur J Med Chem 2010, 45, 2957.
[20] Zhang, M.; Chen, G.-Y.; Li, T.; Liu, B.; Deng, J.-Y.; Zhang, L.; Yang, L.-Q.; Xu, X.-H. J Heterocyclic Chem DOI: 10.1002/jhet.2298.
[21] Zhang, M.; Xu, X. H.; Cui, Y.; Xie, L. G.; Kong, C. H. Pest Manag Sci 2012, 68, 1512.
[22] Liu, B.; Zhang, M.; Xie, L. G.; Li, Y. H.; Xu, X. H. Chem J Chin Univ 2011, 32, 2335 (in Chinese).
[23] Crystallographic data for compound **3e** has been deposited at the Cambridge Crystallographic Data Centre (CCDC No. 1401706).
[24] Teo, C. C.; Kon, O. L.; Sim, K. Y.; Ng, S. C. J Med Chem 1992, 35, 1330.