Synthesis of Ring *A*-Modified Baicalein Derivatives

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Baicalein, an important active constituent of the traditional Chinese herb *Scutellaria baicalensis*, exhibited antitumor activity and inhibitory activity against P-gp 170. The syntheses of 25 baicalein derivatives, **2**–**26** (*Table*), are described here (*Scheme 1*). These compounds were systematically modified with *O*-alkylation and *O*-acylation at HO–C(5), HO–C(6), and HO–C(7), singly or in combination, on the ring *A* of baicalein in order to evaluate the effects of such modifications on their inhibitory activities against multidrug-resistant tumor cell lines and P-gp 170. Highly selective and efficient alkylations at HO–C(7) of peracetylated baicalein were the key to the distinction between HO–C(6) and HO–C(7) of baicalein.

Introduction. – For several decades, multidrug resistance (MDR) as well as dose limiting toxicity (DLT) have been significant drawbacks which limited the success of long-term therapy in patients with chemotherapeutic drugs. The drug resistance is mainly due to the overexpression of the 170 kDa P-glycoprotein (P-gp) which is known to cause subtherapeutic intracellular drug concentrations [1]. Thus, much effort has been devoted to develop agents to act as inhibitors of P-gp 170 and low exhibit toxicity toward normal tissues in drug discovery.

Flavonoids with their polyphenolic structures are found in many fruits, vegetables, and all vascular plants [2][3]. Baicalein (**1**; *Fig.*), a bioactive flavonoid, is extracted from the root of Chinese herb *Scutellaria baicalensis* which has been used to treat allergic and inflammatory diseases since ancient times in China. The pharmacological properties of **1** have been confirmed, including anti-oxidation [4], antivirus [5][6], antiallergy [7][8], anti-inflammatory [9–11], antithrombotic [12], antitumor [13][14] activities.

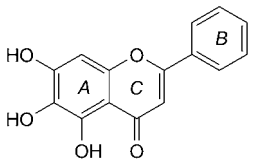

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Figure. *Chemical Structure of Baicalein* (**1**)

Recently, many investigations have been focused on its antitumor activities [15–17], and several molecular mechanisms have been proposed, including pro-oxidative activity, NF-κB inhibition, cell-cycle inhibition, *etc.* [18]. Recent studies have also shown that baicalein (**1**) was an effective antihepatoma agent [19], exhibited the greatest antiproliferative activiy against bladder cancer cell lines [20], and supressed cell-cycle progression in prostate cancer cells [21]. Although the molecular mechanisms of antitumor activity of baicalein have not been disclosed so far, it should be noted that it acted as a multi-target antitumor natural product and has low cytotoxic effect on normal cells [22][23]. *Liao* and *Hu*, and *Walle et al.* reported that flavones *O*-methylated on the *A*-ring and modified on the *B*-ring exhibited better inhibitory activities than the corresponding unmethylated ones *in vitro* [13][24]. Furthermore, compared with unmethylated flavones, methylated ones had substantially increased metabolic stability as well as intestinal transport [25][26], and had high oral absorption and bioavailability. Sealing the polyphenols of flavone, which prevented it from the first-pass effects *in vivo*, may be responsible for their good anti-tumor activities [26]. *Zhang et al.* synthesized many baicalein derivatives modified at C(8) on the *A*-ring. Most compounds exhibited significantly higher cytotoxicities than baicalein (**1**) against all of the tested cancer cell lines [27]. *Cheng* and co-workers found that certain modifications on the *A*-ring of bacalein (**1**) could enhance the interaction with P-gp 170 protein, prevent its substrate efflux activity, and increase anti-P-glycopretein activity [28]. These exciting results indicate that modifications of **1** on ring *A* or *B* can lead baicalein derivatives with high antitumor effect and low toxicity.

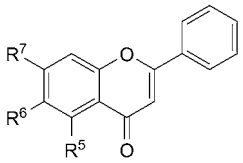
With these information in hand, we designed and synthesized a series of bacalein derivatives which are *O*-alkylated and *O*-acylated at HO–C(5), HO–C(6), and HO–C(7), singly or in combination, on the *A*-ring of baicalein (*Table*). Among them, the 2-hydroxyethoxy and 2-hydroxyacetoxy groups were introduced for modifications of ring *A* to investigate the effects of replacement of phenolic OH with aliphatic OH group(s) on their inhibitory activities against multidrug-resistant tumor cell lines and P-gp 170.

Results and Discussion. – The synthesis of baicalein derivatives modified on the ring *A* was carried out as outlined in *Scheme 1*.

Peracetylization of baicalein (**1**) was performed in Ac_2O with AcONa as the base to give derivative **2** [28] in high yield. Highly selective deacetylation and then alkylation of HO–C(7) of compound **2** to afford corresponding compounds **4** [29], **5** [30], or **17** [29] were achieved in one step by reaction with allyl bromide (AllBr), benzyl bromide (BnBr), or methyl iodide (MeI), respectively, in the presence of an excess of K_2CO_3. The perfect regioselectivity can be attributed to the oxido group at C(7) of ring *A* and its conjugative interaction with C(4)=O of ring *C* (*Scheme 2*). Then, compounds **4**, **5**, and **17** were treated with HCl acid at 60° to afford the deacetylated products **6** [29], **25** [31], and **18** [29], respectively, in quantitative yields. The methylenedioxy derivative **21** was readily prepared by reaction of **6** with $BrCH_2Cl$ in the presence of K_2CO_3 at 60° in 94% yield.

The 2-hydroxyethoxy group was selectively introduced at C(6) of **6** and **18** with 2.5 equiv. of 2-bromoethanol and 3.0 equiv. of K_2CO_3 at 60° to afford the corresponding derivatives **12** and **13**. The *O*-alkylated products **7** and **8** [29] from **6** and **18** were

Table. *A Series of Baicalein Derivatives*

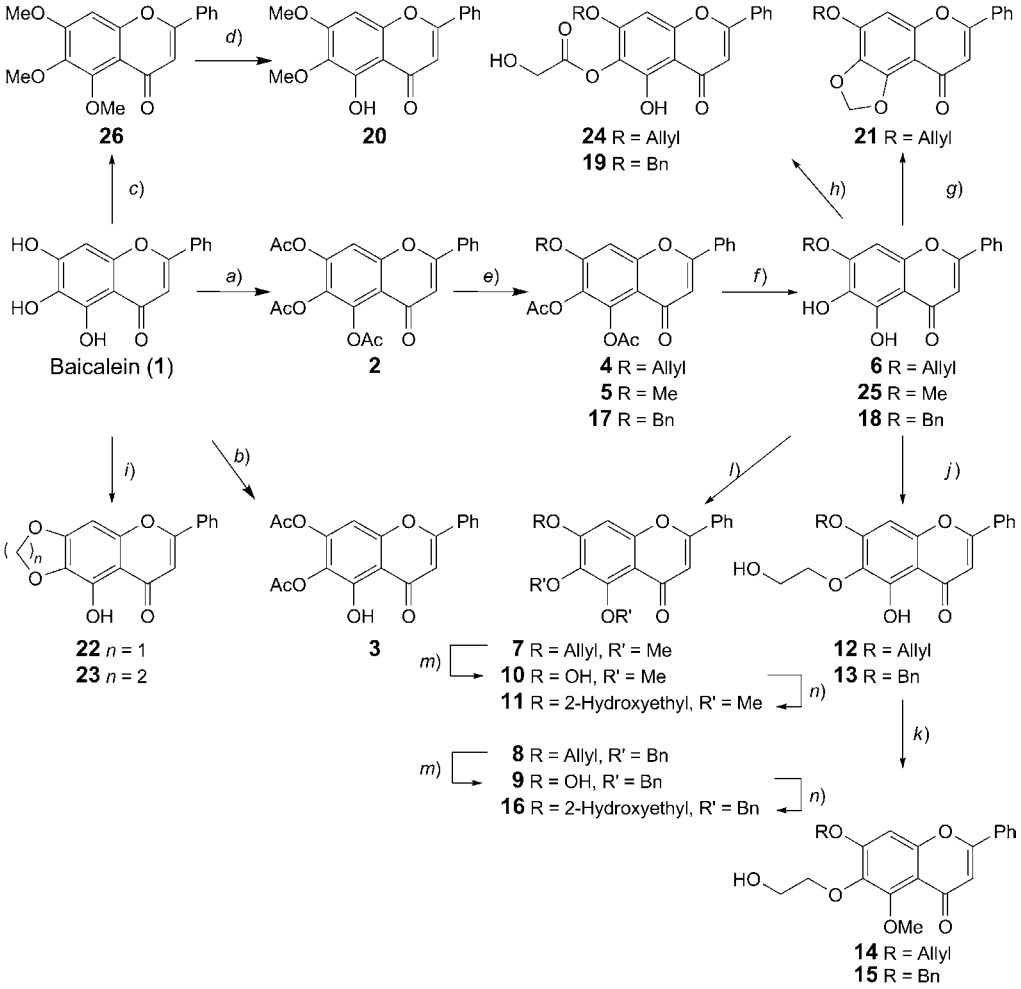


	R^5	R^6	R^7
2	AcO	AcO	AcO
3	OH	AcO	AcO
4	AcO	AcO	Allyloxy
5	AcO	AcO	MeO
6	OH	OH	Allyloxy
7	MeO	MeO	Allyloxy
8	BnO	BnO	Allyloxy
9	BnO	BnO	OH
10	MeO	MeO	OH
11	MeO	MeO	2-Hydroxyethoxy
12	OH	2-Hydroxyethoxy	Allyloxy
13	OH	2-Hydroxyethoxy	BnO
14	MeO	2-Hydroxyethoxy	Allyloxy
15	MeO	2-Hydroxyethoxy	BnO
16	BnO	BnO	2-Hydroxyethoxy
17	AcO	AcO	BnO
18	OH	OH	BnO
19	OH	2-Hydroxyacetoxy	BnO
20	OH	MeO	MeO
21	$-OCH_2O-$		Allyloxy
22	OH		$-OCH_2O-$
23	OH		$-OCH_2CH_2O-$
24	OH	2-Hydroxyacetoxy	Allyloxy
25	OH	OH	MeO
26	MeO	MeO	MeO

prepared by reaction with BnBr and MeI, respectively, in excellent yields. Subsequent removal of the allyl groups of **7** and **8** by $Pd(PPh_3)_4$-catalyzed deallylation gave the flavonoids **10** [32] and **9** [29], respectively, in excellent yields, which were then reacted with 2-bromoethanol to give the derivatives **11** and **16**, respectively. Esterification of HO–C(6) of **6** and **18** with 2.0 equiv. of glycolic acid, 4-(dimethylamino)pyridine (DMAP), and an excess of *N*-[(3-(dimethylamino)propyl]-*N*′-ethylcarbodiimide (EDC) afforded the corresponding derivatives **24** and **19** in acceptable yields. It should be pointed out that addition EDC and DMAP in batches was recommended for these reactions.

Trimethylation of baicalein was readily realized by reaction with MeI in an excellent yield [33]. Subsequent selective demethylation at C(5) using BCl_3 at 0° provided derivative **20** [32] in quantitative yield. Because of the low reactivity of HO–C(5), caused by the intramolecular H-bond between HO–C(5) and C(4)=O of baicalein, the diacetylation of **1** at HO–C(6) and HO–C(7) was smoothly performed in

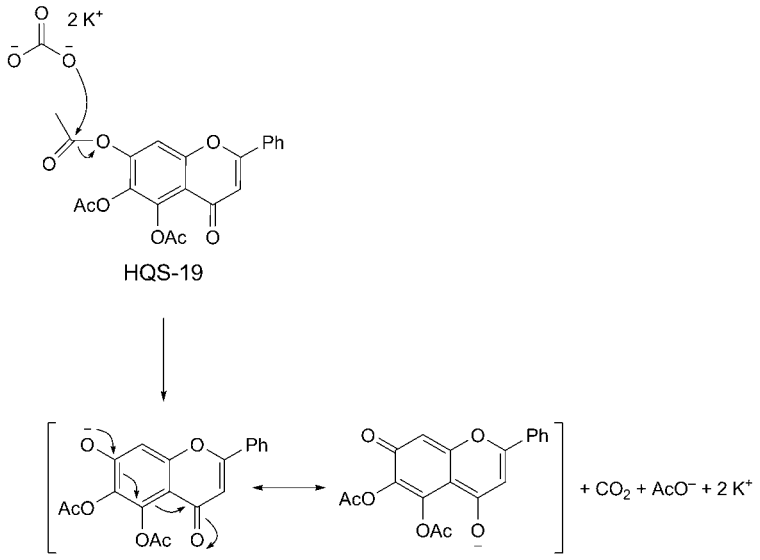
Scheme 1



a) Ac_2O, AcONa, 80°, 2 h, 92%. *b*) Ac_2O/pyridine (py) 5 :1, 120°, 8 h; 84%. *c*) MeI, K_2CO_3, KI, acetone/py 5 :1, 60°, 8 h; 95%. *d*) BCl_3, CH_2Cl_2, 0°, 0.5 h; 99%. *e*) Allyl bromide (for **4**), MeI (for **5**), BnBr (for **17**), K_2CO_3, KI, acetone, 60°, 8 h; 95% for **4**, 58% for **5**, 84% for **17**. *f*) Conc. HCl, EtOH, 60°, 8 h; 97% for **6**, 95% for **25**, 89% for **18**. *g*) $BrCH_2Cl$, K_2CO_3, KI, acetone, 60°, 6 h; 94%. *h*) Glycolic acid, *N*-[3-(dimethylamino)propyl]-*N*′-ethylcarbodiimide (EDC)·HCl, EtN^iPr_2, 4-(dimethylamino)pyridine, (DMAP), CH_2Cl_2, 0° to r.t., 8 h; 61% for **24**, 64% for **19**. *i*) $BrCH_2Cl$ (for **22**), $BrCH_2CH_2Br$ (for **23**), Cs_2CO_3, DMF, 60°, 8 h; 43% for **22**, 49% for **23**. *j*) $BrCH_2CH_2OH$, K_2CO_3, KI, acetone, 60°, 6 h; 90% for **12**, 86% for **13**. *k*) MeI, K_2CO_3, KI, acetone, 60°, 6 h; 78% for **14**, 83% for **15**. *l*) MeI (for **6**), BnBr (for **18**), K_2CO_3, KI, acetone, 60°, 8 h; 96% for **7**, 81% for **8**. *m*) $Pd(PPh_3)_4$, $NaBH_4$, THF, r.t., 4–6 h, 90% for **10**; 88% for **9**. *n*) $BrCH_2CH_2OH$, K_2CO_3, KI, acetone, 60°, 6–10 h, 96% for **11**, 77% for **16**.

Ac_2O/Py 5 :1 (*v*/*v*) at 120° for 8 h in 84% yield. The *O*-methylated derivatives **22** [28] and **23** [34] were obtained by using $BrCH_2Cl$ and 1,2-dibromoethane, respectively, in moderate yields.

Scheme 2



The inhibitory activities against multidrug-resistant tumor cell lines and P-gp 170 of **2**–**25** are underway and will be described subsequently.

Experimental Part

1. *General.* Solvents were purified in the standard way. TLC: Precoated *Merck* silica gel *60* F_{254} plates. Flash column chromatography (CC): silica gel (SiO_2, 200–300 mesh; *Qingdao*, P. R. China). IR Spectra: *FT-IR 7600* instrument. NMR Spectra: *Jeol JNM-ECP 600* MHz spectrometer, if not otherwise stated, in $CDCl_3$, with Me_4Si as the internal standard, and chemical shifts δ in ppm. MS: *Q-TOF GIOBAL* mass spectrometer.

*4-Oxo-2-phenyl-4*H*-1-benzopyran-5,6,7-triyl Triacetate* (**2**). *Baicalein* (**1**; 2.7 g, 10.0 mmol) and AcONa were added to Ac_2O (20 ml), and the soln. was stirred at 80° for 2 h. The reaction was monitored by TLC. The mixture was poured into ice-water (100 ml), and the precipitate was collected by filtration and washed with a small quantity of cool EtOH. The thick solid was dried under vacuum at 80° for 2 h to give **2** (3.6 g, 92%). Gray solid. R_f (AcOEt/hexane 1:2) 0.51. M.p. 193–194°. ^{1}H-NMR: 7.87–7.85 (*m*, 2 arom. H); 7.55–7.50 (*m*, 4 H); 6.66 (*s*, 1 H); 2.45 (*s*, AcO); 2.35 (*s*, AcO); 2.34 (*s*, AcO).

*5-Hydroxy-4-oxo-2-phenyl-4*H*-1-benzopyran-6,7-diyl Diacetate* (**3**). Compound **1** (2.2 g, 8.0 mmol) and AcONa were added to Ac_2O (40 ml) and pyridine (8 ml). The soln. was stirred at 120° for 8 h. The reaction was monitored by TLC. The mixture was poured into ice-water (150 ml), and the precipitate was collected by filtration and washed with a small quantity of cool EtOH. The residue was purified by CC (SiO_2; CH_2Cl_2/MeOH 40:1) to give **3** (2.3 g, 84%). Slightly yellow solid. R_f (AcOEt/hexane 2:3) 0.60. M.p. 202–204°. ^{1}H-NMR: 12.95 (*s*, OH); 7.89 (*dt*, *J* = 8.1, 1.1, 2 arom. H); 7.58 (*dt*, *J* = 6.6, 1.1, 1 arom. H); 7.54 (*td*, *J* = 8.0, 1.1, 2 arom. H); 6.97 (*s*, 1 H); 6.74 (*s*, 1 H); 2.37 (*s*, AcO); 2.35 (*s*, AcO).

*4-Oxo-2-phenyl-7-(prop-2-en-1-yloxy)-4*H*-1-benzopyran-5,6-diyl Diacetate* (**4**). Compound **2** (2.0 g, 5.0 mmol), K_2CO_3 (2.8 g, 20.0 mmol), KI (83.0 mg, 0.5 mmol), and allyl bromide (1.3 ml, 15.0 mmol) were added to dried acetone (100 ml), and the soln. was refluxed at 60° for 8 h. The reaction was monitored by TLC. The hot soln. was filtered, and the filtrate was evaporated. The crude solid was washed with a small quantity of cool AcOEt and dried under vacuum at 80° for 2 h to give **4** (1.8 g, 95%).

White solid. R_f (AcOEt/hexane 1:2) 0.46. M.p. 164–166°. ^{1}H-NMR: 7.85 (*dd*, *J* = 6.6, 1.2, 2 arom. H); 7.54–7.50 (*m*, 3 arom. H); 6.94 (*s*, 1 H); 6.60 (*s*, 1 H); 6.05–5.99 (*m*, CH_2=C*H*); 5.44 (*dd*, *J* = 17.4, 1.2, 1 H of H_2C=); 5.36 (*dd*, *J* = 10.2, 1.2, 1 H of H_2C=); 4.68 (*dt*, *J* = 5.4, 1.8, H_2C=CHCH_2OAr); 2.45 (*s*, AcO); 2.35 (*s*, AcO).

*7-Methoxy-4-oxo-2-phenyl-4*H*-1-benzopyran-5,6-diyl Diacetate* (**5**). Compound **2** (2.0 g, 5.0 mmol), K_2CO_3 (2.8 g, 20.0 mmol), and MeI (1.0 ml, 15.0 mmol) were added to dried acetone (100 ml), and the soln. was heated at 60° for 8 h. The reaction was monitored by TLC. The hot soln. was filtered, and the filtrate was evaporated. The crude solid was washed with a small quantity of cool AcOEt and dried under vacuum at 80° for 2 h to give **5** (1.1 g, 58%). White solid. R_f (AcOEt/hexane 1:2) 0.20. M.p. 149–151°. ^{1}H-NMR (400 MHz): 7.87 (*dd*, *J* = 7.1, 1.6, 2 arom. H); 7.54–7.52 (*m*, 3 arom. H); 6.98 (*s*, 1 H); 6.62 (*s*, 1 H); 3.97 (*s*, MeO); 2.45 (*s*, AcO); 2.36 (*s*, AcO). ^{13}C-NMR (100 MHz): 176.3; 168.7; 167.9; 162.1; 156.2; 155.7; 141.7; 131.5; 131.3; 129.0; 126.1; 111.3; 108.3; 98.2; 56.4; 29.7; 20.8; 20.2. ESI-MS: 369.1 ([*M* + H]$^+$), 391.1 ([*M* + Na]$^+$), 759.2 ([2*M* + Na]$^+$).

*7-(Benzyloxy)-4-oxo-2-phenyl-4*H*-1-benzopyran-5,6-diyl Diacetate* (**17**). Compound **2** (2.0 g, 5.0 mmol), K_2CO_3 (2.8 g, 20.0 mmol), KI (83.0 mg, 0.5 mmol), and BnBr (1.8 ml, 15.0 mmol) were added to dried acetone (100 ml), and the soln. was refluxed at 60° for 8 h. The reaction was monitored by TLC. The hot soln. was filtered, and the filtrate was evaporated. The crude solid was washed with a small quantity of cool AcOEt and dried under vacuum at 80° for 2 h to give **17** (1.8 g, 84%). White solid. R_f (AcOEt/hexane 1:2) 0.29. M.p. 173–175°. ^{1}H-NMR (400 MHz): 7.85 (*dt*, *J* = 7.8, 2.0, 2 arom. H); 7.53–7.50 (*m*, 3 arom. H); 7.41–7.38 (*m*, 5 arom. H); 7.00 (*s*, 1 H); 6.60 (*s*, 1 H); 5.20 (*s*, PhCH_2); 2.46 (*s*, AcO); 2.31 (*s*, AcO).

*5,6-Dihydroxy-2-phenyl-7-(prop-2-en-1-yloxy)-4*H*-1-benzopyran-4-one* (**6**). To a stirred soln. of **4** (1.4 g, 3.5 mmol) in EtOH (100 ml) was added conc. HCl (6.0 ml). The mixture was stirred at 78° for 10 h. The reaction was monitored by TLC. The reaction soln. was concentrated under reduced pressure until a large quantity of yellow solid appeared. The solid was collected by filtration and washed with a small quantity of cool EtOH. The thick solid was dried under vacuum at 80° for 2 h to give **6** (1.0 g, 97%). Yellow solid. R_f (AcOEt/hexane 2:3) 0.52. M.p. 150–152°. ^{1}H-NMR ((D$_6$)DMSO): 12.54 (*s*, OH); 8.79 (*s*, OH); 8.10 (*d*-like, *J* = 7.2, 2 arom. H); 7.63–7.59 (*m*, 3 arom. H); 7.01 (*s*, 1 H); 6.97 (*s*, 1 H); 6.14–6.07 (*m*, CH_2=C*H*); 5.52–5.48 (*m*, 1 H of CH_2=); 5.34–5.31 (*m*, 1 H of HC_2=); 4.75 (*dt*, *J* = 5.4, 1.2, CH_2=CHCH_2).

The flavones **18** and **25** were prepared in the same manner.

*7-(Benzyloxy)-5,6-dihydroxy-2-phenyl-4*H*-1-benzopyran-4-one* (**18**). Yield: 89%. Yellow solid. R_f (AcOEt/hexane 1:1) 0.51. M.p. 193–195°. ^{1}H-NMR: 7.87 (*d*, *J* = 7.2, 2 arom. H); 7.56–7.36 (*m*, 8 arom. H); 6.67 (*s*, 1 H); 6.66 (*s*, 1 H); 5.26 (*s*, ArCH_2). ^{13}C-NMR: 182.7; 164.1; 151.8; 150.5; 145.9; 135.3; 131.8; 131.4; 130.0; 129.0; 128.8; 128.6; 127.6; 126.3; 106.2; 105.4; 91.8; 71.3.

*5,6-Dihydroxy-7-methoxy-2-phenyl-4*H*-1-benzopyran-4-one* (**25**). Yellow solid. Yield: 95%. R_f (AcOEt/hexane 2:3) 0.31. M.p. 221–223°. ^{1}H-NMR (400 MHz): 12.51 (*s*, OH); 7.91 (*d*, *J* = 6.0, 2 arom. H); 7.55–7.53 (*m*, 3 arom. H); 6.70 (*s*, 1 H); 6.64 (*s*, 1 H); 4.02 (*s*, MeO). ^{13}C-NMR (100 MHz): 182.7; 164.1; 152.9; 150.7; 145.6; 131.8; 131.5; 129.6; 129.1; 126.3; 106.1; 105.5; 90.5; 56.5.

*5-Hydroxy-4-oxo-2-phenyl-7-(prop-2-en-1-yloxy)-4*H*-1-benzopyran-6-yl 2-Hydroxyacetate* (**24**). To a stirred soln. of **6** (150.0 mg, 0.5 mmol) in dry CH_2Cl_2 (100 ml) were added EDC·HCl (239.6 mg, 1.3 mmol), Et^{i}Pr$_2$ (0.5 ml, 1.5 mmol), and glycolic acid (94.5 mg, 0.7 mmol). The mixture was stirred at 0° for 30 min, and maintained at 25° for another 4 h. DMAP (12.1 mg, 0.1 mmol) was added. The mixture was stirred at r.t. for another 4 h. The reaction was monitored by TLC. The soln. was concentrated under reduced pressure. The residue was diluted with AcOEt (50 ml). The combined org. phase was washed with aq. 10% citric acid, 5% aq. $NaHCO_3$, brine, dried (Na_2SO_4), and then concentrated. The residue was purified by CC (SiO_2) to give **24** (112.3 mg, 61%). White solid. R_f (AcOEt/hexane 1:2) 0.22. M.p. 173–175°. IR (KBr): 3391*m*, 2922*w*, 1778*m*, 1668*s*, 1615*s*, 1585*m*, 1459*s*, 1372*s*, 1349*s*, 1287*m*, 1155*m*, 1125*m*, 1097*m*, 980*m*, 847*m*, 832*w*, 667*m*, 656*m*. ^{1}H-NMR (400 MHz, (D$_6$)DMSO): 12.89 (*s*, C(5)–OH); 8.11 (*d*-like, *J* = 7.1, 2 arom. H); 7.63–7.56 (*m*, 3 arom. H); 7.09 (*s*, 1 H); 7.07 (*s*, 1 H); 6.02–5.98 (*m*, CH_2=C*H*); 5.73 (*t*, *J* = 6.7, OH); 5.39 (*dd*, *J* = 17.2, 1.4, 1 H of CH_2=); 5.28 (*d*, *J* = 10.6, 1 H of CH_2=); 4.75 (*d*, *J* = 4.7, CH_2=CHCH_2); 4.33 (*d*, *J* = 6.7, CH_2OH). ^{13}C-NMR (100 MHz, (D$_6$)DMSO): 183.2; 171.4; 164.8; 157.1; 155.2; 152.5; 133.2; 131.4; 130.1; 127.4; 123.1; 118.7; 106.1; 93.6; 70.2; 60.0. ESI-MS: 369.2

([M + H]$^+$), 391.1 ([M + Na]$^+$), 759.2 ([2M + Na]$^+$). HR-MS: 369.0977 ([M + H]$^+$, $C_{20}H_{17}O_7^+$; calc. 369.0969).

The flavone **19** was prepared in the same manner.

*7-(Benzyloxy)-5-hydroxy-4-oxo-2-phenyl-4*H*-1-benzopyran-6-yl 2-Hydroxyacetate* (**19**). Yield: 64%. White solid. R_f (AcOEt/hexane 1:2) 0.29. M.p. 162–165°. IR (KBr): 3328*m*, 2926*m*, 2720*w*, 1776*m*, 1667*s*, 1501*w*, 1407*s*, 1368*s*, 1292*w*, 1216*w*, 1162*m*, 1126*m*, 1097*m*, 832*m*, 734*w*, 697*w*. ^{1}H-NMR (400 MHz, (D_6)DMSO): 12.91 (*s*, C(5)–OH); 8.09 (*d*-like, J = 7.0, 2 arom. H); 7.59 (*d*, J = 7.8, 3 arom. H); 7.41–7.34 (*m*, 5 arom. H); 7.15 (*s*, 1 H); 7.09 (*s*, 1 H); 5.75 (*t*, J = 6.7, OH); 5.30 (*s*, PhCH_2); 4.31 (*s*, CH_2OH). ^{13}C-NMR (100 MHz, (D_6)DMSO): 183.2; 171.5; 164.8; 157.2; 155.2; 136.7; 133.2; 131.4; 130.1; 129.5; 129.0; 128.0; 127.4; 123.2; 106.1; 93.7; 71.3; 60.0. ESI-MS: 419.2 ([M + H]$^+$). HR-MS: 419.1143 ([M + H]$^+$, $C_{24}H_{19}O_7^+$; calc. 419.1125).

*7-Phenyl-4-(prop-2-en-1-yloxy)-9*H*-[1,3]dioxolo[4,5-f][1]benzopyran-9-one* (**21**). To a stirred soln. of **6** (310.3 mg, 1.0 mmol) in dry DMF (1.0 ml) were added Cs_2CO_3 (814.6 mg, 2.5 mmol) and $BrCH_2Cl$ (168.0 µl, 2.5 mmol). The mixture was stirred at 80° for 8 h. The reaction was monitored by TLC. The mixture was diluted with CH_2Cl_2 (100 ml), then washed with aq. HCl (1 mol/l) and brine, dried (Na_2SO_4), and then concentrated. The residue was purified by CC (SiO_2) to give **21** (303.0 mg, 94%). White solid. R_f (AcOEt/hexane 4:3) 0.40. M.p. 165–167°. IR (KBr): 3451*m*, 2923*m*, 2725*w*, 1632*s*, 1607*s*, 1491*s*, 1455*s*, 1411*s*, 1341*s*, 1367*s*, 1300*m*, 1188*s*, 1085*s*, 1036*m*, 1026*m*, 948*w*, 915*m*, 832*m*, 798*w*, 704*w*. ^{1}H-NMR (400 MHz): 7.86 (*dt*, J = 6.6, 1.2, 2 arom. H); 7.54–7.49 (*m*, 3 arom. H); 6.70 (*s*, 1 H); 6.69 (*s*, 1 H); 6.23 (*s*, OCH_2O); 6.12–6.05 (*m*, CH_2=C*H*); 5.50 (*dq*, J = 17.4, 1.8, 1 H of CH_2=); 5.38 (*dq*, J = 10.2, 1.2, 1 H of CH_2=); 4.75 (*dt*, J = 5.4, 1.8, CH_2=CHCH_2OAr). ^{13}C-NMR (100 MHz): 176.7; 162.7; 152.4; 146.7; 146.0; 133.5; 131.8; 131.7; 131.5; 129.0; 126.1; 119.1; 107.2; 106.2; 103.7; 96.2; 70.4. ESI-MS: 321.2 ([M – H]$^-$). HR-MS: 323.0914 ([M + H]$^+$, $C_{19}H_{15}O_5^+$; calc. 323.0914).

*5-Hydroxy-6-(2-hydroxyethoxy)-2-phenyl-7-(prop-2-en-1-yloxy)-4*H*-1-benzopyran-4-one* (**12**). Compound **6** (103.7 mg, 0.3 mmol), K_2CO_3 (234.9 mg, 1.7 mmol), and 2-bromoethanol (71.3 µl, 1.0 mmol) were added to dried acetone (20 ml), and the soln. was refluxed at 60° for 6 h. The reaction was monitored by TLC. The hot soln. was filtered, and the filtrate was evaporated. The residue was diluted with AcOEt (50 ml). The org. phase was washed with aq. HCl (1 mol/l), H_2O, and brine, dried (Na_2SO_4), and then concentrated. The residue was purified by CC (SiO_2) to give **12** (108.3 mg, 90%). Yellow solid. R_f (AcOEt/hexane 1:1) 0.46. M.p. 137–139°. IR (KBr): 3443*m*, 2937*m*, 2722*w*, 1650*s*, 1588*s*, 1418*s*, 1362*s*, 1301*m*, 1273*w*, 1132*m*, 1008*m*, 833*m*, 704*w*. ^{1}H-NMR (400 MHz, (D_6)DMSO): 12.77 (*s*, C(5)–OH); 8.08 (*d*-like, J = 7.8, 2 arom. H); 7.63–7.54 (*m*, 3 arom. H); 7.03 (*s*, 1 H); 6.97 (*s*, 1 H); 6.13–6.03 (*m*, CH_2=C*H*); 5.50 (*dd*, J = 3.4, 1.5, 1 H of CH_2=); 5.46 (*dd*, J = 3.4, 1.5, 1 H of CH_2=); 4.73 (*d*, J = 5.4, CH_2=CHCH_2OAr); 4.66 (*t*, J = 5.4, CH_2O*H*); 3.95 (*t*, J = 5.4, ArOCH_2CH$_2$OH); 3.65 (*dd*, J = 10.7, 5.4, ArOCH$_2$CH_2OH). ^{13}C-NMR (100 MHz, (D_6)DMSO): 182.4; 163.5; 157.8; 152.6; 152.2; 132.7; 132.2; 131.3; 130.7; 129.2; 126.5; 117.9; 105.4; 105.0; 92.7; 74.2; 69.3; 60.3. ESI-MS: 355.1 ([M + H]$^+$), 377.2 ([M + Na]$^+$), 731.3 ([2M + Na]$^+$). HR-MS: 355.1186 ([M + H]$^+$, $C_{20}H_{19}O_6^+$; calc. 355.1176).

The flavone **13** was prepared in the same manner.

*7-(Benzyloxy)-5-hydroxy-6-(2-hydroxyethoxy)-2-phenyl-4*H*-1-benzopyran-4-one* (**13**). Yield: 86%. White solid. R_f (AcOEt/hexane 1:1) 0.54. M.p. 194–196°. IR (KBr): 3417*m*, 2951*m*, 2721*w*, 1651*s*, 1409*s*, 1394*s*, 1189*w*, 1127*w*, 1008*w*, 981*m*, 832*m*, 704*w*. ^{1}H-NMR ((D_6)DMSO): 12.81 (*s*, C(5)–OH); 8.11 (*d*-like, J = 7.2, 2 arom. H); 7.64–7.59 (*m*, 3 arom. H); 7.53 (*d*, J = 7.8, 2 arom. H); 7.44 (*t*, J = 7.8, 2 arom. H); 7.38 (*t*, J = 7.2, 1 arom. H); 7.11 (*s*, 1 H); 7.06 (*s*, 1 H); 5.31 (*s*, PhCH_2); 4.64 (*t*, J = 6.0, CH_2O*H*); 3.99 (*t*, J = 5.4, ArOCH_2); 3.67–3.64 (*m*, CH_2OH). ^{13}C-NMR ((D_6)DMSO): 182.4; 163.5; 158.0; 152.7; 152.3; 136.2; 132.2; 131.5; 130.7; 129.2; 128.6; 128.1; 127.6; 126.5; 105.5; 105.1; 92.9; 74.3; 70.4; 60.3. ESI-MS: 405.2 ([M + H]$^+$), 427.1 ([M + Na]$^+$), 831.4 ([2M + Na]$^+$). HR-MS: 405.1348 ([M + H]$^+$, $C_{24}H_{21}O_6^+$; calc. 405.1333).

*6-(2-Hydroxyethoxy)-5-methoxy-2-phenyl-7-(prop-2-en-1-yloxy)-4*H*-1-benzopyran-4-one* (**14**). Compound **12** (88.5 mg, 0.3 mmol), K_2CO_3 (171.4 mg, 1.2 mmol), and MeI (77.0 µl, 1.2 mmol) were added to dried acetone (20 ml), and the soln. was refluxed at 60° for 6 h. The reaction was monitored by TLC. The hot soln. was filtered, and the filtrate was evaporated. The residue was diluted with AcOEt (50 ml). The org. phase was washed with aq. HCl (1 mol/l), H_2O, and brine, dried (Na_2SO_4), and then concentrated. The residue was purified by CC (SiO_2) to give **14** (72.6 mg, 78%). White solid. R_f (AcOEt/

hexane 1:1) 0.15. M.p. 119–122°. IR (KBr): 3489*m*, 2934*m*, 2626*w*, 1635*s*, 1602*s*, 1450*s*, 1367*s*, 1293*w*, 1272*w*, 1196*w*, 1116*m*, 1035*w*, 832*m*, 704*w*. ^{1}H-NMR: 7.88 (*d*-like, $J = 7.2$, 2 arom. H); 7.54–7.50 (*m*, 3 arom. H); 6.86 (*s*, 1 H); 6.73 (*s*, 1 H); 6.15–6.09 (*m*, CH_2=C*H*); 5.52 (*dd*, $J = 17.4, 1.2$, 1 H of CH_2=); 5.42 (*dd*, $J = 10.2, 1.2$, 1 H of CH_2=); 4.71 (*d*, $J = 5.4$, CH_2=CHCH_2OAr); 4.24 (*t*, $J = 4.2$, ArOCH_2CH$_2$OH); 4.02 (*s*, MeO); 3.78 (*t*, $J = 4.2$, CH_2OH). ^{13}C-NMR: 177.0; 161.5; 156.6; 154.6; 152.5; 139.1; 131.6; 131.5; 129.1; 126.2; 119.5; 113.1; 108.4; 97.8; 76.1; 70.1; 62.6; 61.6. ESI-MS: 369.2 ($[M + H]^+$), 759.2 ($[2M + Na]^+$). HR-MS: 369.1337 ($[M+H]^+$, $C_{21}H_{21}O_6^+$; calc. 369.1333).

The flavone **15** was prepared in the same manner.

*7-(Benzyloxy)-6-(2-hydroxyethoxy)-5-methoxy-2-phenyl-4*H*-1-benzopyran-4-one* (**15**). Yield: 83%. White solid. R_f (AcOEt/hexane 1:1) 0.17. M.p. 164–166°. IR (KBr): 3417*m*, 3062*m*, 2932*m*, 2730*w*, 1642*s*, 1606*s*, 1447*s*, 1357*s*, 1312*w*, 1189*w*, 1123*m*, 1099*w*, 1009*w*, 832*m*, 722*w*, 704*w*. ^{1}H-NMR: 7.89 (*d*-like, $J = 6.6$, 2 arom. H); 7.55–7.48 (*m*, 5 arom. H); 7.45 (*t*, $J = 7.8$, 2 arom. H); 7.40 (*t*, $J = 7.2$, 1 arom. H); 6.95 (*s*, 1 H); 6.78 (*s*, 1 H); 5.23 (*s*, PhCH_2); 4.24 (*s*, ArOCH_2); 4.02 (*s*, MeO); 3.75 (*s*, CH_2OH). ^{13}C-NMR: 177.1; 161.7; 156.9; 154.6; 152.5; 139.4; 135.0; 131.5; 131.3; 129.0; 128.9; 128.8; 127.6; 126.1; 113.0; 108.2; 97.9; 76.1; 71.4; 62.5; 61.5. ESI-MS: 419.2 ($[M + H]^+$), 859.3 ($[M + Na]^+$). HR-MS: 419.1502 ($[M+H]^+$, $C_{25}H_{23}O_6^+$; calc. 419.1489).

*5,6,7-Trimethoxy-2-phenyl-4*H*-1-benzopyran-4-one* (**26**). Compound **1** (3.2 mg, 12.0 mmol), K_2CO_3 (24.8 g, 180.0 mmol), and MeI (22.4 ml, 360.0 mmol) were added to dried acetone/pyridine 5:1 (*v*/*v*), and the soln. was refluxed at 60° for 8 h. The reaction was monitored by TLC. The hot soln. was filtered, and the filtrate was evaporated. The crude solid was purified by CC (SiO_2) to give **26** (3.5 g, 95%) as a grey solid. R_f (AcOEt/hexane 4:3) 0.41. M.p. 164–166°. ^{1}H-NMR: 7.88 (*dt*, $J = 5.9, 1.4$, 2 arom. H); 7.53–7.49 (*m*, 3 arom. H); 6.82 (*s*, 1 H); 6.68 (*s*, 1 H); 3.99 (*d*-like, 2 MeO); 3.93 (*s*, MeO).

*5-Hydroxy-6,7-dimethoxy-2-phenyl-4*H*-1-benzopyran-4-one* (**20**). Compound **26** (1.8 g, 6.0 mmol) was added to dried CH_2Cl_2 (100 ml). Then, 1M BCl_3/CH_2Cl_2 (1.2 ml) was added slowly at 0°. The mixture was stirred at 0° for 30 min, and MeOH (15 ml) was added. The mixture was concentrated, and the crude solid was purified by CC (SiO_2) to give **20** (1.7 g, 99%). Grey solid. R_f (AcOEt/hexane 2:3) 0.55. M.p. 158–160°. ^{1}H-NMR: 12.69 (*s*, HO–Ar); 7.89 (*dt*, $J = 6.8, 1.8$, 2 arom. H); 7.57–7.52 (*m*, 3 arom. H); 6.68 (*s*, 1 H); 6.58 (*s*, 1 H); 3.98 (*s*, MeO); 3.93 (*s*, MeO). ESI-MS: 299.0 ($[M + H]^+$), 321.0 ($[M + Na]^+$), 337.0 ($[M + K]^+$), 619.1 ($[2M + Na]^+$).

*9-Hydroxy-6-phenyl-8*H*-[1,3]dioxolo[4,5-*g*][1]-benzopyran-8-one* (**22**). To a stirred soln. of **1** (270.1 mg, 1.0 mmol) in dry DMF (1.0 ml) were added Cs_2CO_3 (814.6 mg, 2.5 mmol) and $BrCH_2Cl$ (168.0 µl, 2.5 mmol). The mixture was stirred at 65° for 10 h. The reaction was monitored by TLC. The mixture was diluted with CH_2Cl_2 (100 ml), then washed with 1M aq. HCl and brine, dried (Na_2SO_4), and then concentrated. The residue was purified by CC (SiO_2) to give **22** (127.7 mg, 43%). Yellow solid. R_f (AcOEt/hexane 1:2) 0.66. M.p. 214–216°. ^{1}H-NMR: 8.08 (*d*-like, $J = 8.4$, 2 arom. H); 7.57–7.51 (*m*, 3 arom. H); 6.69 (*s*, 1 H); 6.60 (*s*, 1 H); 6.11 (*m*, ArOCH_2O). ^{13}C-NMR: 183.0; 164.0; 154.1; 153.3; 142.2; 131.9; 131.1; 130.1; 129.1; 126.2; 107.8; 105.5; 102.7; 89.5. ESI-MS: 283.2 ($[M + H]^+$), 305.0 ($[M + Na]^+$).

*2,3-Dihydro-10-hydroxy-7-phenyl-9*H*-[1,4]dioxino[2,3-*g*][1]-benzopyran-9-one* (**23**). To a stirred soln. of **1** (270.1 mg, 1.0 mmol) in dry DMF (1.0 ml) were added Cs_2CO_3 (814.6 mg, 2.5 mmol) and 1,2-dibromoethane (130.0 µl, 1.5 mmol). The mixture was stirred at 80° for 10 h. The reaction was monitored by TLC. The mixture was diluted with CH_2Cl_2 (100 ml), then washed with 1M aq. HCl and brine, dried (Na_2SO_4), and then concentrated. The residue was purified by CC (SiO_2) to give **23** (145.1 mg, 49%). Yellow solid. R_f (AcOEt/hexane 1:2) 0.51. M.p. 208–210°. ^{1}H-NMR ((D_6)DMSO): 12.87 (*s*, OH); 8.08 (*d*-like, $J = 7.2$, 2 arom. H); 7.62–7.56 (*m*, 3 arom. H); 6.99 (*s*, 1 H); 6.78 (*s*, 1 H); 4.41–4.40 (*m*, ArOCH_2); 4.31–4.30 (*m*, ArOCH_2). ^{13}C-NMR ((D_6)DMSO): 183.0; 164.0; 150.4; 150.2; 148.5; 132.6; 131.2; 129.6; 128.6; 126.9; 105.4; 104.9; 95.5; 65.5; 63.9. ESI-MS: 297.1 ($[M + H]^+$), 318.4 ($[M + Na]^+$), 615.2 ($[2M + Na]^+$).

*5,6-Bis(benzyloxy)-2-phenyl-7-(prop-2-en-1-yloxy)-4*H*-1-benzopyran-4-one* (**8**). Compound **6** (0.9 g, 3.0 mmol), K_2CO_3 (4.3 g, 30.0 mmol), KI (50.0 mg, 0.3 mmol), and BnBr (2.8 ml, 24.0 mmol) were added to dried acetone (80 ml), and the soln. was refluxed at 60° for 8 h. The reaction was monitored by TLC. The hot soln. was filtered, and the filtrate was evaporated. The crude solid was washed with a small quantity of cool EtOH and dried under vacuum at 80° for 2 h to give **8** (1.2 g, 81%). White solid. R_f (AcOEt/hexane 1:2) 0.56. M.p. 156–158°. ^{1}H-NMR: 7.90–7.88 (*m*, 2 arom. H); 7.68–7.66

(*d*-like, $J = 6.6$, 2 arom. H); 7.53–7.50 (*m*, 3 arom. H); 7.46–7.44 (*m*, 2 arom. H); 7.40–7.32 (*m*, 6 arom. H); 6.83 (*s*, 1 H); 6.80 (*s*, 1 H); 6.11–6.05 (*m*, CH_2=C*H*); 5.48 (*d*, $J = 16.8$, 1 H of CH_2=); 5.38 (*d*, $J = 10.8$, 1 H of CH_2=); 5.15 (*s*, PhCH_2); 5.06 (*s*, PhCH_2); 4.66 (*d*, $J = 16.8$, H_2C=CHCH_2OAr).

*5,6-Dimethoxy-2-phenyl-7-(prop-2-en-1-yloxy)-4*H*-1-benzopyran-4-one* (**7**). Compound **6** (1.9 g, 6.1 mmol), K_2CO_3 (5.1 g, 36.5 mmol), KI (100.0 mg, 0.6 mmol), and MeI (11.2 ml, 18.3 mmol) were added to dried acetone (150 ml), and the soln. was refluxed at 60° for 8 h. The reaction was monitored by TLC. The hot soln. was filtered, and the filtrate was evaporated. The crude solid was washed with a small quantity of cool EtOH and dried under vacuum at 80° for 2 h to give **7** (2.0 g, 96%). White solid. R_f (AcOEt/hexane 1:2) 0.32. M.p. 138–140°. IR (KBr): 3416*m*, 2939*m*, 2721*w*, 1635*s*, 1606*s*, 1407*s*, 1370*s*, 1295*w*, 1194*w*, 1127*m*, 1009*m*, 981*w*, 832*m*, 812*w*, 704*w*. ^{1}H-NMR: 7.87 (*dd*, $J = 7.8, 1.8$, 2 arom. H); 7.53–7.48 (*m*, 3 arom. H); 6.81 (*s*, 1 H); 6.75 (*s*, 1 H); 6.14–6.08 (*m*, CH_2=C*H*); 5.50 (*dd*, $J = 17.4, 1.2$, 1 H of CH_2=); 5.38 (*dd*, $J = 10.8, 1.2$, 1 H of CH_2=); 4.71 (*d*, $J = 5.4$, CH_2=CHCH_2OAr); 3.99 (*s*, MeO); 3.92 (*s*, MeO). ^{13}C-NMR ((D_6)DMSO): 177.2; 161.1; 156.7; 154.4; 152.7; 140.6; 131.9; 131.6; 131.2; 129.0; 126.0; 118.6; 113.1; 97.4; 69.7; 62.2; 61.5. ESI-MS: 339.2 ($[M + H]^+$), 699.2 ($[2M + Na]^+$). HR-MS: 339.1228 ($[M+H]^+$, $C_{20}H_{19}O_5^+$; calc. 339.1227).

*5,6-Bis(benzyloxy)-7-hydroxy-2-phenyl-4*H*-1-benzopyran-4-one* (**9**). To a stirred soln. of **8** (1.3 g, 2.6 mmol) in dry THF (100 ml) was added $Pd(PPh_3)_4$ (68.8 mg, 0.06 mmol), and the soln. was stirred. After *ca*. 5 min, $NaBH_4$ (151.2 mg, 4.0 mmol) was added. When the reaction was completed (TLC monitoring), 1M aq. HCl was added until the pH of the soln. was between 4 and 5. The mixture was concentrated, and the residue was purified by CC (SiO_2) to give **9** (0.9 g, 88%). White solid. R_f (AcOEt/hexane 1:2) 0.54. M.p. 189–191°. ^{1}H-NMR: 7.89–7.87 (*m*, 2 arom. H); 7.67 (*d*-like, $J = 6.6$, 2 arom. H); 7.53–7.50 (*m*, 3 arom. H); 7.41 (*tt*, $J = 7.2, 1.8$, 2 arom. H); 7.37–7.35 (*m*, 4 arom. H); 7.32–7.30 (*m*, 2 arom. H); 6.86 (*s*, 1 H); 6.70 (*s*, 1 H); 5.19 (*s*, ArCH_2); 5.17 (*s*, ArCH_2).

*7-Hydroxy-5,6-dimethoxy-2-phenyl-4*H*-1-benzopyran-4-one* (**10**). To a stirred soln. of **7** (338.1 mg, 1.0 mmol) in dry THF (60 ml) was added $Pd(PPh_3)_4$ (27.0 mg, 0.02 mmol), and the soln. was stirred. After *ca*. 5 min, $NaBH_4$ (60.0 mg, 1.5 mmol) was added. When the reaction was complete (TLC monitoring), 1M aq. HCl was added until the pH of the soln. was between 4 and 5. The mixture was concentrated, and the residue was purified by CC (SiO_2) to give **10** (268.2 mg, 90%). White solid. R_f (AcOEt/hexane 2:3) 0.17. M.p. 122–124°. ^{1}H-NMR: 7.88–7.86 (*m*, 2 arom. H); 7.52–7.50 (*m*, 3 arom. H); 7.00 (*s*, 1 H); 6.93 (*s*, 1 H); 4.04 (*s*, MeO); 4.00 (*s*, MeO).

*5,6-Bis(benzyloxy)-7-(2-hydroxyethoxy)-2-phenyl-4*H*-1-benzopyran-4-one* (**16**). Compound **9** (930.0 mg, 3.0 mmol), K_2CO_3 (3.3 g, 24.0 mmol), and 2-bromoethanol (310 µl, 10.0 mmol) were added to dried acetone (80 ml), and the soln. was refluxed at 60° for 8 h. The reaction was monitored by TLC. The hot soln. was filtered, and the filtrate was evaporated. The crude solid was washed with a small quantity of cool EtOH and dried under vacuum at 80° for 2 h to give **16** (1.1 g, 77%). White solid. R_f (CH_2Cl_2/MeOH 20:1) 0.55. M.p. 197–199°. IR (KBr): 3384*m*, 3032*m*, 2951*m*, 1633*s*, 1600*s*, 1448*s*, 1361*s*, 1290*w*, 1268*w*, 1191*w*, 1120*m*, 1077*m*, 982*w*, 833*w*, 771*w*, 734*w*, 697*w*. ^{1}H-NMR: 7.89–7.87 (*m*, 2 arom. H); 7.67 (*dt*, $J = 6.6, 1.8$, 2 arom. H); 7.53–7.47 (*m*, 5 arom. H); 7.40–7.34 (*m*, 6 arom. H); 6.82 (*s*, 1 H); 6.70 (*s*, 1 H); 5.15 (*s*, PhCH_2); 5.07 (*s*, PhCH_2); 4.40–4.38 (*m*, 2 H); 3.72–3.70 (*m*, 2 H). ^{13}C-NMR ((D_6)DMSO): 175.9; 160.2; 157.3; 154.1; 150.4; 139.1; 137.5; 137.3; 131.6; 130.9; 129.1; 128.4; 128.2; 128.1; 128.0; 127.8; 126.1; 112.4; 107.6; 98.3; 75.8; 74.9; 70.9; 59.4. ESI-MS: 495.2 ($[M + H]^+$), 517.3 ($[M + Na]^+$). HR-MS: 495.1806 ($[M+H]^+$, $C_{31}H_{27}O_6^+$; calc. 495.1802).

*7-(2-Hydroxyethoxy)-5,6-dimethoxy-2-phenyl-4*H*-1-benzopyran-4-one* (**11**). Compound **10** (149.4 mg, 0.5 mmol), K_2CO_3 (691.0 mg, 5.0 mmol), and 2-bromoethanol (100.0 µl, 1.5 mmol) were added to dried acetone (80 ml), and the soln. was refluxed at 60° for 10 h. The reaction was monitored by TLC. The hot soln. was filtered, and the filtrate was evaporated. The crude solid was washed with a small quantity of cool EtOH and dried under vacuum at 80° for 2 h to give **11** (128.5 mg, 90%). White solid. R_f (AcOEt/hexane 2:1) 0.15. M.p. 115–117°. IR (KBr): 3419*w*, 2938*w*, 2619*w*, 1634*s*, 1601*m*, 1469*m*, 1418*s*, 1361*m*, 1273*w*, 1194*w*, 1120*m*, 1031*w*, 994*w*, 833*m*, 766*w*, 704*w*. ^{1}H-NMR (400 MHz): 7.87 (*dd*, $J = 7.1, 2.0$, 2 arom. H); 7.52–7.50 (*m*, 3 arom. H); 6.84 (*s*, 1 H); 6.67 (*s*, 1 H); 4.23 (*t*, $J = 4.4$, ArOCH_2); 4.08 (*t*, $J = 4.4$, CH_2OH); 4.00 (*s*, MeO); 3.93 (*s*, MeO). ^{13}C-NMR (100 MHz): 177.2; 161.2; 156.9; 154.4; 152.8; 140.6; 131.5; 131.3; 129.0; 126.0; 113.3; 108.4; 97.5; 70.7; 62.2; 61.6; 61.0. ESI-MS: 343.1 ($[M + H]^+$), 707.2 ($[2M + Na]^+$). HR-MS: 343.1109 ($[M+H]^+$, $C_{19}H_{19}O_6^+$; calc. 343.1176).

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