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A New and Efficient Synthesis of Wedelolactone Derivatives†

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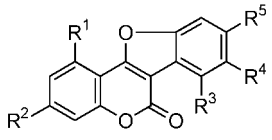
A new and facile method based on an intermolecular cycloaddition was described for the synthesis of wedelolactone derivatives.

Keywords wedelolactone, intermolecular, cycloaddition, coumarin

Introduction

Coumestan, known as 6*H*-benzofuro[3,2-*c*][1]benzopyran-6-one, represents the basic ring system for a number of naturally occurring products, such as wedelolactone, coumestrol, aureol, medicagol, trifiliol, psoralidin as shown in Scheme 1 and many others[1] with a variety of biological activities that include phytoestrogenic, antibacterial, antifungal, antimyotoxic, and phytoalexin effects.[2] Wedelolactone was first isolated from the extract of *Wedelia calendulaceae* in 1956,[3] and later from *Eclipta alba* L[4] and widely used as a traditional medicine for the treatment of liver disorders including liver cirrhosis and infective heptatitis both in China and India.[5] Wedelolactone possesses a wide range of biological activities, and is used as an antibacterial,[6] an antidote for snake venom,[7] and direct inhibition of IKK complex, resulting in suppression of LPS-induced caspase-11 expression.[8] Various methods of preparation of coumestans are reported in the literature.[9] Some years ago we reported a new synthetic approach to coumestan derivatives,[10] which involves an intramolecular palladium-catalyzed ring closure reaction of 3-(2-hydroxyphenyl)-coumarin obtained from condensation of substituted 2-hydroxyphenylacetic acid and 2-hydroxybenzaldehyde. As an extension of our previous work, we herein report a new and efficient synthetic method of wedelolactone derivatives.

Scheme 1

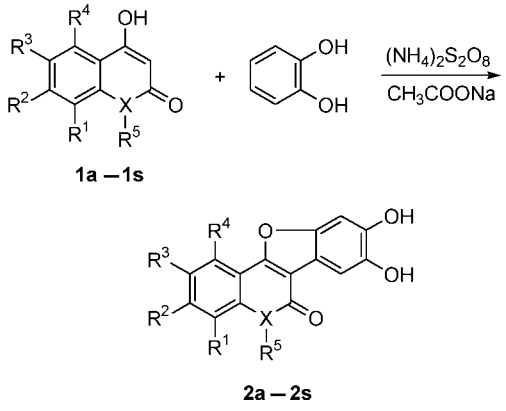


$R^1 = R^2 = R^3 = H$; $R^4 = R^5 = OH$	1,12-Dihydroxy coumestan
$R^1 = R^4 = R^5 = OH$; $R^2 = OMe$; $R^3 = H$	Wedelolactone
$R^1 = R^3 = R^4 = H$; $R^2 = R^5 = OH$	Coumestrol
$R^1 = R^2 = R^5 = OH$; $R^3 = R^4 = H$	Aureol
$R^1 = R^3 = H$; $R^2 = OH$; $R^4 = R^5 = CH_2OCH_2$	Mdicagol
$R^1 = R^4 = H$; $R^2 = R^3 = OH$; $R^5 = OMe$	Tifiliol
$R^1 = R^3 = R^4 = H$; $R^5 = OH$; R^2 = isopentenyl	Psoralidin

Results and discussion

Our synthetic approach leading to wedelolactone derivatives is based on an intermolecular cycloaddition reaction, as shown in Scheme 2.

Scheme 2



The starting 4-hydroxycoumarins were conveniently prepared through two synthetic methods.

In method A (Scheme 3), substituted phenols were converted to the corresponding 2-hydroxyacetophenones via Fries rearrangement.[11] 2-Hydroxyacetophenones were treated with pulverized sodium and diethyl

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carbonate[9f] to give the substituted 4-hydroxycoumarins in moderate yields (Table 1). We found that the reaction temperature put an important influence on the resulting products. When the inner temperature of the reaction mixture was about 95 ℃, it gave the desired products, 4-hydroxycoumarins, and while the reaction temperature was about 130 ℃, 3-ethoxycarbonyl-4-hydroxycoumarin **3** (R^1=R^2=R^4=H, R^3=OCH_3) was obtained in 77% yield (Scheme 3).

In method B (Scheme 4), the substituted phenols were treated with malonic acid, zinc chloride and phosphorus oxychloride around 65 ℃ by one-pot procedure[12] to afford the corresponding 4-hydroxycoumarins. Phenols with an electron-withdrawing group, such as 4-fluorophenol, 4-chlorophenol, 4-nitrophenol, 2,4-dichlorophenol, 2,4-dinitrophenol, were not applicable to this reaction, and no desired products can be isolated.

Our trials, which were based on the oxidation conditions of 4-hydroxycoumarins with a model reaction using 4-hydroxy-6-methylcoumarin with catechol as the starting material, in the presence of an oxidant such as $KClO_3$, $KBrO_3$, KClO, $PdCl_2$, $RhCl_3$, $FeCl_3$, $CuCl_2$, H_2O_2, failed. Only a minor even no desired product was detected. When 4-hydroxy-6-methylcoumarin reacted with catechol in acetone-water (1∶1, *V*∶*V*) at room temperature using $(NH_4)_2Ce(NO_3)_6$ as the oxidant, the corresponding product, 8,9-dihydroxy-2-methyl-6*H*-benzofuro[3,2-*c*][1]benzopyran-6-one, was obtained in 37% yield. However, $(NH_4)_2S_2O_8$ was found to be the most efficient oxidant for this reaction, and the yield could be reached up to 82%. Thus, under the same conditions, other 4-hydroxycoumarins reacted steadily with catechol to afford a series of wedelolactone derivatives in moderate yields (Table 2).

Scheme 3

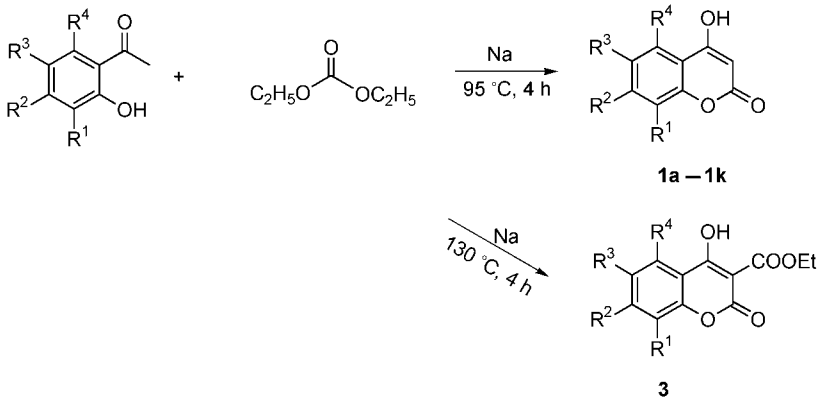
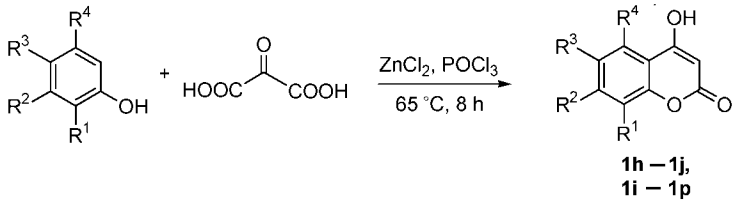


Table 1 Preparation of compounds **1**

Compound	R^1	R^2	R^3	R^4	Preparation method	Yield/%
1a	Cl	H	H	H	A	57
1b	Br	H	H	H	A	61
1c	H	Cl	H	H	A	62
1d	Cl	H	Cl	H	A	57
1e	H	H	F	H	A	79
1f	H	H	Cl	H	A	68
1g	H	H	Br	H	A	70
1h	H	H	CH_3	H	A	86
1h	H	H	CH_3	H	B	65
1i	H	H	*t*-C_4H_9	H	A	49
1i	H	H	*t*-C_4H_9	H	B	58
1j	H	CF_3	H	H	A	52
1j	H	CF_3	H	H	B	48
1k	H	H	CH_3O	H	A	80
1l	$C_6H_5CH_2$	H	H	H	B	25
1m	CH_3	H	H	*i*-C_3H_7	B	35
1n	H	OH	H	H	B	33
1o	H	H	$C_6H_5CH_2$	H	B	38
1p	(CH=CH)$_2$		H	H	B	41

Scheme 4



1h — 1j,
1i — 1p

Table 2 Preparation of Compounds **2**

Compound	R^1	R^2	R^3	R^4	R^5	X	Yield/%
2a	Cl	H	H	H	—	O	51
2b	Br	H	H	H	—	O	43
2c	H	Cl	H	H	—	O	70
2d	Cl	H	Cl	H	—	O	44
2e	H	H	F	H	—	O	40
2f	H	H	Cl	H	—	O	55
2g	H	H	Br	H	—	O	50
2h	H	H	CH_3	H	—	O	82
2i	H	H	*t*-C_4H_9	H	—	O	65
2j	H	CF_3	H	H	—	O	67
2k	H	H	CH_3O	H	—	O	49
2l	$C_6H_5CH_2$	H	H	H	—	O	70
2m	CH_3	H	H	*i*-C_3H_7	—	O	63
2n	H	OH	H	H	—	O	61
2o	H	H	$C_6H_5CH_2$	H	—	O	68
2p	$(CH=CH)_2$		H	H	—	O	42
2q	H	H	H	H	H	N	32
2r	H	H	H	H	CH_3	N	39
2s	H	H	H	H	C_6H_5	N	43

In summary, we developed a new and simple method for the synthesis of substituted wedelolactone derivatives through an intermolecular cycloaddition reaction from the 4-hydroxycoumarins, which are easily prepared from the substituted phenols or 2-hydroxyacetophenones. The reaction conditions are simple, since it is not sensitive to oxygen and water, which makes it easy to operate at room temperature.

Experimental

IR spectra were taken on a Shimadzu-440 spectrometer. The ^{1}H NMR spectra were recorded in $CDCl_3$ solution on a Bruker AM-300 or Varian-360L instrument using TMS as an internal standard. The ^{19}F NMR spectra were obtained on a Varian-360L instrument using $CFCl_3$ as an external standard. EIMS data were obtained on an HP5989A mass spectrometer. HRMS were recorded on a Telsa FTMS spectrometer. The elemental analyses were performed on Heraeus Rapid-CHNO. All solvents were dried prior to use by standard procedures.

General Procedure for the synthesis of 4-hydroxycoumarins 1

Compounds **1q**—**1s** were synthesized by the literature procedure.[12]

Method A

To a stirring mixture of 2-hydroxy-5-methylacetophenone (0.01 mol) and pulverized sodium (0.1 mol) was added dropwise diethyl carbonate (40 mL) at 0 ℃. The mixture was stirred at that temperature for 30 min, then heated to 95 ℃ for 4 h. After the resulting mixture was cooled to room temperature, methanol was carefully added in order to eliminate residual metallic sodium. The solution was poured into cold solution of ice water, and extracted with diethyl ether. When the aqueous layer was acidified with dilute HCl, white or yellow solid appeared. The solid was filtered and washed with water, dried and recrystallized from methanol.

8-Chloro-4-hydroxycoumarin (1a): Light yellow solid; m.p. 274—276 ℃ (lit.[13] 270—275 ℃); ^{1}H

NMR (CD_3COCD_3) δ: 6.07 (s, 1H), 7.71 (t, J=8.1 Hz, 1H), 8.10 (d, J=8.1 Hz, 1H), 8.21 (dd, J=1.8, 7.8 Hz, 1H), 11.64 (s, 1H); MS *m/z* (%): 196 (M^+, 55.66), 198 [$(M+2)^+$, 17.09], 154 (100), 156 (33.62).

8-Bromo-4-hydroxycoumarin (1b): Light yellow solid; m.p. 258—259 ℃; ^{1}H NMR (CD_3COCD_3) δ: 5.62 (s, 1H), 7.27 (t, J=8.1 Hz, 1H), 7.80 (dd, J=7.8 Hz, 1H), 7.92 (dd, J=1.5, 7.8 Hz, 1H), 12.79 (s, 1H); IR (KBr) *v*: 3078, 2922, 1713, 1599, 1552, 1497, 1302, 1250, 1192 cm^{-1}; MS *m/z* (%): 240 (M^+, 48.21), 242 [$(M+2)^+$, 47.02], 198 (100), 200 (94.05), 170 (39.88), 172 (39.88). Anal. calcd for $C_9H_5BrO_3$: C 44.85, H 2.09; found C 45.04, H 2.41.

7-Chloro-4-hydroxycoumarin (1c): Light yellow solid; m.p. 241—243 ℃ (lit.[14] 248 ℃); ^{1}H NMR (CD_3COCD_3) δ: 5.59 (s, 1H), 7.55 (d, J=1.8 Hz, 1H), 7.71 (dd, J=1.8, 8.4 Hz, 1H), 7.78 (d, J=8.4 Hz, 1H), 12.77 (s, 1H); MS *m/z* (%): 196 (M^+, 62.53), 198 [$(M+2)^+$, 20.71], 154 (100), 156 (35.96), 126 (55.50).

6,8-Dichloro-4-hydroxycoumarin (1d): Light yellow solid; m.p. 319—320 ℃ (lit.[15] 320 ℃); ^{1}H NMR (CD_3COCD_3) δ: 5.73 (s, 1H), 7.73 (s, 1H), 8.08 (s, 1H), 12.75 (s, 1H); MS *m/z* (%): 230 (M^+, 37.99), 232 [$(M+2)^+$, 25.16], 188 (100), 190 (67.74), 160 (17.97).

6-Fluoro-4-hydroxycoumarin (1e): White solid; m.p. 245—246 ℃; ^{1}H NMR (CD_3COCD_3) δ: 5.69 (s, 1H), 7.30—7.40 (m, 2H), 7.47—7.51 (m, 1H), 12.47 (s, 1H); ^{19}F NMR ($CDCl_3$/TFA): δ: −7.17 (s, F); IR (KBr) *v*: 3088, 2713, 1704, 1638, 1573, 1511, 1307, 1255, 1225 cm^{-1}; MS *m/z* (%): 180 (M^+, 59.63), 181 [$(M+1)^+$, 7.66], 138 (100), 110 (62.16), 82 (23.70). Anal. calcd for $C_9H_5FO_3$: C 60.01, H 2.80; found C 60.00, H 2.96.

6-Chloro-4-hydroxycoumarin (1f): Light yellow solid; m.p. 270—271 ℃ (lit.[16] 266—268 ℃); ^{1}H NMR (CD_3COCD_3) δ: 5.67 (s, 1H), 7.31 (d, J=9.0 Hz, 1H), 7.55 (dd, J=2.7, 9.0 Hz, 1H), 7.77 (d, J=2.4 Hz, 1H), 12.48 (s, 1H); MS *m/z* (%): 196 (M^+, 52.66), 198 [$(M+2)^+$, 17.00], 154 (100), 156 (35.80), 126 (44.09).

6-Bromo-4-hydroxycoumarin (1g): Light yellow solid; m.p. 277—278 ℃ (lit.[16] 275—277 ℃); ^{1}H NMR (CD_3COCD_3) δ: 5.60 (s, 1H), 7.35 (d, J=8.7 Hz, 1H), 7.78 (dd, J=2.7, 9.0 Hz, 1H), 7.88 (d, J=2.7 Hz, 1H), 12.80 (s, 1H); MS *m/z* (%): 240 (M^+, 47.78), 242 [$(M+2)^+$, 45.77], 198 (100), 200 (97.18), 170 (55.24), 172 (53.63).

4-Hydroxy-6-methylcoumarin (1h): Light green solid; m.p. 257—258 ℃ (lit.[17] 253—254 ℃); ^{1}H NMR (DMSO-d_6) δ: 2.38 (s, 3H), 5.55 (s, 1H), 7.21 (d, J=8.7 Hz, 1H), 7.40 (d, J=8.7 Hz, 1H), 7.59 (s, 1H), 12.38 (s, 1H); IR (KBr) *v*: 2929, 1703, 1688, 1634, 1610, 1577, 1509, 1473, 1306, 1272, 1216, 1098 cm^{-1}; MS *m/z* (%): 176 (M^+, 55.33), 134 (100), 106 (44.90).

4-Hydroxy-6-*tert*-butylcoumarin (1i): White solid; m.p. 199—201 ℃. ^{1}H NMR (CD_3COCD_3) δ: 1.33—1.43 (m, 9H), 5.67 (s, 1H), 7.23 (d, J=8.7 Hz, 1H), 7.64 (d, J=8.7 Hz, 1H), 7.84 (d, J=2.4 Hz, 1H), 12.13 (s, 1H); IR (KBr) *v*: 2961, 2580, 1658, 1593, 1552, 1518, 1295, 1247 cm^{-1}; MS *m/z* (%): 218 (M^+, 10.96), 203 (66.98), 161 (100). Anal. calcd for $C_{13}H_{14}O_3$: C 71.54, H 6.47; found C 71.58, H 6.51.

4-Hydroxy-7-trifluoromethylcoumarin (1j): White solid; m.p. 219—220 ℃; ^{1}H NMR (CD_3COCD_3) δ: 5.65 (s, 1H), 7.55 (dd, J=0.6, 7.5 Hz, 2H), 7.97 (d, J=7.5 Hz, 1H), 11.34 (s, 1H); ^{19}F NMR (CD_3COCD_3/$CFCl_3$): δ: −63.62 (s, CF_3); IR (KBr) *v*: 3365, 3080, 1670, 1633, 1564, 1523, 1341, 1242 cm^{-1}; MS *m/z* (%): 230 (M^+, 65.66), 211 (16.20), 188 (100), 160 (80.60). Anal. calcd for $C_{10}H_5F_3O_3$: C 52.19, H 2.19; found C 52.11, H 2.14.

4-Hydroxy-8-methoxycoumarin (1k): Light yellow solid; m.p. 274—276 ℃ (lit.[18] 272—273 ℃); MS *m/z* (%): 192 (M^+, 100), 164 (15.96), 151 (4.50).

General Procedure for the synthesis of 4-hydroxycoumarins 3

To a stirring mixture of 2-hydroxy-5-methoxyacetophenone (0.01 mol) and pulverized sodium (0.1 mol) was added dropwise diethyl carbonate (40 mL) at 0 ℃. The mixture was stirred at the temperature for 30 minutes, then heated to about 130 ℃ for 4 h. The resulting mixture was cooled to room temperature and quantity of methanol was added in order to consume the excess sodium. The solution was poured into cold solution of ice and water, and extracted with diethyl ether. The aqueous layer was neutralized with dilute HCl while a large number of yellow or white solid appeared. The solid was filtered and washed with water, dried and recrystallized from methanol.

3-Ethoxycarbonyl-4-hydroxy-6-methyoxycoumarin (3): Light yellow solid; m.p. 159—160 ℃; ^{1}H NMR (DMSO-d_6) δ: 1.38 (t, J=7.2 Hz, 3H), 3.96 (d, J=6.6 Hz, 3H), 4.43 (d, J=6.9 Hz, 2H), 6.87 (d, J=2.4 Hz, 1H), 7.00 (dd, J=2.4, 9.0 Hz, 1H), 7.93 (d, J=8.4 Hz, 1H), 14.72 (s, 1H); IR (KBr) *v*: 3090, 2992, 1739, 1623, 1555, 1504, 1417, 1299, 1222, 1107, 1024 cm^{-1}; MS *m/z* (%): 264 (M^+, 24.06), 250 (3.27), 218 (42.79), 150 (100). Anal. calcd for $C_{13}H_{12}O_6$: C 59.09, H 4.58; found C 58.97, H 4.61.

Method B

A stirring mixture of 4-methylphenol (0.01 mol), malonic acid (0.01 mol), anhydrous zinc chloride (0.03 mol) and phosphorus oxychloride (0.03 mol) was heated at 65 ℃ for 8 h, then cooled and decomposed with ice and water, and allowed to stand for some time. The solid was filtered, and dissolved in 10% sodium carbonate aqueous solution, then the resulting solution was acidified to pH=7 with dilute HCl solution. Filtration of the oily solid and acidification of the filtrate gave the crude product. Pure 4-hydroxycoumarin was obtained by recrystallization from methanol.

8-Benzyl-4-hydroxycoumarin (1l): Light yellow solid; m.p. 214—216 ℃; ^{1}H NMR (DMSO-d_6) δ: 4.09 (s, 2H), 5.57 (s, 1H), 7.23—7.29 (m, 6H), 7.47 (dd, J=1.5, 7.8 Hz, 1H), 7.69 (dd, J=1.5, 7.8 Hz, 1H), 12.50 (s, 1H); IR (KBr) *v*: 3090, 2745, 1689, 1605, 1558, 1502, 1319, 1231 cm^{-1}; MS *m/z* (%): 252 (M^+, 36.24), 182 (87.30), 165 (34.92), 152 (100). Anal. calcd for

$C_{16}H_{12}O_3$: C 76.18, H 4.79; found C 76.04, H 4.89.

4-Hydroxy-5-isopropyl-8-methylcoumarin (1m): Light green solid; m.p. 228—230 ℃; ^{1}H NMR (DMSO-d_6) δ: 1.21—1.26 (m, 6H), 2.35 (s, 3H), 4.25—4.34 (m, 1H), 5.27 (s, 1H), 7.16 (d, J=8.4 Hz, 1H), 7.37 (d, J=8.4 Hz, 1H), 12.04 (s, 1H); IR (KBr) v: 3050, 2945, 1685, 1613, 1595, 1561, 1482, 1379, 1299, 1283, 1239 cm^{-1}; MS *m/z* (%): 218 (M^+, 92.22), 219 [$(M+1)^+$, 61.02], 203 (36.52), 177 (100), 158 (71.44), 134 (55.07). Anal. calcd for $C_{13}H_{14}O_3$: C 71.54, H 6.47; found C 71.55, H 6.49.

4,7-Dihydroxycoumarin (1n): Light green solid; m.p. 280—281 ℃ (lit.[19] 286—288 ℃); ^{1}H NMR (CD_3COCD_3) δ: 5.42 (s, 1H), 6.65 (d, J=2.4 Hz, 1H), 6.74 (dd, J=2.4, 8.7 Hz, 1H), 7.62 (d, J=9.0 Hz, 1H), 11.89 (s, 1H); MS *m/z* (%):178 (M^+, 99.18), 150 (14.71), 136 (100), 108 (62.28).

6-Benzyl-4-hydroxycoumarin (1o): Light yellow solid; m.p. 218—220 ℃; ^{1}H NMR (DMSO-d_6) δ: 4.09 (s, 2H), 5.57 (s, 1H), 7.23—7.29 (m, 6H), 7.47 (dd, J=1.5, 7.8 Hz, 1H), 7.69 (dd, J=1.5, 7.8 Hz, 1H), 12.50 (s, 1H); IR (KBr) v: 3083, 2730, 1689, 1631, 1602, 1573, 1512, 1343, 1314, 1208 cm^{-1}; MS *m/z* (%): 252 (M^+, 80.51), 210 (95.61), 181 (100), 165 (27.65), 153 (75.00). Anal. calcd for $C_{16}H_{12}O_3$: C 76.18, H 4.79; found C 75.88, H 4.93.

6,7-Ethylene-4-hydroxycoumarin (1p): Light yellow solid; m.p. 228—230 ℃ (lit.[20] 225—230 ℃). ^{1}H NMR (DMSO-d_6) δ: 5.76 (s, 1H), 7.67—7.99 (m, 6H), 12.36 (s, 1H); MS *m/z* (%): 212 (M^+, 61.00), 170 (100), 143 (17.90), 114 (53.10).

General procedure for the synthesis of wedelolactone derivatives 2

To a stirring mixture of 4-hydroxycoumarin (0.5 mmol), catechol (0.5 mmol), sodium acetate (3 mmol), acetone (2 mL) and water (1 mL) was added dropwise slowly a solution of ammonium persulfate (0.75 mmol) and water (1 mL) during about 2 h. The stirring was continued at room temperature, and monitored by TLC until 4-hydroxycoumarin disappeared completely. The reaction mixture was poured into water, filtered and the crude product was washed with water, and recrystallized from methanol to give pure wedelolactone derivative.

4-Chloro-8,9-dihydroxy-6*H*-benzofuro[3,2-*c*][1]-benzopyran-6-one (2a): Light yellow solid; m.p. 295—296 ℃ (lit.[9f] no m.p. record); ^{1}H NMR (DMSO-d_6) δ: 7.19 (s, 1H), 7.23 (s, 1H), 7.54—7.75 (m, 1H), 7.73 (d, J=8.1 Hz, 1H), 7.91 (t, J=7.8 Hz, 1H), 9.60 (s, 1H), 9.71 (s, 1H, OH); MS *m/z* (%): 302 (M^+, 58.15), 304 [$(M+2)^+$, 20.86], 268 (68.92), 43 (100).

4-Bromo-8,9-dihydroxy-6*H*-benzofuro[3,2-*c*][1]-benzopyran-6-one (2b): Light yellow solid; m.p. 301—302 ℃; ^{1}H NMR (DMSO-d_6) δ: 7.28 (s, 1H), 7.32 (d, J=6.9 Hz, 1H), 7.57 (d, J=6.9 Hz, 1H), 7.82 (s, 1H), 8.04 (d, J=8.4 Hz, 1H), 9.67 (s, 1H), 9.79 (s, 1H); IR (KBr) v: 3531, 3340, 1735, 1710, 1623, 1469, 1328, 1285 cm^{-1}; MS *m/z* (%): 346 (M^+, 100), 348 [$(M+2)^+$, 93.30]; HRMS calcd for $C_{15}H_7BrO_5$ 345.9477, found 345.9481.

3-Chloro-8,9-dihydroxy-6*H*-benzofuro[3,2-*c*][1]-benzopyran-6-one (2c): Light yellow solid; m.p. 297—299 ℃ (lit.[9f] no m.p. record); ^{1}H NMR (DMSO-d_6) δ: 7.21 (s, 1H), 7.26 (s, 1H), 7.50 (d, J=8.7 Hz, 1H), 7.75 (s, 1H), 7.98 (d, J=8.1 Hz, 1H), 9.58 (s, 1H), 9.71 (s, 1H); MS *m/z* (%): 302 (M^+, 100), 304 [$(M+2)^+$, 35.11], 301 [$(M-1)^+$, 5.35].

2,4-Dichloro-8,9-dihydroxy-6*H*-benzofuro[3,2-*c*]-[1]benzopyran-6-one (2d): Light yellow solid; m.p. 323—225 ℃; ^{1}H NMR (DMSO-d_6) δ: 7.19 (s, 1H), 7.34 (s, 1H), 7.81 (s, 1H), 7.93 (s, 1H), 9.65 (s, 1H), 9.78 (s, 1H); IR (KBr) v: 3534, 3193, 1720, 160,5 1465, 1351, 1285 cm^{-1}; MS *m/z* (%): 336 (M^+, 100), 338 [$(M+2)^+$, 63.97], 318 (12.16), 302 (7.64); HRMS calcd for $C_{15}H_6Cl_2O_5$ 335.9592, found 335.95839.

8,9-Dihydroxy-2-fluoro-6*H*-benzofuro[3,2-*c*][1]-benzopyran-6-one (2e): White solid; m.p. 308—310 ℃; ^{1}H NMR (DMSO-d_6) δ: 7.20 (s, 1H), 7.27 (s, 1H), 7.46—7.53 (m, 1H), 7.61 (dd, J=4.2, 9.0 Hz, 1H), 7.79 (dd, J=2.1, 7.5 Hz, 1H), 9.58 (s, 1H), 9.73 (s, 1H); ^{19}F NMR (DMSO-d_6/$CFCl_3$) δ: −9.49 (s, F); IR (KBr) v: 3548, 3327, 3080, 1736, 1710, 1631, 1473, 1322, 1288 cm^{-1}; MS *m/z* (%): 286 (M^+, 100), 287 [$(M+1)^+$, 20.12], 240 (2.76); HRMS calcd for $C_{15}H_7FO_5$ 286.0278, found 286.0311.

2-Chloro-8,9-dihydroxy-6*H*-benzofuro[3,2-*c*][1]-benzopyran-6-one (2f): Light yellow solid; m.p. 299—300 ℃ (lit.[9f] no m.p. record); ^{1}H NMR (DMSO-d_6) δ: 7.19 (s, 1H), 7.26 (s, 1H), 7.56—7.65 (m, 2H), 7.98 (s, 1H), 9.59 (s, 1H), 9.74 (s, 1H); MS *m/z* (%): 302 (M^+, 100), 301 [$(M+1)^+$, 27.11], 304 [$(M+2)^+$, 38.16], 274 (8.29).

2-Bromo-8,9-dihydroxy-6*H*-benzofuro[3,2-*c*][1]-benzopyran-6-one (2g): Light yellow solid; m.p. 303—304 ℃ (lit.[9f] no m.p. record); ^{1}H NMR (DMSO-d_6) δ: 7.21 (s, 1H), 7.28 (s, 1H), 7.53 (d, J=8.7 Hz, 1H), 7.78 (dd, J=2.4, 8.7 Hz, 1H), 8.13 (d, J=2.7 Hz, 1H), 9.69 (s, 1H), 9.80 (s, 1H); MS *m/z* (%): 346 (M^+, 92.11), 348 [$(M+2)^+$, 100], 318 (3.58).

8,9-Dihydroxy-2-methyl-6*H*-benzofuro[3,2-*c*][1]-benzopyran-6-one (2h): White solid; m.p. 343—344 ℃ (lit.[21] 348 ℃); ^{1}H NMR (DMSO-d_6) δ: 2.45 (s, 3H), 7.18 (s, 1H), 7.28 (s, 1H), 7.41—7.43 (m, 2H), 7.77 (s, 1H), 9.54 (s, 1H), 9.66 (s, 1H); MS *m/z* (%): 282 (M^+, 100), 283 [$(M+1)^+$, 15.81], 281 [$(M-1)^+$, 16.56].

8,9-Dihydroxy-2-tert-methyl-6*H*-benzofuro[3,2-*c*]-[1]benzopyran-6-one (2i): White solid; m.p. 280—281 ℃; ^{1}H NMR (DMSO-d_6) δ: 1.35 (s, 9H), 7.23 (s, 1H), 7.27 (s, 1H), 7.59 (d, J=9.0 Hz, 1H), 7.70 (dd, J=2.4, 9.0 Hz, 1H), 7.88 (d, J=2.4 Hz, 1H), 9.52 (s, 1H), 9.63 (s, 1H); IR (KBr) v: 3539, 3146, 2963, 1708, 1632, 1517, 1318, 1289 cm^{-1}; MS *m/z* (%): 324 (M^+, 88.21), 309 (100), 294 (4.80), 281 (28.34), 203 (33.96). Anal. calcd for $C_{19}H_{16}O_5$: C 70.36, H 4.97; found C 70.33, H 4.92.

8,9-Dihydroxy-3-trifluoromethyl-6*H*-benzofuro[3,2-*c*][1]benzopyran-6-one (2j): White solid; m.p. 304—306 ℃. ^{1}H NMR (DMSO-d_6) δ: 7.25 (s, 1H), 7.30 (s, 1H), 7.77 (d, J=7.5 Hz, 1H), 8.00 (s, 1H), 8.18 (d, J=

8.1 Hz, 1H), 9.64 (s, 1H), 9.80 (s, 1H); IR (KBr) *v*: 3529, 3318, 1715, 1633, 1510, 1475, 1338, 1285 cm^{-1}; MS *m/z* (%): 336 (M^+, 100), 337 [$(M+1)^+$, 17.20], 317 (5.59). Anal. calcd for $C_{16}H_7F_3O_5$: C 57.16; H 2.10; found C 57.28, H, 2.08.

8,9-Dihydroxy-2-methoxy-6*H*-benzofuro[3,2-*c*]-[1]benzopyran-6-one (2k): Light green solid; m.p. 310—312 ℃ (lit.[21] no m.p. reported); ^1H NMR (DMSO-d_6) δ: 3.86 (s, 3H), 7.04 (dd, J=1.8, 8.4 Hz, 1H), 7.15—7.17 (m, 2H), 7.23 (s, 1H), 7.88 (d, J=8.4 Hz, 1H), 9.47 (s, 1H), 9.55 (s, 1H); MS *m/z* (%): 298 (M^+, 100), 283 (39.45), 255 (36.28), 227 (14.09).

4-Benzyl-8,9-dihydroxy-6*H*-benzofuro[3,2-*c*][1]-benzopyran-6-one (2l): Light yellow solid; m.p. 294—296 ℃; ^1H NMR (DMSO-d_6) δ: 4.19 (s, 2H), 7.18—7.20 (m, 2H), 7.25—7.32 (m, 5H), 7.39 (t, 1H, J=7.5 Hz), 7.51 (dd, J=1.5, 7.5 Hz, 1H), 7.86 (dd, J=1.5, 7.8 Hz, 1H), 9.52 (s, 1H), 9.65 (s, 1H); IR (KBr) *v*: 3544, 3188, 1699, 1627, 1510, 1494, 1359, 1286 cm^{-1}; MS *m/z* (%): 358 (M^+, 100), 359 [$(M+1)^+$, 24.10], 341 (1.75), 329 (8.50). Anal. calcd for $C_{22}H_{14}O_5$: C 73.74, H 3.94; found C 73.52, H 3.64.

8,9-Dihydroxy-1-isopropyl-4-methyl-6*H*-benzofuro-[3,2-*c*][1]benzopyran-6-one (2m): Light yellow solid; m.p. 295—296 ℃; ^1H NMR (DMSO-d_6) δ: 1.32 (s, 6H), 2.48 (s, 3H) , 3.53—3.62 (m, 1H), 7.17—7.30 (m, 2H), 7.44 (d, J=7.2 Hz, 1H), 7.68 (d, J=7.2 Hz, 1H), 9.53 (s, 1H), 9.65 (s, 1H); IR (KBr) *v*: 3524, 3213, 2964, 1702, 1633, 1593, 1492, 1353, 1282 cm^{-1}; MS *m/z* (%): 324 (M^+, 79.46), 325 [$(M+1)^+$, 22.59], 309 (100). Anal. calcd for $C_{19}H_{16}O_5$: C 70.36, H 4.97; found C 70.28, H 5.31.

3,8,9-Trihydroxy-6*H*-benzofuro[3,2-*c*][1]benzo-pyran-6-one (2n): White solid; m.p. >330 ℃ (lit.[9f] >330 ℃); ^1H NMR (DMSO-d_6) δ: 7.03 (s, 1H), 7.16 (s, 1H), 7.68—7.75 (m, 3H), 9.56 (s, 1H), 9.70 (s, 1H); MS *m/z* (%): 284 (M^+, 100), 285 [$(M+1)^+$, 21.72], 267 (15.59).

2-Benzyl-8,9-dihydroxy-6*H*-benzofuro[3,2-*c*][1]-benzopyran-6-one (2o): Light yellow solid; m.p. 268—269 ℃; ^1H NMR (DMSO-d_6) δ: 4.07 (s, 2H), 7.20 (s, 2H), 7.26—7.30 (m, 5H), 7.49—7.51 (m, 2H), 7.81 (s, 1H), 9.53 (s, 1H), 9.63 (s, 1H); IR (KBr) *v*: 3499, 3256, 1705, 1630, 1569, 1494, 1474, 1331, 1289 cm^{-1}; MS *m/z* (%): 358 (M^+,60.68), 329 (4.60), 281 (6.75), 252 (100). Anal. calcd for $C_{22}H_{14}O_5$: C 73.74, H 3.94; found C 73.54, H 4.65.

8,9-Dihydroxy-5,11-dioxa-indeno[2,1-*a*]phenanth-ren-6-one (2p): Yellow solid; m.p. 340—341 ℃ (lit.[22] m.p. >300 ℃); ^1H NMR (DMSO-d_6) δ: 7.24 (s, 1H), 7.32 (s, 1H), 7.71—8.10 (m, 6H), 9.55 (s, 1H), 9.68 (s, 1H); MS *m/z* (%): 318 (M^+, 100), 319 [$(M+1)^+$, 21.54], 290 (7.65).

8,9-Dihydroxy-5*H*-11-oxa-5-aza-benzo[*a*]fluoren-6-one (2q): Light yellow solid; m.p. >330 ℃ (lit.[9f] 332 ℃); ^1H NMR (DMSO-d_6) δ: 7.25 (s, 1H), 7.30 (s, 1H), 7.40—8.20 (m, 4H), 9.65 (s, 1H), 9.78 (s, 1H); MS *m/z* (%): 267 (M^+, 100), 268 [$(M+1)^+$, 18.63], 266 [$(M-1)^+$, 12.20].

8,9-Dihydroxy-5-methyl-5*H*-11-oxa-5-aza-benzo-[*a*]fluoren-6-one (2r): Light yellow solid; m.p. >330 ℃ (lit.[9f] >330 ℃); ^1H NMR (DMSO-d_6) δ: 3.74 (s, 3H), 7.27 (s, 1H), 7.38 (s, 1H), 7.41—8.16 (m, 4H), 9.62 (s, 1H), 9.75 (s, 1H); MS *m/z* (%): 281 (M^+, 100), 282 [$(M+1)^+$, 17.67], 266 (8.24).

8,9-Dihydroxy-5-phenyl-5*H*-11-oxa-5-aza-benzo-[*a*]fluoren-6-one (2s): Light yellow solid; m.p. >330 ℃ (lit.[9f] >340 ℃); ^1H NMR (DMSO-d_6) δ: 7.15—7.22 (m, 3H), 7.24 (s, 1H), 7.33 (s, 1H), 7.46—8.19 (m, 6H), 9.57 (s, 1H), 9.71 (s, 1H); MS *m/z* (%): 343 (M^+, 100), 344 [$(M+1)^+$, 22.50], 268 (5.19).

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